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Creutzfeldt-Jakob disease:
literature review based on three case reports

Amandha Alencar Maia Carneiro[1], Mateus Aragão Esmeraldo[1], David Elison de Lima e Silva[2], Espártaco Moraes Lima Ribeiro[1,2]

ABSTRACT. Creutzfeldt-Jakob disease (CJD) is one of the transmissible spongiform encephalopathies that lead to rapidly progressive dementia. CJD has a low prevalence, and the average survival is only 1 year after the onset of symptoms. As the patients with CJD develop rapidly progressive dementia, associated with myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism, the hypothesis of CJD must be raised. Classic magnetic resonance imaging (MRI) findings are hypersignals in the caudate nucleus, putamen, and cortical region. CJD must be considered a differential diagnosis of other types of dementia, and there is no effective treatment for this disease. In this article, we present a literature review based on the report of three cases of the sporadic form of this disease.

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

DOENÇA DE CREUTZFELDT-JAKOB: REVISÃO DA LITERATURA BASEADA NO RELATO DE TRÊS CASOS

RESUMO. A doença de Creutzfeldt-Jakob (DCJ) faz parte do grupo das encefalopatias espongiformes transmissíveis que levam a um quadro de demência rapidamente progressiva. A DCJ possui baixa prevalência, e a sobrevida média é de apenas um ano após o início dos sintomas. Diante de um paciente com demência rapidamente progressiva, associada a mioclonias, alterações visuais ou cerebelares, sinais piramidais ou extrapiramidais e mutismo acinético, a hipótese de DCJ deve ser levantada. Os achados clássicos na ressonância magnética são os hipersinais em núcleo caudado, putâmen e região cortical. A DCJ deve ser considerada como um diagnóstico diferencial de outros tipos de demência e não existe um tratamento eficaz para essa doença. Apresentamos neste artigo uma revisão da literatura baseada no relato de três casos da forma esporádica dessa doença.

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

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) was first described in 1920 by Hans Gerhard Creutzfeldt and Alfons Jakob[1]. It belongs to the group of transmissible spongiform encephalopathies (TSE), which are neurodegenerative diseases caused by prions. CJD is a rare disease, with an overall incidence of 1–2 cases per million individuals each year. In Brazil, only 55 cases were confirmed between the years of 2005 and 2014[2]. The other human prion diseases are Kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and variably protease-sensitive prionopathy (VPSPr).

CJD is classified into sporadic, variant, iatrogenic, and familial or genetic forms. The sporadic form (sCJD) corresponds to most cases, which do not have an infectious source or evidence of familial disease. The acquired forms are the variant CJD (vCJD), known as "mad cow disease," and the iatrogenic (iCJD), which is mainly associated with dura mater graft and the use of human growth hormone[3,4]. vCJD was observed in 1980 in the UK population after ingesting contaminated beef[5]. The familial CJD (fCJD) is defined as definite or probable CJD plus definite or probable CJD in a first-degree relative or

This study was conducted by the Santa Casa de Misericórdia de Sobral Hospital, Sobral, Ceará, Brazil.

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a disease-specific *PrP* gene mutation. About 10–15% of CJD cases are familial[6].

The sporadic form has a long incubation period, with an average age of onset of symptoms about 62 years and survival of only 1 year after the onset of the condition. vCJD affects younger age group, with an average age of onset of symptoms of 26 years, and has a longer duration of about 14 months[5,7].

As the patients with CJD develop rapidly progressive dementia, associated with myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism, the hypothesis of CJD must be raised[7]. Suggestive findings on brain magnetic resonance imaging (MRI) and a positive result from a real-time quaking-induced conversion (RT-QuIC) support the diagnosis. However, only brain tissue biopsy provides a definitive diagnosis[7]. Other than clinical support, there is no treatment for this disease, which is uniformly fatal.

The purpose of this article is to review the literature based on the report of three cases of the sporadic form of CJD, which were diagnosed between 2018 and 2021, in the neurology service of the *Santa Casa de Misericórdia de Sobral* hospital in Sobral, Ceará, Brazil.

CASE 1

A 69-year-old female, from Sobral-Ceará, in April 2017 started to experience progressive visual loss, headaches, and vertigo. In October of the same year, she evolved with ataxic gait, upper limb tremors, depressed mood, and short-term episodic memory deficit. In January 2018, the patient was admitted to the hospital with muscle stiffness, spasticity, myoclonus, and akinetic mutism. There were no reports of similar illnesses in the family. Brain MRI showed hyperintensity in the caudate and lentiform nuclei bilaterally and in diffuse cortical gyri on T2-weighted and FLAIR (fluid-attenuated inversion recovery) sequences and restricted diffusion in the same regions in DWI/ADC (diffusion-weighted imaging/apparent diffusion coefficient). The electroencephalogram (EEG) showed diffuse triphasic wave discharges associated with periodic complexes with short periodicity. The immunoassay of the 14-3-3 protein in the cerebrospinal fluid (CSF) was negative. The patient remained in palliative care and died in March 2018.

CASE 2

A 66-year-old male, from Irauçuba-Ceará, in March 2019 presented bradykinesia, ataxic gait, delusions, and attempted suicide. In April of the same year, he developed torpor, right hemiparesis, spastic rigidity, and orofacial and bodily myoclonus, when he was admitted to the hospital. The patient had no previous comorbidities and no family history of similar diseases. The CSF examination did not show alterations, and the immunoassay of the 14-3-3 protein in the CSF was negative. EEG showed generalized periodic discharges with short periodicity, and the brain MRI showed hyperintensity in the head of the caudate nucleus, lentiform nucleus, and diffuse cortical gyri, in addition to a cortical ribbon signal, on the T2-weighted, FLAIR, and DWI sequences. After 7 days of hospitalization, the patient died.

CASE 3

A 47-year-old female, from Crateús-Ceará, in February 2021 started experiencing intense vertigo. In March of the same year, she presented ataxic gait, evolving a month later with loss of ambulation, sensitive aphasia, myoclonus in the upper limbs, oral feeding movements, dullness, confabulations, hyperreligiosity, and hallucinations, when she was admitted to the hospital. The patient presented hyperthyroidism as comorbidity, was treated with tapazol, and revealed a history of first-degree consanguinity between the parents. The analysis of the CSF showed no alterations, with the immunoassay of the 14-3-3 protein being negative. Brain MRI showed a diffusion restriction signal in the putamen and caudate nucleus bilaterally, associated with a cortical strand signal in the frontal region, in the DWI, and T2-weighted sequences. EEG showed periodic generalized bursts of biphasic and triphasic waves. During hospitalization, the patient evolved with severe infectious complications and atrial fibrillation. On the 39th day of hospitalization, the patient died.

DISCUSSION

CJD manifests itself in the presence of prions, which are small particles containing an abnormal isoform (PrPSc) of a protein (PrPc) naturally present in the human body. The deposition of prions in brain tissue is responsible for neuronal dysfunction due to synaptic loss and cellular death, resulting in a spongiform appearance in tissue microscopy[6,7]. Prions are deposited in various regions of the body, but reach higher levels in the brain, retina, and optic nerve, triggering the neurological and visual symptoms of the disease[5].

Demonstration of the transmissibility of CJD was made in 1968, through the reproduction of the disease and pathological findings in chimpanzees. It was observed that in prion diseases there is no detectable immunopathological response, the incubation period

is prolonged, ranging from months to years, and the course of the disease is fatal, from weeks to months[1,8].

The sporadic form of CJD has defined subtypes based on focal neurological findings, which reflect the predominant involvement of certain brain regions, e.g., predominantly visual (Heidenhain variant), cerebellar (Oppenheimer-Brownell variant), cognitive, and affective forms[9].

The main prodromes of CJD are anxiety, dizziness, blurred vision, asthenia, and unusual behavior[8]. Such symptoms were present in the three cases reported. The clinical picture of CJD is quite heterogeneous. A very characteristic sign of the disease is myoclonus, often caused by varied sensory stimuli, which is present in 90% of cases[8].

Neuropsychiatric symptoms include dementia, behavioral and mood changes, such as apathy and depression, in addition to deficits in higher cortical functions, such as apraxia, aphasia, and visuospatial difficulties (e.g., spatial neglect, Balint's syndrome)[10]. Some patients may have psychotic symptoms, especially visual hallucinations[11], such as the patient mentioned in case 3. Cerebellar manifestations, such as nystagmus and ataxia, occur in approximately two-thirds of patients, and signs of involvement of the corticospinal tract, including hyperreflexia, Babinski's sign, and spasticity, appear in 40–80% of cases. Some patients may have extrapyramidal signs such as hypokinesia, bradykinesia, dystonia, and rigidity. The final stage of the disease is characterized by akinetic mutism[12]. All these symptoms are compatible with the clinical picture presented by patients in the three reported cases (Table 1). Evaluation of suspected cases includes brain MRI, EEG, and analysis of CSF[7]. The cranial computed tomography is usually normal, being useful, mainly, to exclude other conditions. The current diagnostic criteria for CJD used in Europe are listed in Table 2[13]. MRI is an important mean of investigation in the sporadic

Table 2. Diagnostic criteria for surveillance of sporadic Creutzfeldt-Jakob disease from January 1, 2017.

1.1 DEFINITE: Progressive neurological syndrome AND Neuropathologically or immunohistochemically or biochemically confirmed
1.2 PROBABLE: 1.2.1: I + two of II and typical electroencephalogram* OR 1.2.2: I + two of II and typical magnetic resonance imaging brain scan+ OR 1.2.3: I + two of II and positive CSF 14-3-3 OR 1.2.4: Progressive neurological syndrome and positive real-time quaking-induced conversion in CSF or other tissues
1.3 POSSIBLE: I + two of II + duration <2 years
I - Rapidly progressive cognitive impairment
II - A Myoclonus B Visual or cerebellar problems C Pyramidal or extrapyramidal features D Akinetic mutism

*Generalized periodic complexes; +high signal in caudate/putamen on magnetic resonance imaging brain scan or at least two cortical regions (temporal, parietal, occipital) on either diffusion-weighted imaging or fluid-attenuated inversion recovery; CSF: cerebrospinal fluid.

Table 1. Review of reported cases.

	Case 1	Case 2	Case 3
Age	69 years	66 years	47 years
Time from symptom onset to death	12 months	3 months	5 months
Main signs and symptoms	Vertigo, rigidity, ataxic gait, myoclonus, and akinetic mutism	Hypokinesia, ataxic gait, psychosis, sensory aphasia, rigidity, and myoclonus	Vertigo, ataxic gait, sensory aphasia, myoclonus, and hallucinations
MRI findings	High signal in caudate nucleus, lentiform, and diffuse cortical gyri on DWI, T2-weighted, and FLAIR	High signal in the head of the caudate nucleus, lentiform nucleus, and diffuse cortical gyri, in addition to "cortical ribboning" signal on T2-weighted, FLAIR, and DWI	Diffusion restriction signal in putamen and caudate nucleus, associated with cortical ribbon signal in frontal region on DWI and T2-weighted
EEG findings	Diffuse repetitive triphasic wave discharges with short periodicity	Diffuse repetitive wave discharges with short periodicity	Diffuse repetitive wave discharges with short periodicity
CSF findings	Normal CSF Negative 14-3-3 protein	Normal CSF Negative 14-3-3 protein	Normal CSF Negative 14-3-3 protein

MRI: magnetic resonance imaging; DWI: diffusion-weighted; FLAIR; fluid-attenuated inversion recovery; EEG: electroencephalogram; CSF: cerebrospinal fluid.

form of CJD, as it is highly sensitive and specific, in addition to being widely available. The classic findings of the disease are T2-FLAIR hyperintensity and restricted diffusion in the caudate, putamen and cortex, which are present in 80% of cases[14]. The sensitivity and specificity of these findings are 83–92% and 87–95%, respectively[15]. The typical EEG pattern shows bilateral synchronous periodic epileptiform discharges, such as biphasic or triphasic waves, with 90% specificity for CJD, in a compatible clinical setting. However, these findings may be present in other conditions, such as end-stage Alzheimer's disease, Lewy body dementia, and metabolic encephalopathies[14]. The three patients reported in this study presented these typical findings on brain MRI and EEG (Figure 1), associated with a compatible clinical picture, thus reinforcing the diagnosis of CJD. CSF analysis is usually normal, although protein levels may be elevated in 40% of patients[8]. Four proteins have been detected by immunoassay or Western blot in CSF, with high sensitivity for the detection of patients

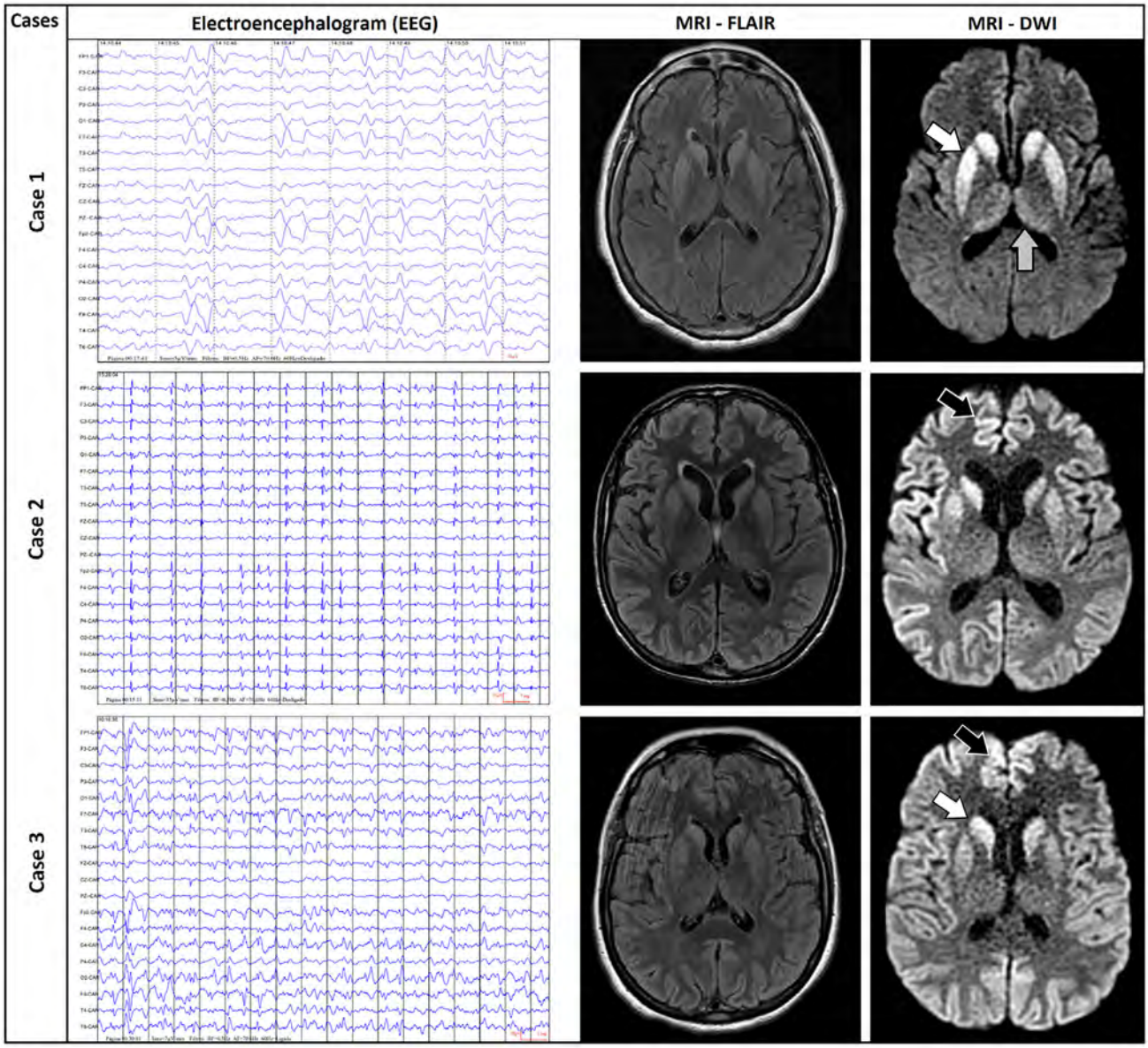

Figure 1. Axial diffusion-weighted and fluid-attenuated inversion recovery images showing bilateral involvement of the basal ganglia (Cases 1 and 3 – white arrows) and thalami (Case 1 – gray arrow). Axial diffusion-weighted shows more widespread signal hyperintensity in the cortical ribbon (Cases 2 and 3 – black arrows). Those findings are reported as usual Creutzfeldt-Jakob disease magnetic resonance imaging signs. Regarding the electroencephalograms, it is possible to note a diffuse repetitive triphasic wave discharges pattern with short periodicity in Case 1 and diffuse repetitive wave discharges pattern with short periodicity in Cases 2 and 3.

with CJD: protein 14-3-3, tau, neuron-specific enolase, and S-100[16,17]. A high level of non-phosphorylated tau protein has greater specificity for the diagnosis of CJD when compared to 14-3-3 protein dosage. 14-3-3 protein dosage is considered an adjunct rather than a diagnostic test, since its 80% of specificity applied to a disease with a prevalence as low as CJD means that most positive tests are actually false positives[18]. A negative test for this protein, as in the three cases reported, does not exclude the diagnosis, as the sensitivity may be lower in the early and late stages of the disease[19,20]. However, the RT-QuIC test has made the diagnosis of CJD easier, because it can detect minimal levels of prion protein in the CSF, increasing the chances of diagnosis while still alive. The sensitivity and specificity of this test are 91 and 98%, respectively[21].

It is important to note that MRI and EEG are easily accessible tests, but the identification of the 14-3-3 protein and the RT-QuIC assay in CSF are still a challenge, because they are not available in some hospitals in Brazil.

Considering the average age of onset of symptoms, it is possible that some cases of CJD are confused with other neurological conditions that commonly affect the elderly, such as Lewy body dementia, autoimmune encephalitis, Alzheimer's disease, and primary psychiatric disorder[5].

Over the past few years, some treatment possibilities for the sporadic form of CJD have been investigated, but none of them have improved symptoms or increased survival. Flupirtine, a centrally acting non-opioid analgesic, showed cytoprotective activity in vitro in neurons inoculated with prion protein, but no significant effects were evidenced in clinical trials. Pentosan polysulfate (PPS) is a high-molecular-weight polymer similar to heparin that appears to interfere with the conversion of PrPC to PrPSC when administered intraventricularly. Studies have shown longer survival with the use of PPS, but there was a frequent association with subdural hemorrhages, not being a viable treatment option. The association of quinacrine use with slower cognitive decline in patients with sCJD remains controversial in the clinical trials performed. Doxycycline was effective in in vitro models and in animals with prion disease, possibly by preventing the abnormal folding of the prion protein, but its clinical benefit remains uncertain[22].

Therefore, there is no effective treatment for CJD, which is uniformly fatal. Supportive measures include symptomatic treatment of neuropsychiatric disorders and myoclonus, which may respond satisfactorily to benzodiazepines, such as clonazepam, and to certain anticonvulsants, such as levetiracetam and valproate[23].

CJD is a rare diagnosis that should be suspected in cases of rapidly progressive dementia mainly associated with myoclonus. Typical findings on brain MRI and EEG support the diagnosis. However, new discoveries about CJD are needed, including earlier diagnostic techniques and a treatment capable of modifying or delaying the fatal evolution of the disease.

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Dance therapy and cognitive impairment in older people:
A review of clinical data

Ana Clara Menezes[1,2], Gabrielle Drumond[1,2], Nadia Shigaeff[1,2]

ABSTRACT. The growing interest for nonpharmacological treatment alternatives to older people with mild cognitive impairment or dementia has increased exponentially for the past few years; in this context, dance therapy is an effective therapeutic tool in improving the cognition of older people. The aim of this study was to verify whether dance therapy is a viable tool in promoting benefits with regard to the cognition and mood of older people with cognitive impairment. A database search covering the past 10 years was carried out. Result: The search found 193 papers; after title, abstract, and duplicity analysis, 14 of those were selected, of which 10 were fully revised. The studies showed positive results regarding the improvement of cognitive function after dance stimulations, as well as beneficial effects on the mood of older people with cognitive impairment.

Keywords: Aged; Cognition; Dance Therapy; Cognitive Dysfunction; Dementia.

DANÇATERAPIA E COMPROMETIMENTO COGNITIVO EM IDOSOS: UMA REVISÃO DE DADOS CLÍNICOS

RESUMO. O interesse por alternativas de tratamento não farmacológico para idosos com demência ou comprometimento cognitivo leve aumentou nos últimos anos. Entre elas, a dança destaca-se como uma eficaz ferramenta terapêutica na cognição de idosos. Dessa forma, o objetivo da presente revisão foi determinar se a dança é uma ferramenta capaz de promover benefícios em relação à cognição e ao humor de idosos comprometidos cognitivamente, por meio de uma revisão das publicações de estudos longitudinais dos últimos dez anos, que avaliaram os efeitos na cognição da terapia por intermédio da dança em idosos com alterações cognitivas, nas bases de dados PubMed, Scientific Electronic Library Online (SciELO) e Cochrane Library. A busca identificou 193 artigos; após a análise de títulos, resumos e duplicidade, 14 foram selecionados, dos quais dez foram revisados. De maneira geral, os estudos apresentaram resultados positivos quanto à melhora das funções cognitivas após a estimulação com dança, além de efeitos positivos também no humor de idosos comprometidos cognitivamente.

Palavras-chave: Idoso; Cognição; Terapia através da Dança; Disfunção Cognitiva; Demência.

INTRODUCTION

The aging process is characterized by changes in the brain and in the global performance of cognitive function. Therefore, cognitive abilities such as memory, processing speed, executive function, and reasoning seem to follow a pattern of decline during old age[1,2]. However, these cognitive declines are not necessarily accompanied by impacts on the individual's functionality, except for some specific circumstances in which the dysfunction is considered pathological, such as in dementia.

Mild cognitive impairment (MCI) refers to a notable, but discreet, alteration in cognitive function, more prevalent during old age and that does not result in any loss of functionality[2,3]. MCI is characterized by the impairment of at least one cognitive domain and can also be defined as amnesic (the most

This study was conducted by the Group Interdisciplinary Group for Research in Neuropsychology and Gerontology, Department of Psychology, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil.

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common subtype) or nonamnesic, depending on whether or not memory is compromised[4-6]. Consequently, the ability to obtain and retain new information is also significantly affected[3,5]. Historically, MCI was defined as a transitional phase between healthy aging and dementia[2,7,8]. It is relevant to note that not all MCI cases will necessarily lead to dementia, although the chances are significantly higher[5]. Indeed, in most cases, the cognitive impairment can be reverted to a performance considered typical to the respective age group[8].

Dementia refers to the process of generalized and progressive deterioration of cognitive functions, at a level severe enough to compromise the individual's independence and negatively impact their ability to perform daily life activities[9]. There is no specific and unique etiology to dementia; it can be caused by a number of different preexisting diseases. In fact, there are more than 100 possible causes of dementia, the most common being Alzheimer's disease[2]. It is estimated that 7% of the world population over 65 years of age is affected by some sort of dementia, and Latin American countries are the most affected[10].

Despite being widely studied, there is still no cure or effective treatment to reverse the symptoms of dementia once the diagnosis has been made. However, there are certain nonpharmacological interventions that can be useful in the delay of the pathology's progression or in controlling the symptoms[5,11,12]. Among those interventions, dance therapy is a relatively recent construct, but some studies have shown it to be effective.

Dance is a universal cultural expression of the human being that crosses the time barrier, motivating and mobilizing all age groups. When music and body movements are involved, several regions of the brain are activated concomitantly, promoting the chance of neuroplasticity and other effects that are the aim of investigations by researchers in the field[13,14].

Given the above fact, dance therapy is considered an excellent nonpharmacological intervention as it provides a body activity that is extremely advantageous together with music that favors an emotional bond, facilitating the adherence of older people to the proposed intervention[15]. Regarding the effects of dance for people with cognitive impairment, evidence of improvement in cognitive performance is found, demonstrating that dance therapy not only acts as a preventive factor for neurodegenerative diseases but is also able to promote the decrease in cognitive impairment, especially of memory[16]. Therefore, in view of some many benefits described in healthy older people or those with some kind of impairment, further investigation to clarify the impacts of dance as therapeutic intervention becomes essential.

However, when considering publications in the area, it is clear that the systematic reviews found include in their methodology studies that have a sample constituted exclusively of cognitively healthy people, in addition to other interventions where the sample had some kind of impairment; similarly, many reviews only consider a specific diagnosis in its inclusion criteria, such as Alzheimer's disease or Parkinson's disease. Therefore, the objective of the present review was to verify whether there are, in the literature, studies that discuss the benefits of dance therapy for the cognition and mood of older people with some degree of cognitive impairment, through the search for publications in the past 10 years. Furthermore, this review also aimed to understand the effect of dance therapy, as a therapeutic tool, for this population, as well as to be able to point out which cognitive domains are most affected by its use, the measurement instruments used in the studies, as well as the data on the possible improvement in the mood of individuals who participated in the intervention through dance.

METHODS

The present systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide its execution and is registered on The International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42021273912. The present study is exempt from the evaluation of the Research Ethics Committee as it is a systematic review. The study contemplated the electronic literature in the area, including original and peer-reviewed studies. The following databases were consulted: PubMed, Cochrane Library, and SciELO, during the months of March and April 2021. The last search was performed on April 25, 2021.

The search terms were chosen by consulting the MeSH (Medical Subject Headings) for the terms in English and the DeCS (Descritores em Ciências da Saúde) for the terms in Portuguese and Spanish. The selected terms, and their variations, were aged, cognition, cognition disorders, dance therapy, and senior dance combined as follows:

1. Aged, cognition, dance therapy;
2. Aged, cognition, senior dance;
3. Aged, cognition disorder, dance therapy; and
4. Aged, cognition disorder, senior dance.

The same search strategy was used across all scientific bases with the three languages: "Aged" AND

"Cognition" OR "Cognition Disorders" AND "Dance Therapy" OR "Senior Dance.

Included studies must be longitudinal, written in English, Portuguese, and/or Spanish, and published within the past 10 years. Study participants must be over 60 years of age and have cognitive impairment of any degree of severity. Studies must have dance as an intervention method, regardless of the duration of the intervention. Furthermore, another important inclusion criterion was the presence of cognitive assessment, in order to measure the effectiveness of the intervention on the participants' cognitive performance. As a secondary objective, it was also verified whether the mood of the participants was assessed, although mood was not, by itself, an inclusion criteria. The exclusion criteria adopted were whether the study was a systematic reviews, meta-analysis, theses, and monographs. Thus, these were excluded from the present systematic review.

The research and evaluation process was carried out by two independent reviewers, following the method mentioned above. Any possible discrepancies were discussed and reviewed among the two reviewers. If there was still disagreement, a third reviewer was asked to decide whether or not to include the study. All publications found were included in a spreadsheet, and the extracted data were compared between the two reviewers before the writing of this review.

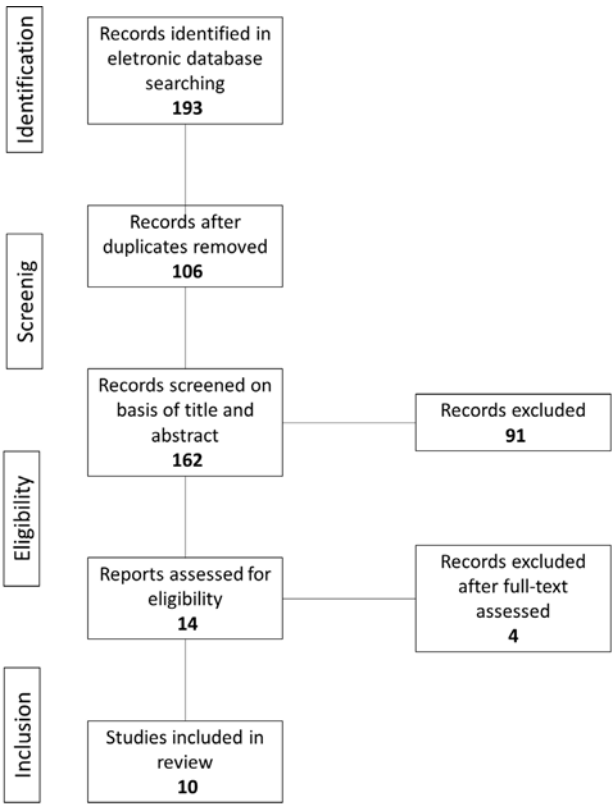

Figure 1. Flowchart of review process and study selection.

RESULTS

In total, 193 papers were found. Of these, 87 were excluded due to duplicity. Of the remaining 106 papers, an analysis of titles and abstracts was performed, taking in consideration the inclusion and exclusion criteria. As a result, 43 papers were excluded due to the age of the participants, 18 because they were not longitudinal studies, 8 for not using dance as an intervention, 12 studies for not carry out cognitive assessment, and 10 studies did not have a sample with cognitive impairment. In total, 91 studies were excluded at this stage, and 14 papers remained eligible to be read in full. This process is shown in the flowchart in Figure 1.

Of the 14 approved publications, 1 was excluded due to impossibility of access by the authors[17], 1 was excluded because it did not present results[18], 1 was excluded because it was a pilot study[19], and 1 was excluded because it did not explain whether the sample had cognitive impairment[20].

Thus, of the 14 publications originally covered, only 10 met the inclusion criteria and described the effects of dance therapy on the cognition of older people with cognitive impairment. Of these 10 scientific publications, 9 were randomized controlled trials (RCT) and 1 was a quasi-experimental study.

Regarding the location of interventions, four studies were carried out in Europe[21-24], one in South America[25], one in North America[26], and four in Asia[27-30]. In total, the 10 studies had 890 participants, who were divided into groups with dance intervention (IG) and 12 control groups (CG). Other types of intervention used for the CG included varied physical activity (two groups)[22,30], activities with a psychoeducational group (two groups)[26,29], playing musical instruments (one group)[29], and relaxation exercise (one group)[27]. In addition, six CG chose to maintain only their regular daily activities throughout the study period, therefore not performing extra activities[21,23-25,28,30]. Of the 890 participants, 412 received specific dance intervention.

Regarding the cognitive performance of the participants, five studies had samples composed of participants with MCI[21,22,27,29], two included participants with the diagnosis of dementia[25,30], and one had participants with Parkinson's disease[26]. Moreover, some studies had a mixed sample of healthy aged participants and others with cognitive impairment[23,24]. These papers were included in this review, since the inclusion of participants with MCI in the sample justifies their participation.

The interventions had different durations and weekly frequencies; five studies had sessions twice a week[21,22,26,27,30], while four studies had sessions three times a week[23-25,28]. Of the 10 studies analyzed, only 3 did not have 60 min sessions, opting for 35, 50, and 90 min, respectively[25,26,28], with the duration of the intervention varying between 6 and 40 weeks[21,27], with 12-week interventions being more performed, found in 4 studies[22,25,28,30].

After analyzing the chosen intervention methods, it is noteworthy that most studies — six of them — opted for a warm-up period at the beginning of the sessions and a moment of along with a cool-down (relaxing) at the end, ranging from 5 to 20 min[21,22,25-28]. The rhythms and styles of dance used throughout the sessions were also diversified. Three studies used ballroom dancing[21,25,29], one study presented the poco-poco dance, a traditional dance from Indonesia[27]; two studies worked with aerobic dance[22,28]; one study approached the tango[26]; two studies performed various rhythms over the weeks[23,24], and, finally, one study described the dance style only as an adaptation of a well-established dance program in the Chinese community[30]. The programs were conducted by different professionals, including physiotherapists[22,27], dance-movement therapist[30], dance instructors[21,26,28,29], and other professionals[23-24].

When it comes to the quality and validity of the studies included in this review, a few factors may also be worth mentioning.

First, most studies applied a method of randomization of participants. In fact, 8 of the 10 studies explicitly stated that participants were randomly allocated between IG or CG. The two studies that did not meet this criterion were excluded because:

1. They did not specify whether the participants were randomized[26] or
2. They stated that there was no randomization and/or blinding involving the allocation of participants[27].

Some studies did not explicitly mention whether allocation secrecy was a factor taken into account during the participant randomization process; in contrast, 5 of the 10 studies used this method, stating that a third independent evaluator participated in the randomization of the participants[21,22,24,28,29]. The study that did not randomize the participants did not present an evaluation regarding allocation confidentiality[27], and the rest of the studies did not mention whether randomization was performed blindly or openly.

The studies that blinded researchers to the sample groups could only be categorized as single-blind studies. This is due to the fact that, due to the very nature of the intervention, there is no way for the dance program instructor not to know the allocation of participants, since the dance group is, necessarily, the IG. However, one strategy adopted to alleviate these effects was the use of evaluators who did not have prior knowledge of participant allocation to assess pre- and post-intervention rates in people who completed the program. Some studies implemented this strategy[21,22,28-30], while others did not mention any type of information about this criterion[23-25,27], and one study reported keeping only some raters blinded instead of all of them[26]. For reasons similar to those of the instructors, in most cases, the participants also had no way of being blinded in relation to their allocation to the groups. In an attempt to mitigate this situation, one study did not inform participants about the study hypothesis or outcome measures[21].

Few studies described, in detail, the way researchers dealt with participant losses or exclusions. However, those who did present at least one of the following information: mean adherence to the program, percentage of losses, or attrition bias rates[21-25,28-30]. Some studies excluded losses from the final analysis. However, one study stated that although some participants dropped out of the program during the course of the study, they were still included in the analysis[29]. It is unclear whether these losses were included in the CG analysis or whether they were incorporated into the groups in which originally belonged. Another study stated that no participant withdrew from the program during the intervention[25].

Before starting the intervention, some studies also calculated the required number of participants in each group so that statistical significance could be achieved; therefore, the researchers took this information into account when planning the intervention and when estimating the total number of participants needed, with the objective of preserving the methodological integrity of the study in possible and eventual cases of loss of participants[22,24,28].

Concerning the instruments used to assess cognition, the studies showed a considerable diversity in tests and tools. To assess global cognition, the instruments most used were the *Mini-Mental State Examination* (MMSE) and the *Montreal Cognitive Assessment Test* (MoCA). Memory was assessed by an incredibly high number of different tests, the most common being the *Logical Memory* subtest from the *Wechsler Memory Scale-III* (WMS-III). Other instruments included *Rivermead Behavioral Memory Test* (RBMT), *Rey Auditory Verbal Learning Test* (RAVLT), and *Taylor Figure Test*. To evaluate executive function and visuospatial abilities, the *Trail-Making Test* (parts A and B) was the most used instrument, followed by *Judgment of Line Orientation*. *Tower of Hanoi* (ToH),

Five-Point Test, *Rey Osterrieth Complex Figure Test,* and *Taylor Figure Test* were also mentioned. Regarding attention, the most used tests were the subtests *Digit Span* and *Symbol Search* from the *Wechsler Adult Intelligence Scale-III* (WAIS-III), although more tests were also used. In language assessment, the tests chosen were *Verbal Fluency F-A-S* (FAS) and *Boston Naming Test*.

Overall, the studies presented positive results regarding the improvement in cognitive performance as a result of dance intervention. A brief summary of the main findings can be found in Table 1. Memory seems to have been the cognitive function that obtained the most benefits from this kind of intervention; 5 of the 10 studies showed an increase in the participants'

Table 1. Main results of included publications.

Authors (year/ country)	Title	Number of participants/ control group	Dance styles and musical rhythms	Tools	Main results
Adam et al.[27] (2016/ Malaysia)	Effectiveness of a combined dance and relaxation intervention on reducing anxiety and depression and improving quality of life among the cognitively impaired elderly	n=84 The CG had relaxation sessions, covering 40 participants of the 84 individuals in the study	A combination of *poco-poco* dance and relaxation exercises	Mini-Mental State Examination (MMSE) Hospital Anxiety and Depression Scale (HADS)	As a result of the 6-week dance intervention, there was a significant difference in the levels of global cognition, anxiety, and depression, measured by the MMSE and HADS, respectively
Bisbe et al.[22] (2020/ Spain)	Comparative cognitive effects of choreographed exercise and multimodal physical therapy in older adults with amnestic mild cognitive impairment: randomized clinical trial	n=31 The comparative group was dedicated to physical exercise, and 14 participants out of the 18 who were initially drafted completed the PE program	Choreographed aerobic dances that used a variety of music styles: salsa, rock, rumba, pop, and jive	MMSE Word list learning from the Wechsler Memory Scale – Third Edition (WMS-III) Visual memory subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Trail-Making Tests A and B (TMT-A and TMT-B) Letter Verbal Fluency (LVF) and Category Verbal Fluency (CVF) Boston Naming Test (BNT) Judgment of Line Orientation	The dance group showed greater benefits with regard to verbal recognition memory, at statistically significant rates. Furthermore, it also showed improvements in delayed visual memory
Borges et al.[25] (2018/ Brazil)	Effects of dance on the postural balance, cognition and functional autonomy of older adults	n=60 30 people were included in the CG, which adopted a life-as-usual approach	The program was based on ballroom dance and included styles such as foxtrot, waltz, rumba, swing, samba, and bolero	HADS MMSE	From the results found after 12 weeks of intervention with dance, it could be observed that the individuals in the experimental group showed an improvement in the mental state exam when compared to the CG, which did not undergo any intervention
Doi et al.[29] (2017/ Japan)	Effects of cognitive leisure activity on cognition in mild cognitive impairment: results of a randomized controlled trial	n=172 117 out of the 172 participants were allocated to groups that were not the dance program; 67 went to a passive CG, and 54 were allocated to a music group	Ballroom dance, including salsa, rumba, waltz, cha-cha, blues, jitterbug, and tango	Story memory and word list memory tests from the National Center for Geriatrics and Gerontology Functional Assessment Tool MMSE Tablet version of the TMT-A and TMT-B	Dance program participants demonstrated an improvement in memory function (more pronounced in patients with amnesic MCI) and in global cognition. No significant differences were found in attention or executive function

Continue…

Table 1. Continuation.

Authors (year/ country)	Title	Number of participants/ control group	Dance styles and musical rhythms	Tools	Main results
Ho et al.[30] (2020/ China)	Psychophysiological effects of dance movement therapy and physical exercise on older adults with mild dementia: a randomized controlled trial	n=166 Participants in the comparative groups were randomized to either exercise or a waitlist control; 56 participants were allocated to the exercise group and 55 were included on the waitlist	According to the authors, the intervention was a modified program from an established dance/ movement therapy program, applied within the Chinese population over the past decade	Full object memory evaluation Digit Span Test from the Wechsler Adult Intelligence Scale (WAIS) TMT-A and TMT-B De Jong Gierveld Loneliness Scale Geriatric Depression Scale (GDS) Visual Analogue Mood Scale	Improvements were observed in the domains of verbal memory and verbal fluency. Furthermore, the rates of depression, loneliness, and negative mood decreased. With the exception of memory and loneliness, the benefits observed were mostly qualitative and did not reach statistical significance
Kropacova et al.[24] (2019/ Czech Republic)	Cognitive effects of dance-movement intervention in a mixed group of seniors are not dependent on hippocampal atrophy	n=99 The CG, which was a life-as-usual CG, included 50 participants	Mentioned dances were Irish country, African dance, Greek dance, and tango	Montreal Cognitive Assessment Test (MoCA) Taylor Figure Test Logical memory from WMS-III Symbol search from Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Digit span from the WAIS-III Tower of Hanoi Five-Point Test Judgment of Line Orientation Test Taylor Figure Test MMSE MoCA Rivermead Behavioral Memory Test (RBMT) Verbal Fluency F-A-S Test (FAS) TMT-B Rey Osterrieth Complex Figure Rey Auditory Verbal Learning Test Test of Everyday Attention (TEA) Neuropsychiatric Inventory (NPI) GDS Beck Depression Inventory (BDI) Hamilton Scale for Depression Perceived Stress Scale (PSS) Beck Anxiety Inventory (BAI)	There was no significant difference among the intervention and the CG. However, slight improvements were observed in the intervention group when compared to its performance at baseline. More specifically, the areas identified as being the most benefited were memory and executive function
Lazarou et al.[21] (2017/ Greece)	International ballroom dancing against neurodegeneration: a randomized controlled trial in Greek community-dwelling elders with mild cognitive impairment	n=129 63 participants out of 129 were allocated to the CG, which received no intervention	Ballroom dance, expressed through styles such as: tango, waltz, Viennese Waltz, foxtrot, tumba, cha-cha, swing, salsa, merengue, Disco-Hustle, and Greek traditional ballroom dancing	MoCA Reverse Corsi Blocks Brooks Spatial Task	The intervention group demonstrated a significant improvement in the domains of global cognition, memory, alternating attention, verbal fluency, executive function, visuospatial skills, processing speed, and learning. The mood of the participants also improved. Comparatively, the CG did not show these benefits

Continue…

Table 1. Continuation.

Authors (year/ country)	Title	Number of participants/ control group	Dance styles and musical rhythms	Tools	Main results
McKee and Hackney[26] (2013/ the United States)	The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease	n=63 Out of the 9 participants allocated to the CG, which underwent education classes, 8 finished the program	Tango	MoCA Taylor Figure Test Logical memory from WMS-III Digit span from the WAIS-III Symbol search from the WAIS-III Five-Point Test Tower of Hanoi Taylor Figure Test Mississippi Aphasia Judgment of Line Orientation Screening Test BDI-II MoCA Logical memory from WMS Symbol Digit Modalities Test (SDMT) TMT-A and TMT-B Forward and Backward Digit Span Task GDS-15	Dance group participants showed qualitative improvement in spatial cognition and disease severity when compared to their performance at baseline, although it did not reach statistical significance when compared to the CG
Rektorova et al.[23] (2020/ Czech Republic)	Brain structure changes in nondemented seniors after six-month dance-exercise intervention	n=62 31 participants assigned to the CG, which was passive, completed the trial	The authors mentioned that the topic of the program was "Travelling Around the World", which was constituted by dance styles like folk, country, African, Greek, and tango dancing"	MoCA Taylor Figure Test Logical memory from WMS-III Digit span from the WAIS-III Symbol search from the WAIS-III Five-Point Test Tower of Hanoi Taylor Figure Test Mississippi Aphasia Judgment of Line Orientation Screening Test BDI-II	The intervention produced a slight improvement on executive function. The sample was mixed, including healthy older people and those with MCI. The results were more pronounced in older persons with MCI. In terms of neuroimaging, an increase in cortical thickness induced by the intervention was obtained compared to the CG in the areas of the inferior right temporal, fusiform, and lateral occipitotemporal gyrus
Zhu et al.[28] (2018/ China)	Effects of a specially designed aerobic dance routine on mild cognitive impairment	n=54 The CG consisted of 31 participants and underwent a life-as-usual approach	Aerobic dance	MoCA Logical memory from WMS SDMT TMT-A and TMT-B Forward and Backward Digit Span Task GDS-15	Participants in the intervention group demonstrated significant improvements in memory, processing speed, and global cognition when compared to their baseline performance. These improvements attenuated after 6 months. The CG showed improvements in global cognition, but these benefits were not maintained over time

CG: control group; MMSE: Mini-Mental State Examination; HADS: Hospital Anxiety and Depression Scale; WMS: Wechsler Memory Scale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; TMT: Trail-Making Tests; LVF: Letter Verbal Fluency; CVF: Category Verbal Fluency; BNT: Boston Naming Test; MCI: mild cognitive impairment ; WAIS: Wechsler Adult Intelligence Scale; GDS: Geriatric Depression Scale; MoCA: Montreal Cognitive Assessment Test; RBMT: Rivermead Behavioral Memory Test; FAS: F-A-S Test; TEA: Test of Everyday Attention; NPI: Neuropsychiatric Inventory; BDI: Beck Depression Inventory; PSS: Perceived Stress Scale; BAI: Beck Anxiety Inventory.

performance in the instruments that assess memory[21,22,24,29,30]. More specifically, verbal memory seems to have been the one more commonly affected[21,22,29,30]. Even though Kropacova et al.[24] findings did not find statistical significance among IG and CG, the subtle improvement may be indicative of a positive effect of dance in this cognitive function.

Global cognition, measured by the MMSE and/or MoCA, was also frequently improved as a result of the intervention[21,25,27-29]. Even though it was less frequent, some of the studies also found improvements in the executive function of the participants[21]; in some cases, these benefits were more qualitative than statistically significant[23,24]. Other functions such as language, visuospatial abilities, processing speed, and learning were sporadically quoted by only a few studies and not consistently.

Among the 10 studies analyzed, 6 used instruments to assess mood, 2 used the *Beck Depression Inventory II* (BDI)[21,23], 2 other used the *Hospital Anxiety and Depression Scale* (HADS)[22,27], and 3 studies opted for the *Geriatric Depression Scale* (GDS)[21,28,30]. In addition, four studies had as exclusion criteria people with major depressive disorder.

It is worth mentioning that three studies presented significant results in terms of improvement in depressive symptoms, one of which used HADS[27]. Doi et al.[29] utilized GDS with instruments that assessed loneliness and negative mood (i.e., *Jong Gierveld Loneliness Scale and Visual Analogue Mood Scale*), obtaining positive results in all of these aspects. Lazarou et al.[21] not only used the GDS but also opted for BDI, achieving improvement in both tests.

On the analysis of the limitations found in the studies, it is possible to conclude that the three most common limitations were participant dropout during the study[22,25], the small sample size[22,27], and the lack of neutral CG[22,27]. In relation to the absence of a neutral CG, one of the studies pointed out as a limitation the inexistence of a CG that did not perform any type of activity. Furthermore, a study points to the participation bias that may occur due to the sample's predisposition to perform physical activities[30]. To avoid this bias, one possibility is to compare individuals with similar levels of physical activity[22]. Regarding participation bias, the number of dropouts was noticeable as pointed out in the limitations, and aiming to limit selection biases, one study chose to use the random allocation and blinding algorithm.

DISCUSSION

The present systematic review is the only one up to the point of writing this paper to present an analysis of the evidence obtained in dance interventions with older people with cognitive impairment, including diagnoses such as Alzheimer's disease, MCI, and Parkinson's disease[25-27]: Other reviews analyzed the impact of dance in healthy individuals, or otherwise with only one kind of impairment[16-21,31]. And so, this study aimed to discuss what are the impacts of dance therapy on older people with different kinds of cognitive impairment.

The interventions performed had a wide variation in the duration of the stimulation time, but the studies that proposed sessions over 6 weeks and those that performed stimulation with a maximum of 40 weeks found significant results of cognitive improvement. The widely varied styles of dance present in the studies can be considered a representation of the cultural expression of dance; along with music, it is widely accepted that dance has a universal nature and takes different formats depending on the environment and society. But even with all this diversity, they all produce similar outcomes by stimulating choreographed and rhythmic body movements accompanied by musical harmony, producing the integration of brain regions that are activated during spatially patterned bipedal and rhythmic movements[32].

Regarding cognition, most studies showed positive results. The effect of physical exercise on the cognition of older people seems to be well documented in the literature, with significant but modest results in those individuals with MCI. The evidence is a little more controversial when it comes to people with dementia[33]. When it comes specifically to the influence of dancing on the brain, previous reviews have pointed out that this type of intervention plays an important role in increasing hippocampal volume as well as gray matter in the prefrontal and parahippocampal gyrus; the integrity of the white matter also seems to benefit[34]. Concerning cognitive aspects, the literature points to improvements due to dance interventions in the cognitive state of participants with Alzheimer's disease[16]. However, as mentioned above, when it comes specifically to older people with dementia and cognitive impairment, simultaneously, so far there is no systematic review in which the evidence is conclusively covered.

Of all the studies, all IG, without exception, showed improvements in — or, at least, the preservation of — their cognitive abilities. Global cognition, measured by the MMSE and MoCA, seems to be the domain that most benefited from the dance intervention[21,25,27-29], along with verbal memory[21,22,24,29,30]. This is in agreement with the findings of Wu et al.[35], in which it is stated that the global cognition of individuals with MCI seems to be more susceptible to dance intervention than that of healthy older people. Santos et al.[36] also denoted

benefits associated with the memory of older people who participated in a Senior Dance program.

Improvements in executive function were also found through the analysis in our review; however, these changes were mostly discrete and not statistically significant in general[23,24], with the exception of one study[21] that achieved statistical significance of $p<0.05$. According to a review carried out by Wang et al.[37] about the influence of body-mind exercise on the cognition of people with cognitive impairment, the effect of the intervention on the executive function of the participants was also not significant. In this review, other domains such as language, attention, visuospatial abilities, learning, and processing speed were identified as benefiting from the intervention. However, these benefits were inconsistently achieved — many of the improvements were found only in one study — which is a result that cannot be considered robust enough to allow us to draw a causal relationship among dance intervention and improvement in cognition. Although the results were promising, future studies are needed to better assess these issues.

Therefore, dance intervention has shown to be a promising strategy for cognitive improvement in people with MCI and dementia with regard to memory (specially verbal memory) and global cognition.

The literature already recognizes some positive effect of dance on mood, specifically with regard to anxiety and depression, which suggests a potential in dance interventions as a possible and important therapeutic complement in the treatment of these pathologies[36]. The results found in this review indicate that, of six studies in which mood was assessed pre- and post-intervention, only three did not achieve positive results. Two of these three studies used major depressive disorder as an exclusion criteria[22,23], and the last one[28] found that the mood of participants allocated to the CG also improved, but depression scores did not reach a significant difference among the CG and IG. The three studies that found benefits did not exclude participants who had depressive symptoms. This suggests that people with depressive symptoms may show benefits from the dance intervention in mood performance as well. It is important to emphasize that the current evidence is not strong enough to establish a causal relationship and that future studies on the subject are still very much needed. In the meantime, based on the results obtained, it is possible to conclude that dance interventions can be useful as a therapeutic tool to improve the mood of people with cognitive impairment and depressive symptoms.

Interestingly, the type of intervention chosen — that is, dance style and/or musical rhythms — did not significantly affect depressive symptoms after the end of the intervention programs. All studies that obtained improvement in depressive symptoms did not associate it with the type of music chosen, which seems to suggest that the dance style has a low influence on the results related to mood performance. Especially in comparison with other variables such as motivation, participation, and adequate instructions, among others, which in turn were associated with improvement in depressive symptoms. It is necessary to reinforce that these data are still limited to affirm or deny a causal relationship between these variables.

Studies have limitations that are regularly found when it comes to research involving older participants, due to the peculiarities of working with this population. The limitation most frequently cited by the authors was the struggles in adherence to the program, which, in result, had a direct impact on the sample size[22,25,27]. It is also important to note that future research is needed to assess possible differences in the effectiveness of the intervention arising from the duration of the dance program, assess whether these improvements withstand the passage of time, and determine whether there is any correlation among the duration of the intervention and the strength of the results when it comes to long-term testing. It is also important to mention the need for further investigation into whether dance interventions are able to prevent or delay cognitive impairment and distinguish the impact of dance according to different kinds of impairment.

This present review also had its fair share of limitations; in the first place, the authors could not have access to the study conducted by Dominguez et al.[17], even though it met all the chosen inclusion criteria. Furthermore, even though the vast majority of studies written in English were performed in countries that had other native languages, the lack of access to papers in other languages also stands out as a limitation, since they could have contributed to expanding the comprehension of impacts of dance in relation to sociocultural influences. In addition, the methodology employed in this review to investigate the studies did not use statistical analysis of the results, nor did it use qualitative analysis protocols, which can also be perceived as a limitation.

Thus, it is still necessary that future studies elucidate some gaps present in the current knowledge on the subject, such as the level of impact attributed to the dance intervention regarding:

1. The cognitive profile of the sample,
2. The chosen rhythm,
3. The professional training of the person responsible for carrying out the intervention, and
4. The degree of cognitive and motor performance required by the choreography.

Furthermore, there are gaps in the literature regarding theoretical-conceptual models of sensory, cognitive, and motor stimulation that take into account differences in cognitive status and functional performance. Future studies should also be dedicated to the creation of dance intervention protocols for the older people, aimed at specific cognitive and motor profiles; finally, the methods of application and the activities performed should also be better explained in future publications.

The recent growth of the older population is accompanied by the expansion of the occurrence of pathological states characterized by cognitive impairment, such as MCI and dementia. Consequently, the search for effective treatments to manage and delay the progress of those syndromes is still very present. Considering the data obtained in the present review, it is possible to claim that the use of dance therapy is a viable alternative as a nonpharmacological treatment for people with cognitive impairment of any kind. Since dance programs are a noninvasive and low-cost strategy, they have great applicability to the population. Through consideration of electronic literature, evidence suggests that programs of dance intervention offer relevant benefits in certain cognitive domains, such as global cognition, memory, and executive function. Other cognitive functions, such as attention and language, still need to be better investigated in future experiments in order to verify the effectiveness of this kind of intervention.

Regarding the mood of the participants, three of the six studies showed effective benefits in the depressive symptomatology of aged people with cognitive impairment, which suggests the potential effectiveness of dance as a therapeutic option in this aspect as well. Therefore, considering the data obtained, it is possible to claim that dance intervention can be a strong ally in the treatment of symptoms arising from cognitive impairment in older people.

As previously mentioned, dance therapy is a relatively low-cost intervention; the only significant expenses would be the monetary resources needed to hire the assistance and expertise of a dance professional who would be able to choreograph the program and coordinate the sessions or, at least, prepare and educate the professionals who apply these sessions. Since this type of intervention clearly does not lose any of its benefits when applied in groups, its practical nature and wide applicability are some of its strongest aspects.

Given the above, the implementation of this type of intervention in primary health care is possible and probably quite feasible. The benefits of physical exercise are well known to most, if not all, and the older population is constantly encouraged to maintain a healthy lifestyle and exercise; it is not a stretch to suggest that health professionals could also encourage these people to participate in dance programs when possible, especially if they are available in their own community. Likewise, the creation and organization of those programs should also be achievable in the context of hospitals, health centers, and nursing homes.

Currently, there is no standardized protocol for a cognitive intervention focused on dance therapy. In this sense, it is clear that there is a gap in knowledge and accessibility of the general public regarding a scientifically reliable dance program for older people with cognitive impairment. Future research in this field can, and should, focus on the creation and organization of dance protocols based on the methodology of studies that have managed to gather significant and relevant results, in order to mitigate this situation.

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45 Years of the Mini-Mental State Examination (MMSE):
a perspective from ibero-america

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ABSTRACT. The Mini-Mental State Examination (MMSE) was created by Marshal Folstein et al. in 1975 as an instrument for brief (5–10 min) assessment of mental status in hospitalized patients. It is considered the most widely used test for standardized cognitive assessment in the clinical setting, especially with the elderly population. It has countless translations in different languages, and according to the different international (PubMed) and regional (SciELO, Redalyc, and Dialnet) scientific databases, it has been widely used by the scientific community. This article describes the historical evolution of the MMSE, highlights its evaluative properties, and provides bibliometric data on its impact on scientific publications, with a special focus on Ibero-America.

Keywords: Mental Status and Dementia Tests; History; Neuropsychology; Cognition; Latin America.

45 AÑOS DEL MINI-MENTAL STATE EXAMINATION (MMSE): UNA PERSPECTIVA HISTÓRICA DESDE IBEROAMÉRICA

RESUMEN. El Mini-Mental State Examination (MMSE) fue creado por Marshal Folstein et al. en 1975 como un instrumento para la evaluación breve (5-10 minutos) del estado mental de pacientes hospitalizados. Se lo considera la prueba más utilizada para la evaluación cognitiva estandarizada en el ámbito clínico, especialmente con la población adulta mayor. Tiene innumerables traducciones a diferentes idiomas y de acuerdo con las diferentes bases de datos científicas internacionales (PudMed) y regionales (Scielo, Redalyc y Dialnet) se puede constatar que ha sido ampliamente utilizada por la comunidad científica. En este trabajo se describe la evolución histórica del MMSE, se destacan sus propiedades evaluativas y se indican datos bibliométricos acerca de su impacto en las publicaciones científicas, con especial énfasis en IberoAmérica.

Palabras Clave: Pruebas de Estado Mental y Demencia; Historia; Neuropsicología; Cognición; América Latina.

INTRODUCTION

It has just been 45 years since the publication of the Mini-Mental State Examination (MMSE): a brief assessment of cognitive performance[1]. The first construction of systematic, scientifically rigorous, psychological, and/or neuropsychological assessment instruments took place during the 20th century, even though there has always existed throughout human thought a need

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for the identification and description of psychological functions, such as character, temperament, personality, and intelligence[2].

In this article, we give a brief history of the MMSE, detailing its advantages and disadvantages, and how it has impacted the neuroscientific community internationally, with a special emphasis on Ibero-America. Regional and international data are presented. The idea is to present a historical overview of the test, but not an in-depth review of all of its aspects, since there are several systematic reviews that could be consulted for this purpose — several of which are mentioned in this article.

Function of the MMSE

This test was designed for brief application due to the excessive length of the existing tests in the mid-1970s[3]. It focused on strictly cognitive issues, leaving out questions related to psychiatric disorders or behavior. Despite its minor modifications over time, the test still consists of two parts. The first part evaluates questions related to orientation, memory, and attention, and the second part assesses verbal and written ability (requiring pencil and paper).

It is a test that has become one of the most widely used internationally for the diagnosis and clinical prognosis of cognitive impairment, mainly in elderly patients. An adaptation of the test given by telephone has even been created[4]. Recently, its performance as a tele-neuropsychological test was evaluated and indicated that there are no substantial differences when applied traditionally or remotely[5].

Throughout its history, a series of advantages and disadvantages have been discovered. Its international acceptance and application, easy administration, short duration, application to large samples, and free access are among some of its advantages. Among the disadvantages are the multiplicity of versions, lack of exploration of all cognitive domains, lack of copyright for several years, and lack of sensitivity to cultural variations and the school level of the participants[6-10].

The creators of the MMSE have recognized the importance of these criticisms and have attempted to improve the original version through increased precision and an indication of the need to comply with copyright; therefore, it is no longer available through public access and thus there is greater control over new translations and adaptations[11].

The international dissemination of the MMSE

Folstein's work has been reported to be among the 50 most cited articles in the Web of Science database during the 20th century, receiving 15,000 citations as of January 2004[3] and 19,721 citations up to February 2007[12]. A more recent study found 29,057 citations up to December 31, 2012[13]. It is also a test that has more than 70 translations into different languages[6]. As of August 18, 2021, in the international database PubMed, 20,032 related documents were retrieved for the keyword "MMSE." Notably, 262 documents were retrieved with this keyword in the regional SciELO database. Table 1 shows the 10 journals with the highest number of mentions of MMSE.

Two Brazilian journals have the highest concentration of these publications (109) according to the SciELO database, which has a predominance of Brazilian journals. However, a search of the Dialnet database, whose coverage is more Ibero-American, retrieved 298 articles, 109 theses, 3 book chapters, and 1 book related to the MMSE. Meanwhile, a search of the Redalyc database, with Latin American coverage, resulted in 376 articles: 221 in Spanish, 86 in English, and 69 in Portuguese. The disciplines referencing MMSE the most, according to Redalyc, are psychology with 146 papers, medicine with 138 papers, and health with 50 papers.

Different review papers on the MMSE have highlighted its wide use in cognitive assessment worldwide[3,9,14]. As noted, there have been several translations and adaptations of the instrument to various national contexts, and in several cases, different versions can be found, some validated and others not validated, as is the case with the Spanish-language versions for Latin America and Spain. This situation has made it difficult to compare the results of this instrument[5]. Comparisons can

Table 1. Journals containing articles on the MMSE.

Nº	Name	Quantity
1	Dementia & Neuropsychologia	67
2	Arquivos de Neuro-Psiquiatria	42
3	Revista Brasileira de Geriatria e Gerontologia	12
4	Ciência & Saúde Coletiva	10
5	Brazilian Journal of Physical Therapy	8
6	Brazilian Journal of Psychiatry	8
7	Cadernos de Saúde Pública	8
8	Jornal Brasileiro de Psiquiatria	8
9	Acta Paulista de Enfermagem	5
10	Revista Médica de Chile	5

Source: SciELO (www.scielo.br), consultation August 18, 2021.

also be difficult due to cultural differences, for example, between applications in Spanish-speaking Latin America and Spanish-speaking communities in the United States[15,16].

The first MMSE was created in Spain in the 1970s; since then, multiple validation efforts have been made[17]. However, despite Spanish being a common language to several countries, it is necessary to create regional versions, for example, in a country like Argentina, where there are normative references for different regions[15,18-21].

In the Portuguese-language setting, and particularly in Brazil, the wide use and the existence of different versions of the MMSE have also been documented[22-25], with 11 versions created for the study of elderly people, according to a review of September 2013[26]. However, according to this review, the most widely used version in Brazil was published by Bertolucci et al.[27], in the *Arquivos de Neuro-Psiquiatria*, in 1994. Subsequently, recommendations were made for adaptation of the measure to hospitals, private practice, and community studies[23]. In Portugal, the first known translation and adaptation of the MMSE were also in 1994[28], and since then, several adaptations have been created for various populations[29,30].

This multiplicity of versions that have been generated over time at the international level has been criticized by the authors who originated the test, and they themselves have tried to rectify this problem by providing a guidance manual and a list of authorized versions and translations[31]. The proliferation of versions reflects not only the internationalization of the MMSE but also the need for a more precise instrument in the cognitive domain which is more in line with sociocultural variations.

The different versions that were established over time (e.g., 3MS, 3MS-R, SMMSE, MMSE-12, MMSE-20, and MMSE-37)[32-35], many of them motivated by improving the assessment of cognitive abilities and covering aspects not covered in the initial version, did not achieve the popularity of the original test. This suggests at least two issues:

1. The new versions probably did not achieve qualitatively different contributions and
2. There is a strong weight of tradition inherited from the original version.

The MMSE has also served as a model and an inspiration for the development of other tests more specific to the assessment of cognitive abilities. Some have been presented as complementary and others are considered as alternatives, for example the following: Montreal Cognitive Assessment (MoCA), Addenbrooke;s Cognitive Examination (ACE), and Mini-Cog. In general, the MMSE is often used comparatively to assess the metric properties and diagnostic value of these new tests. In fact, several comparative studies have analyzed the advantages and disadvantages of each of the different cognitive tests and suggested the best test according to the cognitive function under assessment[36-38]. Overall, however, beyond the discrepancy in results, the MMSE remains a widely recommended and utilized instrument, although the MoCA test has become a substantial competitor to the MMSE, given its increasing use in research undertaken in Latin America[39,40].

The MMSE has become a normative test at the international level, accepted by the neuroscientific community, and recommended by the main clinical practice guidelines on the assessment of cognitive impairment, particularly in older adults. Although it is widely used to test for Alzheimer's or other types of dementia, it should be noted that it was not designed for that purpose. Although somewhat obvious, it should also be noted that the MMSE should never be viewed as a single assessment test, but rather as a tool in the overall clinical evaluation.

Despite certain limitations that have been noted regarding the multiplicity of versions and the comparability of results for different samples, the MMSE's efficacy as a brief test remains valid for clinical practice. In addition, its application has been extended to population studies, since it can be rapidly administered and can be administered by non-specialized personnel.

One of the most notable aspects of the historical evolution of the MMSE lies not only in its frequent and widespread use as a cognitive assessment tool worldwide (including extensively in Latin American countries) but also in the fact that it has inspired the creation of new cognitive tests, many of which have been developed as complementary or alternative tests to the MMSE.

Authors' contributions. MG: conceptualization, formal analysis, supervision, writing – review & editing. MLM: supervision, writing, review & editing. MC: conceptualization, methodology, writing – original draft. PM: conceptualization, investigation, writing original draft. JM: investigation, resources. MC: investigation, methodology. AR: conceptualization, investigation, writing original draft, writing – review & editing. TCR: conceptualization, investigation, writing, review & editing. WALG: conceptualization, investigation, writing – review & editing.

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Construction of face databases for tasks to recognize facial expressions of basic emotions: a systematic review

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ABSTRACT. Recognizing the other's emotions is an important skill for the social context that can be modulated by variables such as gender, age, and race. A number of studies seek to elaborate specific face databases to assess the recognition of basic emotions in different contexts. **Objectives:** This systematic review sought to gather these studies, describing and comparing the methodologies used in their elaboration. **Methods:** The databases used to select the articles were the following: *PubMed, Web of Science, PsycInfo,* and *Scopus*. The following word crossing was used: *"Facial expression database* OR *Stimulus set* AND *development* OR *Validation."* **Results:** A total of 36 articles showed that most of the studies used actors to express the emotions that were elicited from specific situations to generate the most spontaneous emotion possible. The databases were mainly composed of colorful and static stimuli. In addition, most of the studies sought to establish and describe patterns to record the stimuli, such as color of the garments used and background. The psychometric properties of the databases are also described. **Conclusions:** The data presented in this review point to the methodological heterogeneity among the studies. Nevertheless, we describe their patterns, contributing to the planning of new research studies that seek to create databases for new contexts.

Keywords: Facial Expression; Validation Study; Emotions; Facial Recognition; Psychometrics.

CONSTRUÇÃO DE BANCOS DE FACES PARA TAREFAS DE RECONHECIMENTO DE EXPRESSÕES FACIAIS DE EMOÇÕES BÁSICAS: UMA REVISÃO SISTEMÁTICA

RESUMO. Reconhecer as emoções do outro é uma habilidade importante para o contexto social, que pode ser modulada por variáveis como sexo, idade e raça. Vários estudos buscam elaborar bancos de faces específicos para avaliar o reconhecimento de emoções básicas em diferentes contextos. **Objetivos:** Esta revisão sistemática buscou reunir esses estudos, descrevendo e comparando as metodologias utilizadas em sua elaboração. **Métodos:** As bases de dados utilizadas para a seleção dos artigos foram: PubMed, Web of Science, PsycInfo e Scopus. Foi utilizado o seguinte cruzamento de palavras: *"facial expression database* OR *stimulus set* AND *development* OR *validation"*. **Resultados:** O total de 36 artigos mostrou que a maioria dos estudos utilizou atores para expressar as emoções, que foram suscitadas de situações específicas para serem o mais espontâneas possível. Os bancos de faces foram compostos principalmente de estímulos coloridos e estáticos. Além disso, a maioria dos estudos buscou estabelecer e descrever padrões para registrar os estímulos, como a cor das roupas utilizadas e o fundo. As propriedades psicométricas dos bancos de faces também são descritas. **Conclusões:** Os dados apresentados nesta revisão apontam para a heterogeneidade metodológica entre os estudos. Apesar disso, descrevemos seus padrões, contribuindo para o planejamento de novas pesquisas que buscam criar bancos de faces específicos para novos contextos.

Palavras-chave: Expressão Facial; Estudo de Validação; Emoções; Reconhecimento Facial; Psicometria.

This study was conducted by the Study and Research Group on Mental Health, Cognition and Aging – ProViVe, Universidade Federal de São Carlos, São Carlos, SP, Brazil.

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INTRODUCTION

Emotions play an important role in society life, as they enable interaction among people. According to the evolutionary theories, all emotions derive from a set of basic emotions common to both humans and animals and which are genetically determined[1,2]. One of the ways for us to recognize the other's emotion is through facial expressions, since the face is one of the most expressive visual stimuli in society life[3]. The ability to recognize emotions through the face can already be perceived in newborns, a fact that justifies the innate nature of this skill[4].

From a study using a systematized task, Ekman and Friesen[5] postulated six basic emotions, which are related to evolutionary adaptations and can be universally recognized, namely, happiness, sadness, fear, disgust, surprise, and anger. In addition, they identified that the cultural aspects did not modulate the way in which these emotions were expressed[5]. Thus, the evidence indicated that all human beings had the same movements of the facial muscles under certain circumstances[6,7], turning the ability to express emotions into a behavioral phenotype.

However, a number of studies began to notice that, within this phenotype common to human beings, some variables could modulate the way to recognize these facial expressions, such as cultural context[8], age[9], gender[10], and race[11]. Taking these variables into account, several studies started to construct and validate specific face databases to assess the ability to recognize emotions through facial expressions[12-16] since, when selecting a set of facial expression stimuli, it is necessary to consider characteristics of the model that are expressing the emotions, as well as who will recognize them.

Therefore, the existing facial expression databases present great diversity with regard to the physical characteristics of those who express the emotions, the way in which emotions are induced during the construction of the image database, and how they are presented in the validation stage[12-14]. Despite the methodological differences across the studies, they follow important standards for the construction and validation of the series of stimuli. Comparing the methodology used by the studies in the creation of these databases, regardless of the characteristics of who expresses the stimuli, can contribute to the planning of new research studies that seek to create face databases for new contexts. Thus, the objective of this systematic review was to gather studies that constructed face databases to assess the recognition of facial expressions of basic emotions, describing and comparing the methodologies used in the stimuli construction phase.

METHODS

Search strategies and eligibility criteria

The search strategy for this systematic review was created and implemented prior to study selection, in accordance with the checklist presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17]. The databases used to select the articles were the following: *PubMed, Web of Science, PsycInfo,* and *Scopus*. The following word crossing was used: *"Facial expression database* OR *Stimulus set* AND *development* OR *Validation."* The searches were conducted from June to December 8, 2021.

The lists of references of the selected articles were also researched for additional sources. The inclusion criteria were surveys that constructed face databases to assess the recognition of basic emotions, published in original articles or disclosed on official websites, without language or time restrictions. Letters to the editor, books and book chapters, reviews, comments, notes, errata, theses, dissertations, and bibliographic/systematic reviews were excluded. In addition, it is worth noting that only the construction stage of the databases was included in this review.

Therefore, additional studies conducted after construction, such as normative data, were not contemplated in the analysis.

Study selection

All the articles found in the databases were saved in the *Rayyan* electronic reference manager. After removing duplicate articles and according to the inclusion criteria of this study, all articles were evaluated by two independent researchers (DF and BF) through their titles and abstracts. In this stage, the researchers classified the articles as "yes," "no," or "perhaps." Subsequently, the researchers reached consensus as to whether the articles recorded as "perhaps" should be included in the review.

After the inclusion of these studies, three researchers (DM, BF, and MB) read the articles in full and extracted information such as year of publication and study locus, name of the database built, characteristics of the participants who expressed the emotions (number of participants, place of recruitment, gender, age and race), basic emotions expressed, and final total of stimuli included in the database and their specific characteristics (Table 1)[12-16,25-63]. Subsequently, the methodological characteristics of the databases were collected, such as the method used to elicit the emotions, patterns in the capture of stimuli, criteria used in the validation stage, sample characteristics in the validation stage, and psychometric qualities assessed (Table 2)[12-16,25-63].

Table 1. General characteristics of face databases.

Authors and year of publication	Study location	Name of the built database	Theoretical reference	Characteristics of participants who expressed emotions	Basic emotions expressed	Total of stimuli	Specific characteristics of stimuli
Benda and Scherf. (2020)[25]	The United States	Complex Emotion Expression Database (CEED)	Recognition of complex emotions in young people (Empirical)	8 professional actors - Age: 20.9 years; SD=3.1 - Sex: M=4; F=4 - Race: Caucasians (n=4) and Black (n=4)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise	243 images	- Black and white - Static
Chung et al. (2019)[26]	South Korea	Yonsei Face Database (YFace DB)	Basic emotions (Ekman and Friesen, 1975)[56]	74 local community and university volunteers - Age: 19-40 years - Sex: M=37; F=37 - Race: Koreans	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	1,480 stimuli	- Colorful - Static and dynamic *Open and closed mouth *Varied intensities
Conley et al. (2018)[16]	The United States	The racially diverse affective expression (RADIATE)	Racial heterogeneity in emotion recognition (Empirical)	109 community adults - Age: 18-30 years - Sex: M=53; F=56 - Race: Asian (n=22), Black/African-Americans (n=38), Caucasians (n=28), Hispanic (n=20) and others (n=1)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	1,721 images	- Colorful and black and white - Static *Open and closed mouth
Dalrymple et al. (2013)[27]	The United States	The Dartmouth Database of Children's Faces	Recognition of emotions in children (Empirical)	80 community children - Age: 9.84 years; SD=2.33 - Sex: M=40; F=40 - Race: Caucasians	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	964 images	- Colorful - Static *Happiness with closed mouth and happiness showing teeth
Donadon et al. (2019)[28]	Brazil	Baby Faces	Ekman's Neurocultural Theory (1972)[57]	20 babies - Age: 9 months; SD=1.5 - Sex: M=10; F=10 - Race: Caucasians (n=66%), Black (n=17%), and Japanese (n=17%)	1) Happiness 2) Sadness 3) Fear 4) Anger 5) Surprise 6) Neutral	57 images	- Colorful - Static
Ebner et al. (2010)[13]	Germany	Faces--a life-span Database of Facial Expressions	Age differences in emotion recognition (Ruffman et al., 2008)[58]	179 actors and extras recruited from a modeling agency - 61 young (24.3 years; SD=3.5) - 60 middle-age (49.0 years; SD=3.9) - 58 elderly (73.2 years; SD=2.8) - Sex: M=86; F=85 - Race: Caucasians (n=179)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Neutral	2,052 images	- Colorful - Static
Egger et al. (2011)[29]	The United States	NIMH Child Emotional Faces Picture Set (NIMH-ChEFS)	Recognition of emotions in children (Empirical)	59 child actors - Age: 13.6 years - Sex: M=20; F=39 - Race: ND	1) Happiness 2) Sadness 3) Fear 4) Anger 5) Neutral	482 images	- Colorful - Static *Two directions of gazing: direct and avoided

Continue...

Table 1. Continuation.

Authors and year of publication	Study location	Name of the built database	Theoretical reference	Characteristics of participants who expressed emotions	Basic emotions expressed	Total of stimuli	Specific characteristics of stimuli
Ekman and Friesen. (1976)[30]	The United States	Pictures of Facial Affect (POFA)	Pan-cultural elements in facial expressions of emotions (Ekman et al., 1969)[5]	10 individuals - Age: ND - Sex: M=4; F=6 - Race: Caucasians and African-American	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	110 images	- Black and white - Static
Fujimura and Umemura. (2018)[31]	Japan	A facial expression database based on the dimensional and categorical model of emotions	The influence of angles on emotion recognition (Borod et al., 1998)[59]	8 professional actors - Age: 34.25 years; SD=5.47 - Sex: M=4; F=4 - Race: Japanese	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	920 stimuli	- Colorful - Static and dynamic *Open and closed mouth *Varied angles
Franz et al. (2021)[32]	Germany	Picture-Set of Young Children's Affective Facial Expressions (PSYCAFE)	Recognition of emotions in children (Empirical)	35 children - Age: 4-6 years - Sex: M=14; F=21 - Race: ND	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	104 images	- Colorful - Static *Varied intensities
Garrido et al. (2017)[33]	Portugal	Stills and Videos of facial Expressions (SAVE database)	Recognition of emotions in dynamic stimuli (Empirical)	20 students - Age: 21.75 years; SD=1.97 - Sex: M=12; F=8 - Race: ND	1) Happiness 2) Neutral	120 stimuli	- Colorful - Static and dynamic
Giuliani et al. (2017)[15]	The United States	The DuckEES child and adolescent dynamic facial expressions stimulus set	Recognition of emotions in dynamic stimuli (Empirical)	37 children and teenage actors - Age: 13.24 years; SD=2.09 - Sex: M=15; F=22 - Race: Caucasians (n=89%)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Neutral	120 videos	- Colorful - Dynamic
Happy et al. (2015)[34]	India	The Indian Spontaneous Expression Database for Emotion Recognition (ISED)	Basic emotions (Ekman and Friesen, 1975)[56]	50 individuals - Age: 18-22 years - Sex: M=29; F=21 - Race: Indians	1) Happiness 2) Sadness 3) Disgust 4) Surprise	428 videos	- Colorful - Dynamic *Varied intensities
Kaulard et al. (2012)[35]	Germany	The MPI Facial Expression Database	Language and emotions (Empirical)	19 native Germans without professional acting experience - Age: 20-30 years - Sex: M=9; F=10 - Race: Caucasians	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger	18800 videos	- Colorful - Dynamic *Varied angles

Continue...

Table 1. Continuation.

Authors and year of publication	Study location	Name of the built database	Theoretical reference	Characteristics of participants who expressed emotions	Basic emotions expressed	Total of stimuli	Specific characteristics of stimuli
Keutmann et al. (2015)[36]	The United States	Visual and vocal emotional expressions of adult and child actors	Item Response Theory in face database construction (Empirical)	150 actors (Adults: n=139 and kids: n=11) - Age: 36.1 years; SD=15.6 - Sex: M=73; F=77 - Race: Caucasians (n=98), African-American (n=35), Hawaiian (n=1), mixed (n=1), and others (n=1)	1) Happiness 2) Sadness 3) Fear 4) Anger 5) Neutral	152 stimuli	- Colorful - Static and dynamic *Varied intensities
Kim et al. (2017)[37]	South Korea	Korea University Facial Expression Collection – Second Edition (KUFEC-II)	The role of culture in recognizing emotions (Empirical)	57 actors - Age: ND - Sex: M=32; F=36 - Race: Koreans	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	399 images	- Colorful - Static
Langner et al. (2010)[38]	Netherlands	Radboud Faces Database	The influence of angles and direction of gaze on emotion recognition (Empirical)	49 young and children Young: 39 Children: 10 - Age: ND - Sex: M=24; M=25 - Race: Caucasians (n=49)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	5,880 images	- Colorful - Static *Three directions of gaze: front, right, and left *Varied face angles
LoBue and Thrasher. (2015)[14]	The United States	The Child Affective Facial Expression (CAFE)	Recognition of emotions in children's faces of different races (Empirical)	154 children - Age: 5.3 years - Sex: M=64; F=90 - Race: African-Americans (n=27), Caucasians (n=77), Asians (n=16), Latinos (n=23), and South Asia (n=11)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	1,192 images	- Colorful - Static *Open and closed mouth
Lundqvist et al. (1998)[39]	Sweden	Karolinska Directed Emotional Faces (KDEF) Database	-	70 actors - Age: 25 years (20-30 years) - Sex: M=35; F=35 - Race: ND	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	490 images	- Colorful - Static *Varied face angles
Ma et al. (2020)[40]	China	Han, Hui, and Tibetan Chinese facial expression database	The role of culture in recognizing emotions (Empirical)	630 volunteers - Age: Han (22 years; SD=2.7); Hui (22.8 years; SD=2.4); and Tibet (21.4 years; SD=2.5) - Sex: M=315; F=315 - Race: Chinese from different regions	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	930 images	- Colorful - Static
Ma et al. (2015)[41]	The United States	Chicago Face Database (CFD)	Limitations of existing face databases (Empirical)	158 individuals from the University of Chicago Laboratory and amateur actors - Age: 13.6 years - Sex: M=73; F=85 - Race: Black (n=85) and Caucasians (n=73)	1) Happiness 2) Fear 3) Neutral	158 images	- Colorful - Static *Two directions of gaze: direct and averted

Continue...

Table 1. Continuation.

Authors and year of publication	Study location	Name of the built database	Theoretical reference	Characteristics of participants who expressed emotions	Basic emotions expressed	Total of stimuli	Specific characteristics of stimuli
Maack et al. (2017)[42]	Norway	The Tromso Infant Faces Database (TIF)	Influence of child stimuli on the adult attention system (Brosch et al., 2007; Parsons et al., 2011; Borgi et al., 2014)[60-62]	18 babies - Age: 4-12 months - Sex: M=8; F=10 - Race: Caucasians	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	119 images	- Colorful - Static
Meuwissen et al. (2017)[43]	The United States	Developmental Emotional Faces Stimulus Set (DEFSS)	Limitations of existing face databases (Empirical)	116 volunteers 42 children 44 teenagers 30 adults - Age: ND - Sex: M=43; F=73 - Race: White (n=102), non-White (n=15)	1) Happiness 2) Sadness 3) Fear 4) Anger 5) Neutral	404 images	- Colorful - Static
Minear and Park. (2004)[44]	The United States	A lifespan database of adult facial stimuli	Influence of age on emotion recognition (Empirical)	576 community volunteers - Age: 18-93 years - Sex: M=219; F=357 - Race: Caucasians (n=435), African-American (n=89), and others (n=52)	1) Happiness 2) Neutral	1,142 images	- Colorful - Static
Negrão et al. (2021)[45]	Brazil	The Child Emotion Facial Expression Set	Recognition of emotions in children (Empirical)	132 children - Age: 4-6 years - Sex: M=42%; F=58% - Race: Caucasian (n=71%), African (n=24%), Asian (5%)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	971 stimuli	- Colorful - Static and dynamic
Novello et al. (2018)[46]	Brazil	Youth Emotion Picture Set	Recognition of Facial Emotions in Teens (Empirical)	31 randomly selected volunteers - Age: 17.4 years; SD=2.7 - Sex: M=14; F=17 - Race: Caucasians (n=27), Blacks (n=1), and mixed (n=3)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	42 images	- Black and white - Static
O'Reilly et al. (2016)[47]	The United Kingdom	The EU-Emotion Stimulus Set	Limitations of existing face databases (Empirical)	19 actors - Age: 10-70 years - Sex: M=9; F=10 - Race: Caucasians (n=13), Afro-Caribbean/British-Asian (n=2), Blacks (n=2), mixed white/Asian (n=1), Mediterranean/Asian-British (n=1)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	249 videos	- Colorful - Dynamic
Olszanowski et al. (2015)[48]	Poland	Warsaw set of emotional facial expression. pictures (WSEFEP)	Limitations of existing face databases (Empirical)	30 professional actors - Age: 20-30 years - Sex: M=14; F=16 - Race: Polish	1) Happiness 2) Sadness 3) Fear 4) Anger 5) Surprise 6) Neutral	210 images	- Colorful - Static

Continue...

Table 1. Continuation.

Authors and year of publication	Study location	Name of the built database	Theoretical reference	Characteristics of participants who expressed emotions	Basic emotions expressed	Total of stimuli	Specific characteristics of stimuli
Passareli et al. (2018)[49]	Italy	Facial Expression Recognition Test (FERT)	Basic emotions (Ekman e Friesen, 1975)[56] and Item Response Theory (Reise and Revicki, 2014)[63]	6 professional actors - Age: ND - Sex: M=3; F=3 - Race: ND	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	42 images	- Colorful - Static
Romani-Sponchiado et al. (2015)[50]	Brazil	Child Emotions Picture Set	Recognition of facial emotions in children (Empirical)	18 children - Age: 6-7 years (6.93 years; SD=0.3); 8-9 years (9.12 years; SD=0.57), and 10-11 years (10.72 years; SD=0.61) - Sex: M=9; F=9 - Race: Caucasians (n=14), African-American (n=3), and Indigenous (n=1)	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	225 images	- Black and white - Static *Varied intensities
Samuelsson et al. (2012)[51]	Sweden	Umeå University Database of Facial Expressions	Limitations of existing face databases (Empirical)	60 community individuals - Age: 17-67 years (30.19 years; SD=10.66) - Sex: M=30; F=30 - Race: Swedes, Central Europe, Arabs, and Asians	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	424 images	- Colorful - Static
Sharma and Bhushan. (2019)[52]	India	Indian Affective Picture	Basic emotions (Ekman and Friesen, 1975)[56] and limitations of existing face databases (Empirical)	4 professional actors - Age: 25.25 years; SD=3.77 - Sex: M=2; F=2 - Race: Indians	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	140 images	- Colorful - Static *Varied face angles
Tottenham et al. (2009)[12]	The United States	The NimStim set of facial expressions	Basic emotions (Ekman and Friesen, 1975)[56] and limitations of existing face databases (Empirical)	43 professional actors - Age: 21-30 years - Sex: M=25; F=18 - Race: Africans, Europeans, and Latin Americans	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	672 images	- Colorful - Static *Open and closed mouth
Tracy et al. (2009)[53]	Canada	Universidade da Califórnia, Davis, Set of Emotion Expressions (UCDS)	Basic emotions (Ekman and Friesen, 1975)[56] and limitations of existing face databases (Empirical)	28 community individuals - Age: 27.0 years - Sex: M=14; F=14 - Race: White and African	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise	73 images	- Colorful - Static

Continue...

Table 1. Continuation.

Authors and year of publication	Study location	Name of the built database	Theoretical reference	Characteristics of participants who expressed emotions	Basic emotions expressed	Total of stimuli	Specific characteristics of stimuli
Vaiman et al. (2017)[54]	Argentina	Expresiones de Emociones Faciales (FACS)	The role of culture in recognizing emotions (Empirical)	14 Argentines from the community - Age: 25.53 years; SD=8.72 - Sex: M=8; F=6 - Race: ND	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	60 images	- Colorful - Static
Yang et al. (2020)[55]	China	Tsinghua facial expression database	The role of culture in recognizing emotions (Empirical)	63 young and 47 elderly Chinese natives with an interest in acting Young - Age: 23.82 years; SD=4.18 - Sex: M=32; F=31 - Race: Chinese Elderly - Age: 64.40 years; SD=3.51 - Sex: M=21; F=26 - Race: Chinese	1) Happiness 2) Sadness 3) Fear 4) Disgust 5) Anger 6) Surprise 7) Neutral	880 images	- Colorful - Static

ND: not declared; M: male; F: female; SD: standard deviation. *Additional features of the face database.

Risk of bias

The studies selected in this review are for the construction of face databases. In this sense, the traditional risk of bias tools used in randomized and nonrandomized studies is not applicable. The task elaborated by the studies must offer valid and interpretable data for the assessment of facial recognition of basic emotions of individuals in certain contexts. Therefore, the quality of the studies included can be observed based on the analyses performed for the reliability and validity of the databases elaborated[18,19].

Data analysis

We analyzed the psychometric properties assessed by the studies in the stage for the validation of the stimuli (Table 2)[64,65]. This information is important to assess the quality of the database that was elaborated. Qualitatively, we followed the standards for educational and psychological testing of the American Educational Research Association[20] and the stages specified in Resolution 09-2018 of the Brazilian Federal Council of Psychology[21], which regulates the dimensions necessary for the assessment of psychological tests. Consequently, information based on the analysis of the database items and the measures for validity evidence were obtained (Table 2).

In addition, we sought to identify in Table 2 when the psychometric measure assessed by the studies presented satisfactory indexes. For accuracy, as a reference standard we used the consensus among most of the studies on the construction of face databases that include stimuli with recognition rates ≥70%. In some cases, the studies established other rates for recognition, which were indicated as symbols in the table.

Since accuracy is a fundamental indicator for stimuli selection and has been widely used as a quality parameter for construction studies, this variable is included in the table as an indicator of both precision and content-based validity evidence, since it is a precision measure that was used to validate the database content. For agreement among the evaluators, the studies generally use Cohen's or Fleiss' kappa indexes. Therefore, we used value ≥60% as a reference[22,23]. For internal consistency, we used Cronbach's alpha value >0.70 as a reference[24].

RESULTS

Selection and presentation of the studies

Figure 1 presents the search and selection process for the 36 articles included in this systematic review[12-17,25-63].

Table 2. Methodological characteristics used in the studies to create the databases.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Benda and Scherf. (2020)[25]	Complex Emotion Expression Database (CEED)	1) Presentation of an equivalent photograph expressing the emotion 2) Emotions elicited from specific situations	- Background: White - Clothes: ND - Distractors removed: ND	Accuracy ≥50%	796 volunteers recruited through MTurk - Age: 34. years; SD=11.6 - Gender: M=403; F=388 - Race: ND	- Analysis of the items: Accuracy* - Validity evidence: Content-based: Accuracy and error in each item
Chung et al. (2019)[26]	Yonsei Face Database (YFace DB)	1) Presentation of an equivalent photograph expressing the emotion 2) Instruction on muscle movement of the emotions based on the FACS 3) Emotions elicited from specific situations	- Background: White - Clothes: Black T-shirt - Distractors removed: Beards, glasses, makeup, and bangs	Accuracy, intensity, and naturalness	212 students from the Seoul University - Age: 18-28 years - Gender: M=97; F=115 - Race: ND	- Analysis of the items: Accuracy† - Precision: Accuracy - Validity evidence: Content-based: Accuracy Based on the relationship with other variables: ANOVA for difference in precision between genders of the stimuli and evaluators, t-test for difference in mean accuracy between genders and emotions, and post-hoc Bonferroni analysis for items with significant differences‡
Conley et al. (2018)[16]	The racially diverse affective expression (RADIATE)	Presentation of an equivalent photograph expressing the emotion	- Background: White - Clothes: White sheet - Distractors removed: Glasses, headband, hats	Accuracy and Cohen's kappa	662 participants recruited through MTurk - Age: 18-35 years (27.6 years; SD=3.8) - Gender: M=402; F=260 - Race: Asian (n=48), Black/African-American (n=70), Caucasian (n=470), Hispanic (n=63), and others (n=11)	- Precision: Reliability (test-retest)† - Validity evidence: Content-based: Accuracy†; Cohen's kappa† and variability in precision by race of the model
Dalrymple et al. (2013)[27]	The Dartmouth Database of Children's Faces	Emotions elicited from specific situations	- Background: Black - Clothes: Black dresses and black hats - Distractors removed: Glasses and jewelry	Images recognized with ≥70% accuracy	163 students and members of the Dartmouth College academic community - Age: 19.6 years; SD=4.15 - Gender: M=67; F=96 - Race: ND	- Precision: Accuracy† and Cohen's kappa among the evaluators† - Validity evidence: Content-based: Accuracy and Cohen's kappa among the evaluators Based on the relationship with other variables: ANOVA for difference in precision between gender of the stimuli and evaluators‡

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Donadon et al. (2019)[28]	Baby Faces	The parents were instructed and trained to provoke the intended emotions	ND	Rasch model to minimize floor and ceiling effects with values from 0.50 to 1.50 Rate of correct answers according to Kringelbach et al. 2008[64]	Validation 119 volunteers from the community - Age: 36 years; SD=12.8 - Gender: M=36.1%; F=63.9% - Race: Caucasian (n=69.7%), Black (n=26.1%), and Japanese (n=4.2%) Retest 31 volunteers from the community - Age: 38.06 years; SD=11.57 - Gender: M=35.5%; F=64.5% - Race: Caucasian (n=74%), Black (n=19.5%), and Japanese (n=6.5%)	- Analysis of the items: Adjustment and difficulty of the items by the Rasch model - Precision: Reliability (test-retest)† - Validity evidence: Content-based: Accuracy§ Based on the relationship with other variables: ANCOVA to assess the differences between groups considering the sociodemographic variables (gender, race, schooling level of the adults, and gender and race of the faces in the stimulus)‡
Ebner et al. (2010)[13]	Faces--a life-span Database of Facial Expressions	1) Emotion induction through photographs and videos 2) Emotions elicited from specific situations	- Background: Gray - Clothes: Gray T-shirt - Distractors removed: Jewelry, glasses, and makeup	Agreement among evaluators for (1) purity of the facial expression and (2) high intensity facial expression	154 students - Age: 20-81 years - Gender: M=78; F=76 - Race: Caucasian	- Precision: Accuracy† and consensus among the evaluators† - Validity evidence: Content-based: Accuracy and consensus among the evaluators Based on the relationship with other variables: ANOVA for face age × evaluator's age × emotion expressed‡
Egger et al. (2011)[29]	NIMH Child Emotional Faces Picture Set (NIMH-ChEFS)		- Background: Gray - Clothes: ND - Distractors removed: ND	The cutoff point for the image to be included was that ≥15 evaluators identified the intended emotion	20 professors and employees of the Duke University Medical Center - Age: 38.3 years - Gender: M=7; F=13 - Race: ND	- Analysis of the items: Accuracy† - Difficulty of the items: Intensity and representativeness scores - Precision: Agreement among the evaluators// - Validity evidence: Content-based: Accuracy and agreement among the evaluators
Ekman and Friesen. (1976)[30]	Pictures of Facial Affect (POFA)	Instruction on muscle movement of the emotions based on FACS	ND	ND	ND	ND

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Fujimura and Umemura (2018)[31]	A facial expression database based on the dimensional and categorical model of emotions	1) Emotions elicited from specific situations 2) Instruction on muscle movement of the emotions based on FACS	- Background: White - Clothes: White T-shirt - Distractors removed: Glasses and strong makeup	Agreement among the evaluators Mean of 69% agreement among the evaluators (SD=21%)	39 university students - Age: 21.33 years; SD=2.39 - Gender: M=19; F=20 - Race: Japanese natives	- Precision: Accuracy† - Validity evidence: Content-based: Accuracy and confusion matrix of agreement rates for images of dynamic and static expressions of each model
Franz et al. (2021)[32]	Picture-Set of Young Children's Affective Facial Expressions (PSYCAFE)	1) Guidance of emotions in theater workshops 2) Directed Facial Action Task used to guide the movement of anatomical landmarks	- Background: White - Clothes: ND (just face) - Distractors removed: ND (just face)	Step 1 Confirmatory hierarchical cluster analysis by Ward Step 2 Intensity, authenticity, and likeability. Accuracy (77-100%) and AFFDEX Software	Step 1 197 volunteers from the community - Age: 32.9 years; SD=16.1 - Gender: M=33%; F=67% - Race: ND Step 2 44 volunteers from the community - Age: 25.7 years; SD=5.9) - Gender: M=48%; F=52% - Race: ND	- Precision: Accuracy† - Validity evidence: Based on the relationship with other variables: Stimulus age × expressed emotion × accuracy
Garrido et al. (2017)[33]	Stills and Videos of facial Expressions (SAVE database)	Emotions elicited from specific situations	- Background: Gray - Clothes: White T-shirt - Distractors removed: Jewelry, glasses, and makeup	Stimuli with an assessment of 2.5 SD above or below the mean	120 university students - Age: 20.62 years; SD=3.39 - Gender: M=22.5%; F=77.5% - Race: Caucasian	- Precision: Accuracy† - Validity evidence: Content-based: Accuracy and interest dimensions (valence, excitement, clarity, intensity, appeal, similarity, and familiarity) Based on the relationship with other variables: Accuracy × gender of the model and the participant¶
Giuliani et al. (2017)[15]	The DuckEES child and adolescent dynamic facial expressions stimulus set	Emotions elicited from specific situations	- Background: White - Clothes: ND - Distractors removed: ND	Images recognized with ≥70% accuracy	36 volunteers from the Oregon University - Age: 19.5 years; SD=1.95 - Gender: M=14; F=22 - Race: ND	- Precision: Accuracy† - Validity evidence: Content-based: Accuracy and Fleiss' kappa†

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Happy et al. (2015)[34]	The Indian Spontaneous Expression Database for Emotion Recognition (ISED)	Emotion induction through videos	- Background: ND - Clothes: ND - Distractors removed: ND	Agreement among the evaluators (Fleiss' Kappa)	Four trained evaluators - Age: ND - Gender: M=2; F=2 - Race: ND	- Precision: Accuracy† - Validity evidence: Content-based: Accuracy and Fleiss' kappa†
Kaulard et al. (2012)[35]	The MPI Facial Expression Database	Emotions elicited from specific situations	- Background: Black - Clothes: Black cape and hats - Distractors removed: Makeup and beards	Consistency among the evaluators (Fleiss' Kappa)	20 German natives - Age: 19-33 years - Gender: M=10; F=10 - Race: ND	- Precision: Accuracy† - Validity evidence: Content-based: Accuracy and Fleiss' kappa†
Keutmann et al. (2015)[36]	Visual and vocal emotional expressions of adult and child actors	Emotions elicited from specific situations	- Background: Green - Clothes: ND - Distractors removed: ND	Accuracy	510 students, 226 from Drexel University and 284 from the University of Central Florida - Age: ND - Gender: ND - Race: ND	- Analysis of the items: Difficulty analysis and item discrimination by means of the classical test theory - Precision: Accuracy† - Validity evidence: Content-based: Accuracy
Kim et al. (2017)[37]	Korea University Facial Expression Collection – Second Edition (KUFEC-II)	Instruction on muscle movement of the emotions based on FACS	- Background: Gray - Clothes: Pattern - Distractors removed: Makeup, accessories, and dyed hair	Internal consistency Accuracy	75 evaluators - Age: 19-69 years (26.17 years, SD=5.69) - Gender: M=39; F=36 - Race: ND	- Precision: Accuracy† - Validity evidence: Content-based: Accuracy; agreement among the evaluators† and scores for purity, valence, and intensity Based on the relationship with other variables: ANOVA to test the effects of gender on recognition‡ and correlations between the participant's emotional state and task performance¶
Langner et al. (2010)[38]	Radboud Faces Database	Instruction on muscle movement of the emotions based on FACS	- Background: White - Clothes: Black T-shirt - Distractors removed: Glasses, earrings and makeup	Accuracy	276 students from Radboud University - Age: 21.2 years; SD=4.0 - Gender: M=38; F=238 - Race: ND	- Precision: Accuracy† - Validity evidence: Content-based: Accuracy and dimensions of interest (type of expression, intensity, clarity, genuineness, and valence) Based on the relationship with other variables: ANOVA comparing each of the precision variables with age, gender, expression, and gaze direction‡

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
LoBue and Thrasher. (2015)[14]	The Child Affective Facial Expression (CAFE)	Instruction on muscle movement of the emotions based on FACS was carried out during improvised games	- Background: White - Clothes: White sheet - Distractors removed: ND	Images recognized with ≥60% accuracy	100 undergraduate students from Rutgers University - Age: ND - Gender: M=50; F=50 - Race: African-American (n=17%), Asian (n=27%), White (n=30%), Latin (n=17%), and others (n=9%)	- Analysis of the items: Difficulty of the items: Rasch model - Precision: Test-retest reliability† and accuracy# - Validity evidence: Content-based: Accuracy
Lundqvist et al. (1998)[39]	Karolinska Directed Emotional Faces (KDEF) Database	The participants were free to express the emotion as they wished	Background: Neutral Clothes: Gray T-shirt Distractors removed: Beard, mustache, earrings, glasses, and makeup	ND	ND	ND
Ma et al. (2020)[40]	Han, Hui, and Tibetan Chinese facial expression database	1) Emotion induction through photographs and videos 2) Instruction on muscle movement of the emotions based on FACS	- Background: Black - Clothes: ND - Distractors removed: Jewelry	Images recognized with ≥60% accuracy	240 volunteers (80 from each study region) - Age: 23 years; SD=1.7 - Gender: M=120; F=120 - Race: Chinese	- Precision: Accuracy** and method of halves - Validity evidence: Content-based: Accuracy Based on internal consistency: Cronbach's alpha†
Ma et al. (2015)[41]	Chicago Face Database (CFD)	1) Emotions expressed from verbal instructions 2) Presentation of an equivalent photograph expressing the emotion	- Background: White - Clothes: Gray T-shirt - Distractors removed: ND	Two independent judges assessed how believable the expression was on a Likert scale from 1 to 9 (1=not at all believable; 9=very believable)	1,087 evaluators (convenience sample) - Age: 26.7 years; SD=10.5 - Gender: M=308; F=552 - Race: White (n=516), Asian (n=117), Black (n=74), bi- or multi-race (n=72), Latin (n=57), others (n=18), and did not report (n=233)	- Precision: Accuracy - Validity evidence: Based on the internal structure: exploratory factor analysis (Varimax rotation) Content-based: Accuracy; agreement among the evaluators† and effects of race and gender of the stimuli (criteria for item construction)

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Maack et al. (2017)[42]	The Tromso Infant Faces Database (TIF)	The parents were instructed to elicit the intended emotions with games and specific stimuli	- Background: White - Clothes: White overalls and hat - Distractors removed: ND	The photographs with best agreement among the evaluators were selected Mean classification of clarity and intensity below 2.5 Validation: (a) expression portrayed, (b) clarity of expression, (c) intensity of the expression, and (d) valence of the expression	720 participants - Age: 18-70 years (32.8 years; SD=10.4) - Gender: M=21%; F=79% - Race: ND	- Precision: Accuracy†† - Validity evidence: Content-based: dimensions of interest (type of expression, clarity, intensity, and valence) Based on the relationship with other variables: ANOVA to compare performance × child-rearing stage × gender × mood¶
Meuwissen et al. (2017)[43]	Developmental Emotional Faces Stimulus Set (DEFSS)	1) Emotions elicited from specific situations 2) Presentation of an equivalent photograph expressing the emotion	- Background: Gray - Clothes: ND - Distractors removed: Jewelry	The images recognized by less of 55% of the evaluators were excluded	228 university students between undergraduate and graduate levels and children preappointed by the family via the Internet - Age: 8-30 years - Gender: M=150; F=254 Race: White (n=81%), non-White (n=17%)	- Precision: Accuracy‡‡ - Validity evidence: Content-based: correct answers by age group, intensity, and emotion
Minear and Park. (2004)[44]	A life span database of adult facial stimuli	Emotions expressed from verbal instructions	- Background: Gray - Clothes: ND - Distractors removed: ND	ND	ND	ND
Negrão et al. (2021)[45]	The Child Emotion Facial Expression Set	1) Presentation of an equivalent photograph expressing the emotion 2) Emotions elicited from specific situations	- Background: White - Clothes: White - Distractors removed: ND	Step 1: 100% agreement between two evaluators Step 2: 100% agreement between other two evaluators (two of each step)	Four judges - Age: ND - Gender: ND - Race: ND	- Precision: Accuracy† and Cohen's kappa† - Validity evidence: Based on the relationship with other variables: accuracy × gender × age¶; emotion × race‡

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Novello et al. (2018)[46]	Youth Emotion Picture Set	1) Emotions elicited from specific situations 2) Presentation of an equivalent photograph expressing the emotion 3) Presentation of videos and a game to specifically elicit the emotion of anger	- Background: ND - Clothes: Black cape - Distractors removed: Jewelry	Images recognized with ≥75% accuracy	Adults: 101 volunteers recruited through the snowball method - Age: 18-77 years - Gender: M=31.7%; F=68.3% - Race: ND Adolescents: 54 volunteers from state schools - Age: 12-17 years - Gender: M=40.7%; F=59.3% - Race: ND	- Precision: Accuracy† and Cohen's kappa† - Validity evidence: Based on the relationship with other variables: comparison of performance by age¶
O'Reilly et al. (2016)[47]	The EU-Emotion Stimulus Set	Emotions elicited from specific situations	- Background: White - Clothes: ND - Distractors removed: ND	Accuracy	1,231 volunteers - Age: 44 years; SD=16.7 - Gender: M=428; F=803 - Race: ND	- Precision: Accuracy_ and Cohen's kappa† - Validity evidence: Content-based: performance comparison by expression type, valence, and excitation
Olszanowski et al. (2015)[48]	Warsaw Set of Emotional Facial Expression Pictures (WSEFEP)	Instruction on muscle movement of the emotions based on FACS	- Background: White - Clothes: Black T-shirt - Distractors removed: Beards, mustaches, earrings, and glasses	Agreement in recognition	1,362 participants - Age: 26.6 years; SD=11.6 - Gender: M=261; F=1,101 - Race: ND	- Precision: agreement among the evaluators - Validity evidence: Content-based: purity analysis and intensity coefficient
Passareli et al. (2018)[49]	Facial Expression Recognition Test (FERT)	Presentation of an equivalent photograph expressing the emotion	- Background: Black - Clothes: Black T-shirt - Distractors removed: ND	Unidimensional model	794 volunteers from the community - Age: 36.13 years; SD=13.79 - Gender: M=36.2%; F=63.8% - Race: ND	- Validity evidence: Based on the internal structure: factor analysis through the two-parameter Bayesian model - Based on the relationship with other variables; performance comparison between gender and age‡ - Analysis of the items: Discrimination and difficulty through the Item Response Theory (IRT)

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Romani-Sponchiado et al. (2015)[50]	Child Emotions Picture Set	Emotion induction through videos	- Background: ND - Clothes: ND - Distractors removed: ND	Images recognized with ≥60% accuracy	30 psychologists with experience in child development - Age: ND - Gender: ND - Race: ND	- Precision: Accuracy** and Fleiss' Kappa† - Analysis of the items: Accuracy - Validity evidence: Content-based: Fleiss' kappa; chi-square to compare the proportion of posed and spontaneous photographs
Samuelsson et al. (2012)[51]	Umeå University Database of Facial Expressions	Instruction on muscle movement of the emotions based on FACS	- Background: ND - Clothes: ND - Distractors removed: Makeup	Accuracy	526 participants - Age: 18-73 years (37.7 years; SD=13.0) - Gender: M=157; F=369 - Race: ND	- Precision: Accuracy† - Validity evidence: - Based on the relationship with other variables; performance comparison by gender and age¶
Sharma and Bhushan. (2019)[52]	Indian Affective Picture	1) Presentation of an equivalent photograph expressing the emotion 2) Emotions elicited from specific situations	- Background: ND - Clothes: ND - Distractors removed: Beards, glasses, and makeup	Accuracy Intensity (9-point scale)	350 undergraduate students - Age: 20.58 years; SD=1.13 - Gender: M=320; F=30 - Race: ND	- Analysis of the items: Accuracy† - Validity evidence: Based on the relationship with other variables: t-test to compare men's and women's performance¶
Tottenham et al. (2009)[12]	The NimStim set of facial expressions	Emotions expressed from verbal instructions	- Background: ND - Clothes: ND - Distractors removed: Makeup	Validity (accuracy and Cohen's kappa) and reliability	Group 1 47 university students - Age: 19.4 years (SD=1.2) - Gender: M=39; F=47 - Race: European-American (81%), African-American (6%), Asian-American (9%), and Hispanic-American (4%) Group 2 34 volunteers from the community - Age: 25.8 years (SD=4.1) - Gender: M=22; F=12 - Race: European-American (59%), African-American (18%), Asian-American (6%), Hispanic-American (6%), and other races (12%)	- Precision: Accuracy† and test-retest† - Validity evidence: Content-based: Accuracy and test-retest

Continue...

Table 2. Continuation.

Authors and year of publication	Name of the database elaborated	Method used to elicit the emotions	Patterns in stimulus capture	Criteria used in the validation stage for inclusion of stimuli in the final database	Sample characteristics in the stage for the validation of the stimuli	Psychometric properties assessed
Tracy et al. (2009)[53]	University of California, Davis, Set of Emotion Expressions (UCDS)	Instruction on muscle movement of the emotions based on FACS	- Background: Gray - Clothes: White T-shirt - Distractors removed: Jewelry	Accuracy (the most recognized emotion of each expression was included in the final database)	Study 1 175 undergraduate students - Age: ND - Gender: M=35%; F=65% - Race: ND Study 2 234 undergraduate students - Age: ND - Gender: M=21%; F=79% - Race: ND	- Analysis of the items: Accuracy[§§] - Validity evidence: Content-based: Accuracy and performance based on race and gender of stimulus
Vaiman et al. (2017)[54]	FACS	Emotions elicited from specific situations	- Background: Blue - Clothes: White T-shirt - Distractors removed: Hair back (hair up)	Images recognized with ≥70% accuracy	466 students from the Psychology School of the National University of Córdoba. - Age: 20.29 years; SD=4.33 - Gender: M=23%; F=79% - Race: ND	- Precision: Accuracy[†] - Analysis of the items: Discrimination - Validity evidence: Based on the convergent relationship: Descriptive comparison of database performance vs. POFA database performance[†]
Yang et al. (2020)[55]	Tsinghua facial expression database	1) Emotions elicited from specific situations 2) Instruction on muscle movement of the emotions based on FACS	- Background: White - Clothes: ND - Distractors removed: Tattoos, piercings, jewelry, glasses, and makeup.	Images recognized with ≥70% accuracy	34 young individuals and 31 older adults, Chinese Young individuals - Age: 19-35 years (23.50 years; SD=4.41) - Gender: M=19; F=15 - Race: Chinese Older adults - Age: 58-72 years (65.06 years; SD=3.50) - Gender: M=13; F=18 - Race: Chinese	- Precision: Accuracy[†] and kappa agreement among the evaluators[†] - Validity evidence: Content-based: Accuracy and kappa agreement among the evaluators

ND: not declared; M: male; F: female; MTurk: Amazon Mechanical Turk; FACS: Facial Action Coding System (Ekman and Friesen, 1978)[65]; ANCOVA: analysis of covariance; ANOVA: repeated-measure analysis of variance.

*Only images with ≥50% accuracy were included in the final database; [†]Satisfactory indexes; [‡]There was a significant difference in precision between the analyzed variables; [§]The mean rate of correct identification of the emotions was 62.5%; [//]Only images recognized by ≥15 evaluators were included in the final database; [¶]There was no significant difference in precision between the analyzed variables; [#]The mean rate of correct identification of the emotions was 66%; **Only images with ≥60% accuracy were included in the final; [††]Accuracy is presented for each emotion and varied from 44 to 100%; [‡‡]Only images recognized by at least 55% of the evaluators were included in the final database. The mean recognition of the final database was 63%; [§§]The mean recognition rate of the final database varied from 47 to 94%.

Table 1 presents the general characteristics of the face databases included and Table 2 presents the methodological characteristics used to create each of them.

General characteristics of the face databases included

The articles included were published between 1976 and 2020, the majority dating from 2015 and 2017. Of the 36 articles included, 30.56% were carried out in the

United States. In relation to the theoretical framework used for the construction of the databases, 75% of the studies were empirically based. In other words, the limitations of the databases already built were the basis for this construction.

Most of the articles (61.1%) elaborated databases made up by six basic emotions (i.e., happiness, sadness, fear, anger, disgust, and surprise), as well as neutral faces. Some databases did not neutral faces, or surprise and disgust. Two databases only included happiness and neutral faces, one database only included happiness, fear, and neutral; and another included only happiness, sadness, anger, and surprise.

In relation to the participants, 41.7% of the studies selected resorted to actors (either amateur or professional) to express the emotions. The mean age of the actors varied from 13.24 to 73.2 years, with four studies including different age groups in their databases. Only five of the studies with actors included different races in their samples, and seven studies included any of the specific race, namely, Caucasian, Japanese, Korean, Polish, Indian, or Chinese. Three studies did not report the actors' race.

In relation to the other studies, that is, those that present the basic emotions expressed by community-dwelling individuals, inserted in various contexts, presented ages varying from 4 months to 93 years, and five of these studies included volunteers of different ages. Of these, 10 studies included participants of different races and the remaining studies included only one race, namely, Korean, Caucasian, Indian, and Chinese. Three studies did not report the participants' race. With regard to the presentation of the stimuli, 86.1% of the studies included colored faces in their databases, four studies used black and white faces, and one study included both colored and black and white faces in its database.

Most of the databases included (75%) present static stimuli, four studies are of dynamic stimuli, and five databases have both static and dynamic stimuli. Five studies presented open and closed mouth expressions, and other studies included additional features such as varying intensities and varying angles. The final total stimuli included in the databases varied from 42 to 18,800.

Methodological characteristics used in the studies

Method used to elicit the emotions

The method used to elicit the emotions varied across the studies. In general, more than one method was used in this stage. Predominantly, 44.4% of the studies used specific situations as one of the ways to elicit the intended emotions, such as "Imagine that you have just won the lottery; imagine that you have just lost a loved one." The studies also used instructions based on the muscle movement of the emotions considering protocols such as the Investigator's Guide for the Facial Action Coding

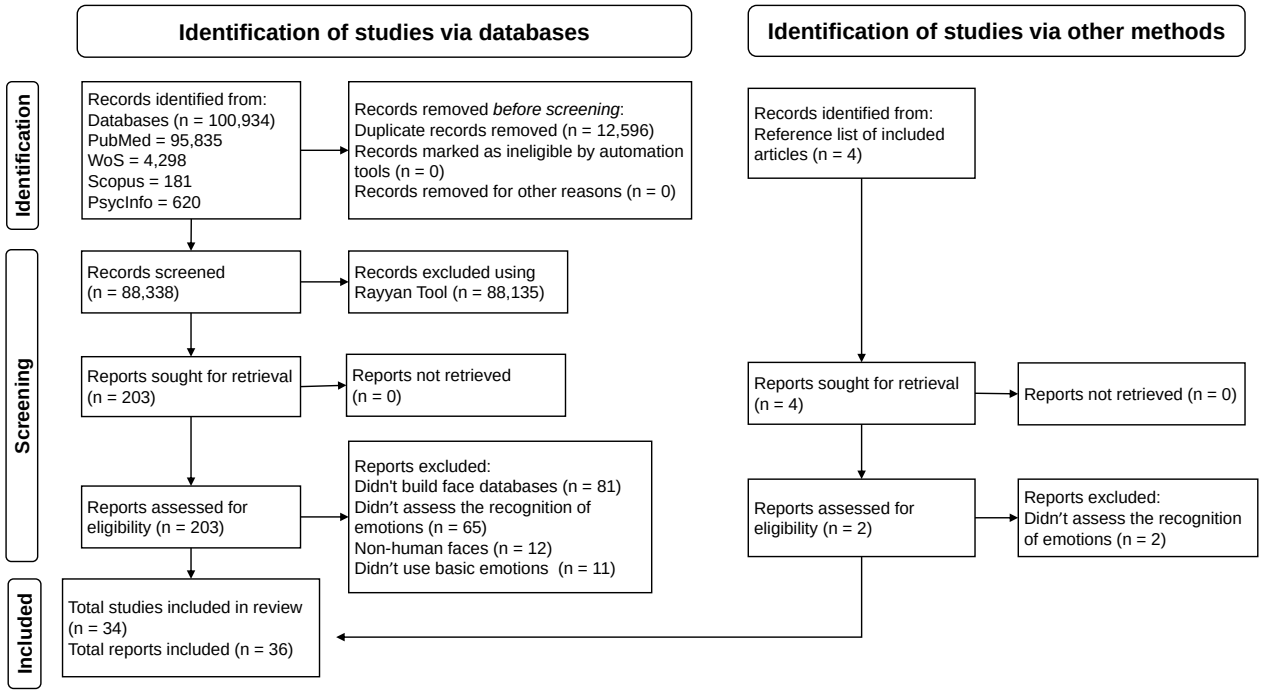

Figure 1. The article selection process according to the PRISMA initiative recommendations[17].

System (FACS), others used a photograph as a model, and others elicited the emotions from photographs and/or videos.

Two studies that built faces with infants and children used an instructional protocol, performed by the parents, to elicit the intended emotions. In one study, the individuals could express the emotion any way they wanted. Three studies elicited emotions in the participants through verbal instructions, such as "Make a happy face" and one study used workshops to teach children how to express basic emotions as well as a Directed Facial Action Task used to guide movement of anatomical landmarks.

Recording the stimuli

Most of the studies sought to establish and describe patterns to record the stimuli. For example, the images were photographed against a white background, black, or gray, and the individuals wore black or white garments. In addition, 55.6% of the studies established distractors that should be removed from the volunteers so that the images could be recorded, such as jewelry, accessories, and strong makeup.

Validation stage

The number of participants who validated the faces constructed by the studies varied from 4 to 1,362, and most of the participants who validated the stimuli were inserted in a university context. The way to validate the final stimuli in the database varied across the studies. The majority included recognition accuracy as one of the criteria, with images included reaching recognition percentages from >50 to ≥75%. The studies also used other criteria to include the stimuli in the final database, such as agreement among the evaluators.

Psychometric properties of the final database

Only one study did not include accuracy as a precision measure. In most of the cases, it was also used to validate the task content and even for item analysis. One study also used the method of halves as a precision measure. In 66.7% of the studies, the stimuli were recognized with ≥70% accuracy.

Test-retest reliability was a variable used to assess task precision in four studies, all presenting satisfactory indexes for this dimension. Regarding the measures of validity evidence, 10 studies used Cohen's kappa or Fleiss' kappa to validate the task content according to the agreement among the evaluators. All of them presented satisfactory indexes in this dimension. Only one study used Cronbach's alpha to assess internal consistency, also reporting a satisfactory value.

Six studies analyzed the items' difficulty. Three studies used Item Response Theory (IRT); one study analyzed difficulty according to the intensity and representativeness scores; one study used the Classical Test Theory (CTT); and one study used discrimination.

Two studies presented validity evidence based on the internal structure. One of them used exploratory factor analysis and the other resorted to factor analysis through the two-parameter Bayesian model. In addition, the other study presented validity evidence based on the convergent relationship, presenting a descriptive comparison of the database built with the POFA bank, with satisfactory indexes.

Fourteen (38.9%) studies presented validity evidence based on the relationship with other variables.

DISCUSSION

The ability to recognize emotional facial expressions can be modulated by variables such as gender, age, and race. In this sense, a number of studies sought to elaborate valid facial expression databases to assess recognition of emotions in specific populations and contexts. However, the methodological heterogeneity among construction studies can make it difficult to create patterns for the construction of these stimuli, regardless of the context and characteristics of who express them. This systematic review sought to gather the studies that built face databases to assess recognition of basic emotions, describing and comparing the methodologies used in its development.

General characteristics of the face databases included

The way to present the stimuli of an emotion recognition test has already been target of discussions among researchers in the area, since a pioneering study showed that the recognition of static and dynamic facial emotional stimuli involves different neural areas[66]. In this review, most of the studies consist of static stimulus databases. The difference in the recognition of static or dynamic stimuli is still an unanswered discussion, given that some studies report a higher rate of recognition of dynamic stimuli[67,68] while others point to a minimal or no difference in the recognition of these stimuli[69,70].

Khosdelazad et al.[71] investigated the differences in the performance of 3 emotion recognition tests in 84 healthy participants. The results point to a clear difference in the performance of tests with static or dynamic stimuli, with the stimuli that change from a neutral face to the intended emotion (dynamic) being the most difficult to be recognized, given the low performance in the test[71]. However, it is noteworthy that variables such

as age and schooling also modulated performance in the tests, highlighting the importance of normative data regardless of the type of stimulus chosen[71].

Several stimuli databases for facial expressions of emotions were developed in order to be used in specific populations and cultures[72]. Cultural issues must be taken into account when understanding these emotional expressions, as they can exert an influence on their recognition[73]. A study that considered ethnicity as an influencing factor in the performance of emotion recognition tasks and compared this ability to identify emotions between Australian and Chinese individuals verified that people perform worse when classifying emotions that are expressed on faces of another ethnicity[74]. In this sense, the cultural characteristics of the stimulus presented can also modulate performance in the test.

In addition to the difference in the pattern of response when recognizing emotions from another culture, studies showed that there is still a difference in the pattern of intensity recognized, regardless of the race or gender of the stimulus presented[75,76]. This fact happens probably because we manage our emotions according to the our learnings throughout our lives, clearly shaped by the cultural context in which we are inserted[76,77]. Thus, we learned in certain situations to hide or amplify our emotions, consequently affecting how we recognize emotions and highlighting the clear influences of culture on our social and cognitive abilities[76,78].

Furthermore, when we think about the modulating character of the cultural context in the recognition of emotions, it is important to highlight the impact that socioeconomic status can also have on this ability. In particular, some countries and regions with greater socioeconomic disparities may reflect different patterns of cognitive abilities[79]. For example, a large international study investigated, in 12 countries and 587 participants, the influence of nationality on core social cognition skills[80].

After controlling the analyses for other modulating variables such as age, sex, and education, the results showed that a variation of 20.76% (95%CI 8.26–35.69) in the test score that evaluated emotion recognition can be attributed to the nationality of the individuals evaluated[80]. These results make us reflect on the cultural disparities that exist in underdeveloped countries and how these aspects can influence the social and cognitive variables, as well as the recognition of emotions discussed here.

In addition, aspects related to the participant's profile can also interfere in task performance. Five studies in this review presented open and closed mouth expressions and other studies included additional features such as varying intensities, gaze directions, and varying angles. These variables can also modulate task performance. Emotions expressed with the mouth open seem to increase the intensity of the emotion perceived by the subject[81,82]. Consequently, incorporating this face variation to the database can be important to assess the emotion experienced by the individual who recognizes the stimuli. In addition, open-mouthed facial expressions seem to draw more the attention of the respondent than closed-mouthed expressions[81].

Hoffmann et al.[83] found a correlation between the intensity and accuracy of recognition of an emotion, where higher intensities were associated with greater accuracy in the perception of the face. However, Wingenbach et al.[84] did not find effects of the intensity level on expression recognition. Despite the controversial results regarding emotion intensity, it can still be an important variable to be taken into account in the construction of databases in order to compare recognition between different degrees of intensities.

The perception of the emotion expressed can also be modulated by the gaze direction of the person expressing it[85] so that when gaze is directed at the participant, this recognition is greater than when compared to the look avoided[86]. In addition, photographing the expressions from different angles can increase the ecological validity of the database built[38].

Methodological characteristics used in the studies

Method used to elicit the emotions

An important methodological choice in the studies that elaborate face databases is the way in which the stimuli will be elicited and who is going to express them. Our results show that most of the studies included in this systematic review resort to actors (either amateur or professional) to express the emotions. Such methodological choice can be justified by the fact that people who have experience in acting are able to express more realistic emotions than individuals without any experience[87]. Thus, resorting to actors to act out emotions can be advantageous with regard to bringing the emotions expressed to a more real context.

The literature indicates that there are three different ways to induce emotions, namely:

- Posed emotions;
- Induced emotions; and
- Spontaneous emotions[88,89].

Posed emotions are those expressed by actors or under specific guidance, tending to be less representative of an emotion expressed in a real context[89]. Induced emotions have a more genuine character than posed emotions, as varied eliciting stimuli are presented to the participant in order to generate the most spontaneous emotion possible[89]. However, it is noteworthy that this way of inducing emotion can also have limitations as to its veracity, since induction is carried out in a context controlled by the researcher[89]. Spontaneous emotions are considered closer to a real-life context. However, due to their observable character, their recording could only be possible when the individuals are not aware that they are being recorded. Thus, any research procedure can bias this spontaneity[89].

To increase induction effectiveness, the studies use a combination of techniques and procedures to facilitate achievement of the intended emotions. Among the 36 studies analyzed in this review, 44.4% used specific hypothetical situations as one of the ways to elicit the intended emotions, such as "Imagine that you have just won the lottery; imagine that you have just lost a loved one." Thus, despite induction being generated in a controlled context, using hypothetical everyday situations aims at remedying the limitation of expressions that are not very representative of real life.

Recording the stimuli

All construction studies try to capture stimuli following some kind of pattern. Some explore this pattern more in detail and others are more objective. Despite this, the data included in this review indicate that it is important to standardize the clothes worn by the participants and the background they are positioned against during the capture of stimuli.

In addition, most construction studies have established distractors that should be removed prior to image capture, such as jewelry, accessories, and strong makeup. Our hypothesis is that these distractors could direct the attention of those who respond to the task and exert an impact on recognition performance, since attention can be a modulating variable in emotional tasks[90].

Validation stage

The way to validate the stimuli in the databases elaborated varies greatly across the studies. Based on the methods used in the construction, the validation criteria are defined. Accuracy is the most used precision indicator in the development and validation of face databases that assess recognition of emotions[12,13], which is why it was presented in most of the studies included. Recognition rate ≥70% is the most frequently used. However, the choice of which criterion to adopt at this stage is varied, and it is common to adopt other rates and criteria to validate the database, such as intensity, clarity, and agreement between evaluators.

Psychometric properties of the final database

We seek to follow the standards established by Resolution 09-2018 of the Federal Council of Psychology, which regulates the necessary dimensions for the assessment of psychological tests to verify the psychometric qualities of the databases. Although the studies present construction of tasks and not instruments, recognition of emotions is an important skill that allows for interaction in society and can be used to assess social cognition to predict the diagnosis of mental disorders[91].

The analyses presented by the studies in this stage are also heterogeneous. However, some dimensions presented in the studies become strictly necessary to verify the quality of the database elaborated. With regard to the technical requirements, it is important to evaluate dimensions related to precision and validity evidence of the constructed task[20,21]. It is worth noting that normative data are also important to assess the quality of the task. However, this variable and other important analyses were not included in this review as they are found in articles published separately.

This review showed that the studies that elaborate face databases for the recognition of emotions present heterogeneous methods. However, similarities between the studies allow us to trace important patterns for the development of these stimuli, such as using more than one method to elicit the most spontaneous emotion possible, standardizing the characteristics of the volunteers for capturing the stimuli, validating the database based on preestablished criteria, and presenting data referring to precision and validity evidence. With regard to future directions related to the research methods, greater standardization of the methods for eliciting and validating emotions would make the choice of the type of task to be used in each context more reliable.

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Evidence from Cochrane systematic reviews on pharmacological treatment compared to placebo for panic disorder

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ABSTRACT. Panic disorder is an anxiety condition characterized by recurrent and unexpected panic attacks. The comparison between active treatment and placebo is essential to analyze an intervention's efficacy and safety. It is important to identify and summarize the studies with higher evidence to assist health professionals and public policy managers in clinical decision-making. **Objective:** The aim of this study was to identify and summarize all Cochrane systematic reviews (SRs) that compared the efficacy and safety of any drug treatment compared to placebo for panic disorder patients. **Methods:** SRs published in the Cochrane Library were included without date restriction. All outcomes presented were analyzed. The methodological quality of the SRs was evaluated using the AMSTAR-2 tool. **Results:** We included three Cochrane SRs of high methodological quality on the effects of antidepressants, benzodiazepines, and azapirones for panic disorder. All medications showed benefits in response to treatment, symptom improvement, and reduced panic attacks. Dropouts were lower with tricyclic antidepressants and benzodiazepines and higher with azapirones. The occurrence of adverse events was higher for drug groups. **Conclusions:** Very low to moderate certainty evidence (GRADE) showed that antidepressants and benzodiazepines seem to improve clinical symptoms in individuals with short-term panic disorder compared to placebo. In addition, the use of azapirones seems to have greater adherence by patients than placebo. However, there is insufficient evidence to support its clinical efficacy.

Keywords: Panic Disorder; Drug Therapy; Systematic Review; Evidence-Based Medicine.

EVIDÊNCIAS DAS REVISÕES SISTEMÁTICAS COCHRANE SOBRE O TRATAMENTO FARMACOLÓGICO COMPARADO AO PLACEBO PARA TRANSTORNO DE PÂNICO

RESUMO. O transtorno de pânico é uma condição de ansiedade caracterizada por ataques de pânico recorrentes e inesperados. A comparação entre tratamento ativo e placebo é essencial para analisar a eficácia e a segurança de uma intervenção. É importante identificar os estudos com maiores evidências para auxiliar os profissionais de saúde e gestores de políticas públicas nas decisões clínicas. **Objetivo:** Identificar e sumarizar todas as revisões sistemáticas (RS) publicadas na Cochrane que relatam a eficácia e a segurança de qualquer tratamento medicamentoso comparado ao placebo para pacientes com transtorno de pânico. **Métodos:** Foram selecionadas e analisadas todas as RS publicadas na base de dados Cochrane, sem restrição de data. A qualidade metodológica das RS foi avaliada utilizando a ferramenta AMSTAR-2. **Resultados:** Foram incluídas três RS Cochrane com alta qualidade metodológica que avaliaram os efeitos de antidepressivos, benzodiazepínicos e azapironas para transtorno de pânico. Todos os medicamentos mostraram benefícios na resposta ao tratamento, melhora dos sintomas e redução das crises de pânico. O número de desistências do tratamento foi baixo com antidepressivos tricíclicos e benzodiazepínicos e alto com azapironas. A ocorrência de eventos adversos foi elevada para os grupos das medicações analisadas. **Conclusões:** Evidências de certeza muito baixa a moderada (pela Classificação de Recomendações, Avaliação, Desenvolvimento e Análises — GRADE) mostraram que antidepressivos e benzodiazepínicos parecem melhorar os sintomas clínicos em indivíduos com transtorno de pânico em menor prazo, em comparação ao placebo. Além disso, o uso de azapironas parece ter maior adesão por parte dos pacientes do que o placebo. No entanto, não há evidências suficientes para comprovar sua eficácia clínica.

Palavras-chave: Transtorno de Pânico; Tratamento Farmacológico; Revisão Sistemática; Medicina Baseada em Evidências.

This study was conducted by the Group of Postgraduate Program in Health and Environment, School of Medicine, Universidade Metropolitana de Santos, Santos SP, Brazil.

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INTRODUCTION

Panic disorder is an anxiety condition characterized by recurrent and unexpected panic attacks, leading to impaired functional capacity and a worse quality of life for the individual[1-3]. These are periods of fear, apprehension, or anxiety of rapid onset and with a typical duration of minutes, in which at least 4 of the 13 characteristic symptoms are experienced: fast heartbeat, sweat, tremor, feeling short of breath, chest pain, dizziness, a sensation of asphyxiation, paresthesia or tingling, choking, hot flashes, nausea or abdominal pain, feeling of detachment, feeling of losing control, and/or dying[1,4,5]. Data from the *World Mental Health Surveys* of 25 countries with 142,000 people showed that 13.2% had panic attacks at some point in their lives, and 12.8% met the criteria for diagnosing panic disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[6]. Estimates indicate that about 3.5% of the population will meet panic disorder criteria during life[5-7].

Most clinical studies assess the efficacy of panic disorder medications by changing the frequency of symptomatic attacks. However, panic attacks are only one component of this syndrome, and the reduction of attacks does not entirely represent a clinical improvement. Studies report that more than 50% of patients treated with placebo reduced the frequency of attacks but remained to show higher anticipatory anxiety, phobic distress, and depression[8-10].

The comparison between active treatment and placebo is essential to analyze an intervention's efficacy and safety[11]. Clinical studies on the treatment of panic disorder have increased significantly due to the higher diagnosis and/or incidence of the disease and, consequently, many available medications. Considering the clinical and economic relevance, it is important to identify and summarize the studies with higher evidence to assist health professionals and public policy managers in clinical decision-making regarding panic disorder medications' efficacy and safety.

Systematic reviews (SRs) are the appropriate studies to map the literature and summarize the available evidence, as they present a rigorous methodology to minimize the risk of bias. New methodological approaches were developed to synthesize this evidence to keep up with the growing volume of SRs. The overviews or reviews of SRs aim to gather, evaluate, and synthesize these studies' results on a given subject. The overviews have evolved to meet the need to filter the burden, improve access to information, and assist in health decision-making[12-14]. This review's objective was to identify and summarize all the SRs published in Cochrane that compared the efficacy and safety of any drug treatment compared to placebo for panic disorder patients.

METHODS

This overview of SRs followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[15], considering the sections for a review of SRs. In addition, the reporting was conducted according to the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[16], with appropriate adaptations for an overview.

Criteria for inclusion of studies

Type of study

All SRs published in Cochrane (with and without meta-analysis) on pharmacological treatment compared to placebo in patients with panic disorder were included. There was no restriction on the date of publication of the SR. Protocols of Cochrane reviews and reviews withdrawals from the Cochrane Library were excluded.

Participants

Adults (18 years and older) were diagnosed with panic disorder according to the following criteria: Diagnostic and Statistical Manual of Mental Disorders (DSM)[5], International Statistical Classification of Diseases and Related Health Problems (ICD-10), Feighner criteria[17], or Research Diagnostic Criteria (RDC)[18].

Interventions

Any type of pharmacological treatment was compared to placebo, regardless of dose, duration, and frequency of treatment.

Outcomes

All the outcomes analyzed by the SRs were presented.

Search for studies

The systematized and sensitized search was performed in the Cochrane Database of Systematic Reviews – CDSR (via Wiley) on October 8, 2021, using the unique descriptor: "Panic Disorder" and its synonyms.

Selection of studies

The SRs identified were selected by two researchers independently. These researchers analyzed the eligibility of reviews by reading titles and abstracts. The eligible SRs were then evaluated in full text and classified as included or excluded. If there was disagreement regarding

the inclusion of the reviews, a consensus was made for inclusion or exclusion. The SRs were selected through the *Rayyan online* platform[19].

Data extraction and collection

The included SRs had their data extracted through a standardized form with information on methodological characteristics of the reviews, characteristics of the participants, and results of the outcomes evaluated. Two independent researchers extracted the data with disagreements resolved by consensus.

Methodological quality assessment

The SRs were evaluated for their methodological quality using the AMSTAR-2 tool *(Assessing the Methodological Quality of Systematic Reviews)*[20].

The AMSTAR-2 is a tool composed of 16 items:

1. Research question and inclusion criteria according to the components of PICO (Population, Intervention, Comparators, Outcomes);
2. Study planning protocol;
3. Justification for the selection of the study design for inclusion in the review;
4. Comprehensive literature search strategy;
5. Study selection in duplicate;
6. Data extraction in duplicate;
7. Report of excluded studies and justifications for exclusions;
8. Characteristics of the included studies described in adequate detail;
9. Methods to assess the risk of bias in the included studies;
10. Reporting of the funding sources of the included studies;
11. Methods for statistical combination of results (meta-analysis);
12. Potential impact of the risk of bias in meta-analyses;
13. Consideration of the risk of bias in the interpretation and discussion of the results;
14. Discussion and explanation of heterogeneity;
15. Investigation of publication bias; and
16. Conflict of interest report of the authors of the review. Each domain is classified as entirely suitable ("yes"), partially adequate ("partially yes"), or not applicable.

Some of these are considered critical (items 1, 4, 7, 9, 11, 13, and 15). The assessment classifies the SRs according to the following degrees of confidence: critically low (more than one critical failure), low (a critical failure), moderate (more than one noncritical failure), and high (none or one noncritical failure)[20]. The evidence set's confidence was generated through the *checklist* available on the AMSTAR-2 website (http://amstar.ca/Amstar_Checklist.php).

Data synthesis

The results of the included SRs were presented narratively, considering the methodological quality evaluated by AMSTAR-2. Identifying and analyzing overlapping primary studies were unnecessary since each SR considered a specific pharmacological treatment compared to placebo. Even if a randomized clinical trial (RCT) assessed more than one intervention arm, only the treatment of interest for each SR would be included.

RESULTS

The Cochrane Library database search identified eight SRs; three were considered eligible[21-23].

Characteristics of the included SRs

The included SRs were published between 2014 and 2019 and evaluated the effects of three classes of drugs to treat panic disorder compared to placebo: antidepressants, benzodiazepines, and azapirones. All SRs included only RCTs as a primary study, and total samples ranged from 170 to 8,252 participants. Table 1 presents the main characteristics of the included SRs.

Methodological quality assessment

The methodological quality of the included SRs was evaluated by the AMSTAR-2 tool, and all of them were classified as high quality. Table 2 presents the details of the evaluation.

Main results from the included SRs

Table 3 presents the main results from the meta-analyses of the primary outcomes assessed in the SRs. Most of the analyzed treatments showed benefits regarding treatment response compared to placebo. However, there were higher rates of dropouts due to any cause and losses due to adverse events. Regarding secondary outcomes, a possible benefit of antidepressants and benzodiazepines was also observed for disease remission, social interaction, panic symptoms, frequency of attacks, agoraphobia, anxiety, and depression. There was no observed difference in the quality of life improvement between groups.

It is important to note that the included studies did not assess the treatment's long-term effects and risks of dependence and abstinence symptoms.

Table 1. Main characteristics of the included systematic reviews.

Systematic review, year	Number of included RCTs	Participants	Intervention	Outcomes	Time points	Certainty of the evidence (GRADE)
Bighelli et al. (2018)[21]	41	n=8,525 30.6–61.2 years old	Antidepressants	Treatment response Dropouts Losses due to adverse events Disease remission Panic symptoms Frequency of panic attacks Quality of life	2–6 months	Very low to moderate
Breilmann et al. (2019)[22]	24	n=4,233 18 and 73 years old	Benzodiazepines	Treatment response Dropouts Losses due to adverse events Disease remission Social interaction Panic symptoms Frequency of panic attacks Agoraphobia, anxiety, and depression	1–6 months	Very low to low
Imai et al. (2014)[23]	3	n=170 Over 18 years old	Azapirones	Treatment response Dropouts Losses due to adverse events	2 months	Low to moderate

RCT: randomized clinical trial; GRADE: Grading of Recommendations Assessment, Development and Evaluation; n: number of participants.

Table 2. Main findings from the included systematic reviews.

AMSTAR-2 tool domains	Systematic reviews		
	Bighelli et al. (2018)[21]	Breilmann et al. (2019)[22]	Imai et al. (2014)[23]
1. Search question (PICO)	Yes	Yes	Yes
2. Study planning (protocol)	Yes	Yes	Yes
3. Justification for the selection of the study design	Yes	Yes	Yes
4. Search strategies	Yes	Yes	Yes
5. Selection of peer studies	Yes	Yes	Yes
6. Data extraction in pairs	Yes	Yes	Yes
7. Report of excluded studies	Yes	Yes	Yes
8. Characteristics of the studies included	Yes	Yes	Yes
9. Risk assessment of bias	Yes	Yes	Yes
10. Reporting of the sources of funding for the studies	Yes	Yes	Yes
11. Appropriate statistical methods	Yes	Yes	Yes
12. Assessment of the impact of the risk of bias in meta-analyses	Yes	Yes	Yes
13. Risk of bias in interpretation and results	Yes	Yes	Yes
14. Discussion and explanation of heterogeneity	Yes	Yes	Yes
15. Investigation of publication bias	Yes	Yes	Yes
16. Report of conflict of interest of the authors of the review	Yes	Yes	Yes
Total (quality)	High quality	High quality	High quality

Evaluated by the http://amstar.ca/Amstar_Checklist.php.

Table 3. Evaluation of the methodological quality of the included systematic reviews.

	Main results (95%CI)		
	Treatment response rate	**Number of dropouts (for any reason)**	**Losses from adverse events**
Antidepressants versus placebo			
Any class	RR 0.72 [0.66–0.79]* 30 RCT, n=6,500 Low-certainty evidence	RR 0.88 [0.81–0.97]* 38 RCT, n=7,850 Low-certainty evidence	RR 1.49 [1.25–1.78]* 33 RCT, n=7,688 Low-certainty evidence
Tricyclic antidepressants	RR 0.73 [0.63–0.86]* 9 RCT, n=829	RR 0.74 [0.63–0.86]* 17 RCT, n=1,906	RR 1.97 [1.33–2.91]* 10 RCT, n=1,641
Selective Serotonin Reuptake Inhibitors (SSRIs)	RR 0.75 [0.67–0.84]* 21 RCT, n=4,000	No difference with placebo	RR 1.45 [1.16–1.81]* 22 CT, n=4,131
Monoamine oxidase inhibitors (MAOIs)	RR 0.55 [0.34–0.88]* 1 RCT, n=29	NA	NA
Selective serotonin-norepinephrine reuptake inhibitors (ISRSN)	RR 0.61 [0.41–0.91]* 4 RCT, n=1,531	No difference with placebo	No difference with placebo
Noradrenergic resorption inhibitors	RR 0.71 [0.51–0.97]* 1 RCT, n=82	RR 0.50 [0.28–0.90]* 1 RCT, n=82	No difference with placebo
Benzodiazepines versus placebo	RR 1.65 [1.39–1.96]* 16 RCT, n=2,476 Low-certainty evidence	RR 0.50 [0.39–0.64]* 21 RCT, n=3,558 Low-certainty evidence	RR 1.58 [1.16–2.15]* 5 RCT, n=3,263 Low-certainty evidence
Azapirones versus placebo	NA	RR 2.13 [1.11–4.07]* 3 RCT, n=170 Moderate-certainty evidence	NA

95%CI: 95% confidence interval; RR: relative risk; RCT: randomized clinical trial; n: total number of participants; NA: not assessed. *Benefits in favor of the intervention.

DISCUSSION

The Cochrane SRs identified three classes of drugs compared to placebo: antidepressants, benzodiazepines, and azapirones. All SRs were evaluated by the AMSTAR-2 tool as of high methodological quality, which was expected given Cochrane's methodological rigor in the elaboration and conduction of the SRs.

According to the evaluation by the GRADE approach (The Grading of Recommendations Assessment, Development and Evaluation)[24], the certainty of the evidence varied from very low to moderate, which means that new RCTs are likely to modify the results found. All clinical trials included in the SRs presented methodological flaws, such as the risk of bias and inaccuracy in the results (wide confidence interval).

The absence of blind participants and outcome assessors may increase the risk of preventable biases such as subjective adverse events and treatment satisfaction[25]. Although most RCTs have been described as "double-blind" studies, many authors have not provided additional information on the blinding process used (e.g., using identical capsules and packaging to make it impossible to identify the placebo). This lack of information has limited the risk of bias assessment in the included SRs. For example, among the RCTs on antidepressants and benzodiazepines, only 39% and 54% were classified as low risk of bias for blinding domains. However, the three RCTs included in the review on azapirones were classified as low risk of bias, because they provided the necessary information on the blinding of participants. It is noteworthy that the meta-analysis of these three RCTs showed a higher rate of dropouts in the intervention group, reinforcing the uncertainty about the absence of the blind. Patients may give up treatment in the event of actual adverse events, for any other justifiable reason, or simply because they are aware of their allocation to the placebo group.

Few RCTs included in the SRs evaluated outcomes such as quality of life and cost-effectiveness analyses of the drugs studied. Furthermore, assessing clinical improvement of individuals with panic disorder is almost always subjective through scales and questionnaires. It does not always consider all aspects and the complexity of the disease[21], which may limit the applicability of RCT results. The patients' follow-up time was short-term, and it was impossible to determine these medications'

long-term effects. For this reason, the results of these SRs should be interpreted with caution, as the treatment choice should balance the benefits and harms of treatment from a long-term perspective.

There are no overview studies similar to the present work published in the literature. Therefore, the authors could not compare the results. The authors found no new reviews with high methodological quality on the drug treatment for panic disorder published after the publication of the SR included in this overview that could add to the results presented here. The authors chose to include only Cochrane SRs due to the rigorous methodology that gives greater confidence in the estimates of the interventions' effects. Besides, the included SRs were recently published and show the current clinical studies scenario on the drugs analyzed for panic disorder.

It is important to note that the choice for clinical practice is not between medicine and placebo but between the different drug therapies in terms of efficacy and safety. However, comparison with placebo in clinical studies allows for better proof of treatment effects beyond psychological or subjective outcomes, provided that the masking process is conducted correctly. New RCTs must be performed with appropriate methodology according to CONSORT[26], including evaluating outcomes and long-term follow-up of patients. Only this way can one determine the efficacy of panic disorder medications, the risk of adverse events, and the impact of their continued use.

In conclusion, evidence of very low to moderate certainty has shown that antidepressants and benzodiazepines seem to improve clinical symptoms in individuals with short-term panic disorder compared to placebo. The use of azapirones seems to have greater adherence by patients than placebo. However, there is insufficient evidence to support its clinical efficacy.

Authors' contributions. MMBR: conceptualization, methodology, project administration, software, validation; visualization; writing – original draft; and writing – review & editing. YDF: conceptualization, software, supervision, validation; visualization; writing – original draft; and writing – review & editing. ACLS: conceptualization, data curation, validation; visualization; writing – original draft; and writing – review & editing. GRC: conceptualization, data curation, validation; visualization; writing – original draft; and writing – review & editing. MESC: conceptualization, data curation, formal analysis, methodology, validation; visualization; writing – original draft; and writing – review & editing. ECM: conceptualization, resources, validation; visualization; writing – original draft; and writing – review & editing. ALCM: conceptualization, formal analysis, methodology, project administration, software, supervision, validation; visualization; writing – original draft; and writing – review & editing.

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Effects of working memory training on cognition in healthy older adults: a systematic review

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ABSTRACT. The working memory (WM) training in older adults can benefit their cognition. However, there is a dearth of literature reviews on the subject. **Objective:** This study aimed to investigate and evaluate the effects of WM training on the cognition of healthy older adults, in individual and group interventions reported in the literature. **Methods:** This is a systematic review involving a qualitative analysis of publications on the SciELO, LILACS, and MEDLINE databases carried out between March and June 2021. **Results:** A total of 47 studies were identified and analyzed, comprising 40 in older adults only and 7 comparing older and younger adults, investigating individual or group WM training or other types of intervention focused on WM effects. **Conclusions:** Both individual and group intervention contributed to the maintenance and/or improvement of cognition in older adults exploiting brain plasticity to promote mental health and prevent cognitive problems that can negatively impact quality of life of this group.

Keywords: Memory, Short-Term; Cognitive Aging; Executive Function; Spatial Memory; Mental Health.

EFEITOS DO TREINO DE MEMÓRIA OPERACIONAL NA COGNIÇÃO DE IDOSOS SAUDÁVEIS: UM ESTUDO DE REVISÃO SISTEMÁTICA

RESUMO. O treino da memória operacional (WM) com idosos pode gerar benefícios em sua cognição. Entretanto, há escassez de revisões da literatura sobre o tema. **Objetivo:** Investigar e avaliar, na literatura, os efeitos do treino da WM na cognição de idosos saudáveis, em intervenções individuais e grupais. **Métodos:** Estudo de revisão sistemática realizado entre março e junho de 2021, utilizando-se as bases Scientific Electronic Library Online (SciELO), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Medical Literature Analysis and Retrieval System Online (MEDLINE). **Resultados:** Foram identificados e analisados 47 estudos, 40 apenas com idosos, e sete comparativos entre idosos e adultos mais jovens, que realizaram treino individual ou em grupo com foco nos efeitos na WM. **Conclusões:** Os trabalhos analisados mostraram que ambos os tipos de intervenções podem contribuir para a manutenção e/ou melhoria da cognição de pessoas idosas, aproveitando sua plasticidade cerebral e, portanto, para a promoção de sua saúde mental e para a prevenção de problemas cognitivos que podem interferir em sua qualidade de vida.

Palavras-chave: Memória de Curto Prazo; Envelhecimento Cognitivo; Função Executiva; Memória Espacial; Saúde Mental.

INTRODUCTION

The growth in the population of older people has led to a shift in epidemiological profile, changes that pose a major challenge to health systems worldwide. Multidisciplinary, preventive actions involving monitoring of the aging process are needed to reduce this burden[1].

A prevalent health issue associated with aging is dementia. According to the World

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Health Organization[2], the number of individuals presenting some degree of dementia syndrome may triple by 2050 compared with 2012 levels, with low- to middle-income countries set to be most affected[3].

Memory is a cognitive function that can be negatively impacted by different types of dementia or cognitive impairments that are precursors of a dementia syndrome diagnosis. Working memory (WM) is a type of short-term memory involved in the concurrent storage and processing of information before and during the execution of a given task[4,5].

Literature reveals that memory can be understood as long term or short term. The first is associated with the permanent storage of information, which can be retrieved and recalled at any time. The second, in turn, is related to the ability to memorize a limited amount of information over a short period of time. Long-term memory is subdivided into episodic, semantic, autobiographical, prospective, procedural, preactivation, and conditioning memory. While short-term memory refers to immediate memory and WM[6].

According to the literature review by Chai et al., different models describe the concept of WM, among which two stand out. The first is known as the multicomponent WM model, in which WM is seen as a system capable of providing information for the execution of more complex cognitive activities. In this model, there is a center that manages visuospatial skills, speech therapy, and multimodal information related to episodic memory, forming the WM. The second model highlights the influence of attentional cognitive ability in the formation of WM, in addition to identifying this subtype of memory as an integrated part of long-term memory[7].

Working memory is one of the most affected cognitive functions in the aging process. The literature explains that the areas of the prefrontal cortex, the region responsible for the functioning of WM, can suffer more significant impacts over time, which impairs the execution of tasks that require the processing and temporary storage of information, such as visuospatial information and verbal. Through visuospatial memory, the individual has the ability to understand their own spatial location, as well as the arrangement of objects in spaces and the identification of colors, textures, and shapes. Verbal memory is related to the skills of remembering, evoking, and understanding words, either written or verbal[8].

In this context, nonpharmacological interventions, including cognitive interventions, emerge as viable strategies for preventing cognitive decline and promoting mental health. Intervention strategies as a way of maintaining and improving the functioning of cognitive skills are possible due to the brain's plasticity capacity. Neuroplasticity refers to the increase in the formation of the number of dendrites, axons, and synapses, from external events, which favor cognitive functionality[9].

The deliberate practice of one or more cognitive skills via standardized activities is referred to as cognitive training (CT), which can be characterized as strategy-based cognitive training (SCT) or procedure-based cognitive training (PCT). The SCT is configured as an intervention with an emphasis on compensatory practices in which a facilitator provides instructions and resources that help in the execution of specific tasks and activities that present some commitment. The use of lists, calendars, and organization methods are some examples[10].

In relation to PCT, this modality aims to achieve better functioning of specific cognitive functions, but does not provide compensatory strategies as in the model mentioned above. Due to this characteristic, the PCT presents a greater possibility of obtaining benefits for other skills in addition to the trained one[11]. An example of this type of cognitive intervention is WM training, which aimed at stimulating cognition through exercises for enhancing attention, memory performance, and concentration[5]. Brum[5] demonstrated the effectiveness of WM training in cognitively healthy older adults, who showed performance gains on cognitive tests performed pre- and post-intervention.

Brum et al.[12] carried out a study using individual WM training involving an adaptive scheme that allowed difficulty levels to be personalized. The results showed that three sessions of individual training promoted long-term gains in the cognitive skills trained plus a transfer effect to nontrained skills. The benefits, however, extended to include improvements in fluid intelligence, text comprehension, processing speed, and activities of daily living (ADLs).

From the research studies on the effects of WM training, those that present transfer results allow the association of this training modality to greater neuroplasticity, since the more cognitive regions are stimulated, the better performance of the respective functions is achieved, new skills are learned, and available cognitive resources are put to better use[13].

Although the results by Brum et al were positive, there are controversies in the literature about the benefits of close transference (for WM) and distant transference (for other cognitive skills) in WM training. The meta-analysis conducted by Sala et al, for example, aimed to investigate the effects of WM training on the cognitive abilities of the elderly. Only trained skills demonstrate significant improvement, indicating the absence of general benefits[14].

Recent evidence suggests WM training interventions in healthy older adults can potentiate brain plasticity, leading to not only near-transfer effects in performance on tasks measured within the same CT construct but also nontrained and far-transfer effects, improving performance on tasks measured under constructs not targeted by the CT. Factors such as age and education level can influence the short- and long-term effects[15].

In the meta-analysis, Karbach and Verhaeghen[11] analyzed the efficacy of WM training in enhancing the capacity and functioning of WM, and of executive functions training, focused on improving performance on dual-task, inhibitory and interference control, task switching, and general forms of attention, comparing the differences between young adults and older. The findings showed gains in the cognitive skills trained and small-to-moderate transfer effects to the global cognitive system. The authors concluded that training based on WM processes and executive functions was highly effective, suggesting that this type of cognitive intervention in older adults can help promote healthy aging[11].

Other more recent meta-analyses have evaluated the results of WM training, considering transfer effects as well as long-term effects. However, unlike what the present review proposes to do, there was no comparison between effects in young and elderly adults[14,16-18], or samples with multiple age groups were included, or only computerized CT was considered[19].

The objective of this systematic review, involving a qualitative analysis, was to investigate and evaluate the effects of WM training on the cognition in healthy older adults, based on individual and group interventions reported in the literature.

METHODS

A systematic review involving a qualitative analysis was conducted between March and June 2021. All relevant articles published in Portuguese or English were selected according to predefined inclusion and exclusion criteria. The SciELO, LILACS, and MEDLINE electronic databases were searched using the following combination of keywords: (idosa OR idoso OR idosos OR idosas) OR (elder OR "older person" OR "older persons" OR "older people" OR "senior citizen" "senior citizens" OR elderly OR "aging people" OR "aging person" OR "aging persons" OR "older adult" OR "older adults") AND ("intervenção cognitiva" OR "intervenções cognitivas" OR "treino cognitivo" OR "cognitive intervention" OR "cognitive interventions" OR "cognitive training") AND ("memória operacional" OR "memória de trabalho" OR "working memory" OR "operational memory") AND (envelhecimento OR aging).

Inclusion criteria were as follows: randomized clinically controlled trials published in Portuguese or English in scientific journals from 2011 onward; CT interventions focused on WM training, individual or group based; healthy participants aged over 60 years; and the use of cognitive and/or neuropsychological tests to determine the effects of the interventions.

The exclusion criteria adopted were as follows: publications of masters' dissertations, book chapters, doctoral theses, letters to the editor, case studies, systematic and meta-analysis reviews, and research protocols; studies involving cognitive interventions combined with physical training, other types of intervention, and/or multimode intervention studies; participants aged <60 years (in studies of older adults only) presenting cognitive impairment or risk of developing dementia or cognitive decline; trials performed in residential care homes, such as Long-term Care Facilities (LTCFs); and studies that do not assess intervention effects on cognitive performance of participants.

To guide the stages of identifying, screening, and determining eligibility of studies, two independent reviewers performed the steps of the Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA)[20]. The initial identification of studies entailed searches of the databases specified. During the screening stage, duplicate studies were removed and titles and abstracts analyzed by applying the predefined inclusion and exclusion criteria. For the eligibility stage, the selected studies were read in full and analyzed against the same criteria. The studies remaining after this stage were included in the review.

The scope of the study's systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO)[21] under registration number CRD42021245439. In addition, the included studies were rated for quality according to the Downs and Black Checklist[22]. This evaluation tool devised by Downs and Black comprises 27 items distributed between 5 sub-scales: reporting or assessment (10 items), external validity (3), internal validity of the measurements described and outcome bias (7), Confounding factors (6), and Power (1). Checklist items were scored 0 or 1, except for the item assessing the reporting of confounding factors, which score 0–2 points, and the item on power (item 27) modified as per other studies[22,23], whose original scoring of 0–5 points was changed to score 0 or 1 point, with a score of 1 given if the article reported calculation of power and/or sample size and 0 if these calculations had not been performed. Thus, the total scores on the Checklist ranged from 0 to 28 points. To improve the reading of the data obtained, scores

were converted into percentages for each domain and an overall mean total score for all domains was calculated. A system for classifying the quality of articles was defined as follows: ≤0.39 poor, 0.40–0.69 regular, 0.70–0.79 good, and ≥0.80 excellent.

RESULTS

A total of 229 studies were retrieved in the initial search, 6 of which were subsequently excluded because they were duplicates. Titles and abstracts of the remaining 223 studies were read and screened for relevance to the review and selected according to the inclusion and exclusion criteria. Thus, 71 articles were read in full and, after rigorous application of the criteria, a further 24 were excluded, of which 4 did not have a control group and a training group, 3 did not evaluate the effects of the intervention, 9 did not use a strategy directed to WM, 5 included elderly and nonelderly in the same groups, 2 had a group of elderly people with mild cognitive impairment (MCI), and 1 was published in Spanish. The study selection process is shown in the flow diagram[20] depicted in Figure 1.

The objectives, methods, and results of the 47 studies selected for analysis are listed in Tables 1 and 2. Regarding the sample profiles, 40 studies involved older adults only, of which 34 performed WM training. Of this total, 25 applied individual interventions[13,24-57]. Seven studies of older adults performed a variety of interventions centered on WM effects, comprising two with individual training[58,59] and five with group training[60-63]. The other seven studies analyzed involved young and older adults who underwent individual WM training, comparing the performance of the two age groups[64-70].

The number of participants in the studies involving older adults only ranged from 14 to 235 subjects and maximum age was 95 years. Intervention duration ranged from 1 to 26 weeks, with a minimum of 5 and maximum of 50 sessions, and session length of 20–150 min each. Follow-up assessments took place within a period of 3 years post-intervention.

In studies comparing younger and older adults, the number of participants ranged from 43 to 123, mean age of older adults was 60–77 years, age of younger adults was 19–36 years, intervention duration was 2–5 weeks, and the number of sessions ranged from 10 to 25, with session duration of 10–60 min. Follow-up assessments were carried out within a period of 18 months post-intervention.

Finally, according to the scores for the categories of the methodological quality Checklist, none of the articles scored <0.68 points and 43 scored >0.70, attaining

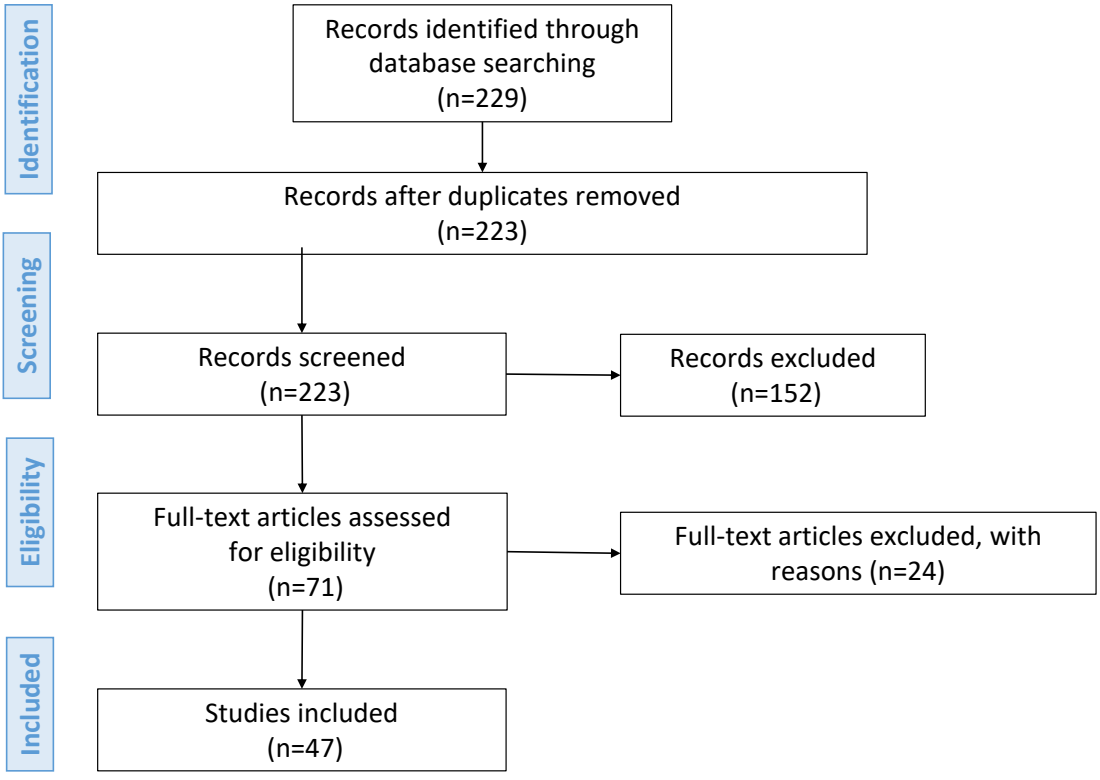

Figure 1. Flowchart of study search and review process.

Table 1. Studies with older adults.

Authors	Objectives	Methods	Results found
Richmond et al.[42]	To investigate gains in WM through WM training in older adults and whether near- and far-transfer effects to other measures exist.	n=40; age=60–80; intervention: individual, 4–5 weeks, 4–5 sessions of 20–30 min per week; study groups: WM training (n=21), active control (n=19); assessments: pre- and post-test.	Primary outcome: the training group showed the ability to inhibit the repetition of items already retrieved from memory and in a measure of attention (self-report); Transfer effects: short-term memory and WM; Long-term effects: not mentioned.
Irigaray et al.[50]	To verify the effects of an attention, memory, and executive functions training intervention on the cognition of healthy older adults.	n=76; age=60–89; intervention: group based, 12 weeks, 1 session of 90 min per week; study groups: WM training (n=38), passive control (n=38); assessments: pre- and post-test.	Primary outcome: better performance in tasks of attention, WM, language (inferences and spontaneous writing), constructional praxis, problem-solving, and executive functions; Transfer effects: not mentioned; Long-term effects: not mentioned.
van Muijden et al.[56]	To test whether CCT with online games can improve cognitive control in healthy older adults.	n=72; age=60–77; intervention: group based, 7 weeks, 1 session of 30 min per day; study groups: online games (n=53), active control: documentary (n=19); assessments: pre- and post-test.	Primary outcome: the study as a whole provides only modest support for the potential of video game training to improve cognitive control in healthy older adults; Transfer effects: inhibition and inductive reasoning; Long-term effects: not mentioned.
Anguera et al.[24]	To examine whether older adults participating in CCT (neuroRacer game) in multitasking mode showed improvement in multitasking performance on the game and in cognitive control abilities.	n=46; age=60–85; intervention: individual, 4 weeks, 3 sessions of 60 min per week; study groups: MTT (n=16), active control (n=15), passive control (n=15); assessments: pre- and post-test; follow-up: 6 months.	Primary outcome: older adults improved multitasking performance; Transfer effects: WM (delayed recognition task with and without distraction) and sustained attention; Long-term effects: yes, after 6 months.
Borella et al.[13]	To examine whether verbal WM training can improve WM performance in old-old individuals and to what extent it can promote and maintain transfer effects on tasks not trained directly.	n=36; age=75–87; intervention: individual, 2 weeks, 3 sessions of 60 min; study groups: verbal WM training (n=18), active control (n=18); assessments: pre- and post-test; follow-up: after 8 months.	Primary outcome: there was improvement in verbal memory performance; Transfer effects: inhibitory mechanisms; Long-term effects: yes, after 8 months.
McAvinue et al.[40]	To examine the efficacy of a WM training scheme to improve WM capacity in a group of older adults.	n=36; age=64–79; intervention: individual, 5 weeks, 5 sessions of 30 min per week; study groups: WM training (n=19), active control (n=17); assessments: pre- and post-test; follow-up: 3 and 6 months.	Primary outcome: there was expansion of short-term auditory memory, but no improvement was identified in WM overall; Transfer effects: episodic long-term memory; Long-term effects: yes, after 3 and 6 months.
Netto et al.[54]	To examine the effects of a WM training program on processing of WM and other related cognitive functions in healthy older adults.	n=20; age=60–80; intervention: group based, 12 weeks, 1 session of 90 min per week; study groups: WM training (n=9), passive control (n=11); assessments: pre- and post-test.	Primary outcome: significant improvements were found in focused attention, learning, and short-term and episodic memory in the training group. In the control group, improvements were found, in a more modest way, in concentrated attention and episodic memory; Transfer effects: episodic memory; Long-term effects: not investigated.
Borella et al.[29]	To test the efficacy of visuospatial WM training for transfer effects and maintenance of these effects in young-old and old-old.	n=80; age=65–84; intervention: individual, 2 weeks, 3 sessions of 60 min; study groups: WM training (n=20, 65–75 years; n=20, 76–84 years), active control (n=20, 65–75 years; n=20, 76–84 years); assessments: pre- and post-test; follow-up: after 8 months.	Primary outcome: participants in the training group showed improvement in visuospatial WM performance; Transfer effects: Verbal WM; Long-term effects: transfer effects were not maintained after 8 months.

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Table 1. Continuation.

Authors	Objectives	Methods	Results found
Stamenova et al.[45]	To examine the potential transfer effects of a recollection training paradigm and determine which cognitive functions are predictors of training effects.	n=51; mean age=68; intervention: individual, 2 weeks, 3 sessions of 20–30 min per week; study groups: recollection training n=30), active control (n=21); assessments: pre- and post-test; follow-up: 4 weeks.	Primary outcome: there were quite significant training gains with the trained recall tasks, but the transfer effects were relatively weak; Transfer effects: verbal learning, visuospatial memory, and WM (weak); Long-term effects: not investigated.
Stepankova et al.[46]	To examine the effects of a CCT WM intervention on nontrained measures of WM and visuospatial skills in healthy older adults.	n=65; age: 65–74 years; intervention: individual, 5 weeks, 2 or 4 sessions of 25 min per week; study groups: low-frequency WM CCT (n=20), high-frequency WM CCT (n=20), passive control: (n=25); assessments: pre- and post-test.	Primary outcome: improvement was found in the performance of older adults in training with the N-Back task and transfer effects; Transfer effects: WM and visuospatial skills; Long-term effects: not investigated.
Strenziok et al.[47]	To test whether CT provides far-transfer effects to attentional control demands mediated by the dorsal attention network and trained sensory cortex.	n=42; age: 69.70±6.9; interventions: individual, 6 weeks, 6 sessions of 60 min per week; study groups using games: BF (n=14), SF (n=14), RON (n=14); assessments: pre- and post-test.	Primary outcome: results showed that auditory perception CT (BF) may be particularly effective as an intervention against cognitive decline; Transfer effects: problem-solving and reasoning; Long-term effects: not investigated.
Zimmermann et al.[57]	To determine whether differences in older adults exist between structured WM training program and poetry-based stimulation program.	n=14; age=62–74; intervention: group, 6 weeks, 12 sessions of 120 min; study groups: WM training (n=8), active control: poetry (n=6); assessments: pre- and post-test.	Primary outcome: the WM group improved performance on measures of WM, inhibition, and cognitive flexibility, while the Poetry group improved on verbal fluency and narrative speech tasks; Transfer effects: executive functions; Long-term effects: not investigated.
Zinke et al.[49]	To investigate the effects of a process-based training intervention in a mixed sample of older adults and explore possible moderators of training and transfer effects.	n=80; age=65–95; intervention: individual, 3 weeks, 3 sessions of 30 min per week; study groups: WM training (n=40), passive control (n=40); assessments: pre- and post-test; follow-up: 9 months.	Primary outcome: there was significant improvement for the three trained tasks (visual-spatial, verbal and executive WM); Transference effects: verbal and fluid intelligence; Long-term effects: yes, after 9 months.
Basak and O'Connell[27]	To assess the role of cognitive control in WM training, comparing two different strategies for optimizing cognition in older adults during a short period of time.	n=46; age=60–86 years; intervention: individual, 2 weeks, 5 sessions of 60 min; study groups: predictable WM training (n=22), unpredictable WM training (n=24); assessments: pre- and post-test; follow-up: after 8 weeks.	Primary outcome: there were significant improvements in WM and episodic memory; Transfer effects: episodic memory; Long-term effects: not investigated.
Binder et al.[28]	To test whether multidomain CT promotes improvement in high-level executive functions and in each component function of CT, and also increase the likelihood of overlap with measures of transfer and demands of ADLs in older adults.	n=84; age=64–75; intervention: individual, 10 weeks, 5 sessions of 45–60 min per week; study groups: imbibition (n=22), visuomotor function (n=21), spatial navigation (n=20); multidomain (inhibition, visuomotor function and spatial navigation, n=21); assessments: pre- and post-test; follow-up: 6 months.	Primary outcome: training promoted improvements in executive functions, distal transfer, and attention; Transfer effects: executive attention control; Long-term effects: yes, after 6 months.
Cantarella et al.[33]	To assess the efficacy of verbal WM training in older adults, in terms of specific gain and transfer effects to everyday life competences and reasoning skills.	n=36; age=65–75; intervention: individual, 6 weeks, 2 sessions of 30–40 min per week; study groups: WM training (n=18), active control (n=18); assessments: pre- and post-test.	Primary outcome: there were benefits in trained skills; Transfer effects: everyday tasks and logical reasoning; Long-term effects: not investigated.

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Table 1. Continuation.

Authors	Objectives	Methods	Results found
Cujzek and Vranic[58]	To investigate whether practice on computerized card games would transfer to performance of old-old on tasks measuring the cognitive skills required by this cognitively stimulating activity.	n=29; intervention: individual, 6 weeks, 2 sessions of 30 min per week; study groups: digital card games (n=15, age =72.60±9.83), active control: digital dice game (n=14, age= 73.71±9.97); assessments: pre- and post-test; follow-up: 4 months.	Primary outcome: there were improvements in reasoning skills were only in the training group. Traditional board games are perceived as much more enjoyable than traditional strategy training and extensive practice tasks, and this pleasure can ensure greater motivation and adherence of long-lived elderly to video game training; Transfer effects: not mentioned; Long-term effects: yes, after 4 months.
Heinzel et al.[71]	To investigate whether changes induced by training on neuronal activation in older adults reflect increases in processing efficiency, whether transfer effects accompany the overlap of neuronal activation and whether this overlap is related to near- and far-behavioral effects.	n=29; age=60–75; intervention: individual, 4 weeks, 3 sessions of 45 min per week; study groups: WM training (n=15), passive control (n=14); assessments: pre- and post-test.	Primary outcome: WM performance improved with training; Transfer effects: executive functions, processing speed, and fluid intelligence; Long-term effects: not investigated.
Ji et al.[51]	To determine whether inhibition training can stimulate differential plasticity in inhibitory processes (access, exclusion, and contention) and lead to far-transfer to WM skills and Gf related to inhibition, and also to other less related skills.	n=34; age=61–81; intervention: group based, 4 weeks, 3 sessions of 45–60 min per week; study groups: inhibition training (n=18), active control (n=16); assessments: pre- and post-test; follow-up: after 3 months.	Primary outcome: there were performance improvements in all three inhibitory processes trained; Transfer effects: process of exclusion and fluid intelligence; Long-term effects: yes, after 3 months.
Loosli et al.[53]	To investigate whether resistance to PI can be effectively improved by WM training with different PI demands.	n=25; age=68.8±5.5; intervention: group, 2 weeks, 4 sessions of 30 min per week; study groups: high PI (n=14), low PI (n=11); assessments: pre- and post-test; follow-up: after 2 months.	Primary outcome: there was an overall improvement in WM performance in both training groups. Resistance to PI can be reduced in the elderly by short, repetitive WM training; Transfer effects: not investigated; Long-term effects: not investigated.
Toril et al.[59]	To investigate the effects of videogame training on visuospatial WM and episodic memory of health older adults.	n=39; intervention: individual, 7–8 weeks, 15 sessions of 60 min; study groups: memory training (n=19, 70±6.73), passive control (n=20, 73.2±6.5); assessments: pre- and post-test; follow-up: 3 months.	Primary outcome: there was an improvement in performance in all games trained, mainly in visuospatial WM assessment tasks, but also episodic memory and short-term memory; Transfer effects: episodic memory; Long-term effects: yes, after 3 months.
Wilkinson and Yang[48]	To examine long-term maintenance of inhibition training benefits in older adults.	n=56; age=60–84; intervention: individual, 2 weeks, 3 sessions of 30 min per week; study groups: inhibition training with feedback (n=14), with summarized feedback (n=14), without feedback (n=14), passive control (n=14); assessments: pre- and post-test; follow-up: 1 year (n=33) and 3 years (n=26).	Primary end point: the results demonstrate the durability of gains from inhibition training in the elderly for a period of up to 3 years; Transfer effects: not investigated; Long-term effects: yes, within 1 and 3 years.
Borella et al.[32]	To test the efficacy of adaptive WM in older adults and compare its effects with same WM training together with the use of strategy based on construction of visual mental images.	n=54; age=65–75; intervention: individual, 2 weeks, 3 sessions of 30–40 min; study groups: WM (n=18), WM + construction of visual mental image strategy (n=18) and active control (n=18); assessments: pre- and post-test.	Primary outcome: the combination of teaching an effective strategy with a WM training procedure increases WM performance, encouraging the use of efficient strategies that are flexibly implemented; Transfer effects: verbal and visuospatial WM, short-term memory, processing and reasoning speed; Long-term effects: yes, after 6 months.

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Table 1. Continuation.

Authors	Objectives	Methods	Results found
Guye and von Bastian[35]	To investigate training gains and transfer effects after a process-based WM training intervention in older adults.	n=142; age=65–80; intervention: individual, 5 weeks, 5 sessions of 30–45 min per week; study groups: WM training (n=68), active control: visual search training (n=74); assessments: pre- and post-test.	Primary outcome: results suggest that WM training is not an effective way to improve general cognitive functioning in old age; Transfer effects: none; Long-term effects: not investigated.
Heinzel et al.[36]	To investigate whether single-task WM training and training-related alterations in neural activity might support performance in a dual-task setting, thus assessing transfer effects to higher order control processes in the context of dual-task coordination.	n=38; age=60–72; intervention: individual, 4 weeks, 3 sessions of 45 min per week; study groups: WM training (n=18), passive control (n=16); assessments: pre- and post-test.	Primary outcome: the results indicate that 12 N-Back numerical training sessions can improve performance in the trained task; Transfer effects: performance on a dual task; Long-term effects: Not investigated.
Payne and Stine-Morrow[41]	To examine the effects of a CCT on changes in verbal WM and language comprehension in healthy older adults.	n=41; age=61–75; intervention: individual, 3 weeks, 5 sessions of 30 min per week; study groups: WM training (n=22), active control (n=19); assessments: pre- and post-test.	Primary outcome: WM training participants showed improvements in untrained verbal WM tasks and selective improvements in untrained dimensions of language, including sentence memory, verbal fluency, and understanding of syntactically ambiguous sentences. The results suggest that WM is plastic even in old age, at least in the short term; Transfer effects: untrained verbal measures of WM; Long-term effects: not investigated.
Degé and Kerkovius[61]	To investigate the effect of music training on WM (verbal, visual, and central executive processing).	n=24; age=77±4.33; intervention: group based, 15 weeks, 1 session of 60 min per week; study groups: musical training program (n=8), active control (n=7), passive control (n=9); assessments: pre- and post-test.	Primary outcome: the study provides preliminary support for the conclusion that musical training (percussion and singing) may have an influence on verbal and visual WM in old age; Transfer effects: not investigated; Long-term effects: not investigated.
Lebedev et al.[37]	To assess whether solving complex reasoning problems involves the same cognitive processes as solving WM tasks.	n=53; age=65–75; intervention: individual, 4 weeks, 5 sessions of 40 min per week; study groups: WM training (n=27), active control: perceptual correspondence (n=26); assessments: pre- and post-test.	Primary outcome: WM training promoted little improvement in complex reasoning. The use of WM training interventions to try to achieve effects that carry over to broader cognition should be reconsidered; Transfer effects: none; Long-term effects: not investigated.
Simon et al.[44]	To evaluate the efficacy of CCT focused on WM in healthy older adults.	n=82; age=65–89; intervention: individual, 5 weeks, 5 sessions of 60 approx. 40 min per week; study groups: CCT adaptive WM (n=41), active control: CCT nonadaptive WM (n=41), assessments: pre- and post-test.	Primary outcome: adapted WM CCT appears more effective than nonadapted training in older adults of different cultural backgrounds. There was evidence of improvement in trained tasks and in an untrained task of WM and processing speed; Transfer effects: distal transfer in WM (low); Long-term effects: not investigated.
Weicker et al.[55]	To evaluate the efficacy of a CCT WM training program (WOME).	n=60; age=60–79; intervention: group based, 4 weeks, 3 sessions of 45 min per week; study groups: high-level WM (WOME: n=20), active control: low level WM (n=20), passive control (n=20); assessments: pre- and post-test; follow-up: after 3 months.	Primary outcome: WOME led to a significant improvement in WM performance on an untrained transfer task and there was evidence of a positive impact on everyday life; Transfer effects: WM (low); Long-term effects: there were no long-term effects after 3 months.

Continue…

Table 1. Continuation.

Authors	Objectives	Methods	Results found
Borella et al.[30]	To assess gains related to WM training, in short and long term in abilities required in everyday life, and in cognitive measures in old-old adults.	n= 32; age=75–85, intervention: individual, 2 weeks, 3 sessions of 30–40 min; study groups: WM training (n=8), active control (n=14); assessments: pre- and post-test.	Primary outcome: there were specific gains in the CWMS task and in the TIADL in the short term; Transfer effects: solving everyday problems; Long-term effects: yes, at follow-up, gains in CWMS were maintained after 9 months.
Borella et al.[31]	To examine whether music listening together with WM training in healthy older adults could enhance short- and long-term gains in transfer effects of training.	n=72; age= 65–75; intervention: individual, 2 weeks, 3 sessions of 60 min per week; study groups: Mozart WM training (n=19), Albinoni WM training (n=19), white noise WM training (n=16), active control (n=18); assessments: pre- and post-test; follow-up: after 6 months.	Primary outcome: regardless of the listening condition, the trained groups outperformed the control group. The Albinoni group showed greater short-term specific training gains on the CWMS task; Transfer effects: reasoning; Long-term effects: yes, after 6 months.
Matysiak et al.[39]	To investigate the impact of WM training on variety of cognitive tasks performance among older adults and the impact of the initial WM capacity on the training efficiency.	n=84; age=66; intervention: individual, 5 weeks, 5 sessions per week; study groups: WM training (n=42), active control: memory training (n=42); assessments: pre- and post-test.	Primary outcome: there were improvements in WM training and memory in all cognitive tests, except for inhibition and short-term memory; Transfer effects: N-back task (WM and attention) in the elderly; Long-term effects: not investigated.
Schmicker et al.[43]	To examine whether value-based decision-making can be improved in the elderly by CT.	n=31; age=60–75; intervention: group based, 5 days, 1 session of 45 min per day; study groups: attention training (n=12), WM training (n=10) and passive control (n=9); assessments: pre- and post-test.	Primary outcome: attentional filter training improves the performance of older adults in a decision-making task by alleviating disadvantageous behaviors. WM training provided improvement in WM; Transfer effects: none; Long-term effects: not investigated.
Wong et al.[63]	To assess whether learning a new language in older adults is beneficial.	n=235; age=60–85; intervention: group based, 26 weeks, 1 session of 60 min per week; study groups: language training (n=53), active control: computer games (n=51), passive control: music appreciation (n=49); assessments: pre- and post-test; follow-up: after 3 months.	Primary outcome: the study provides preliminary evidence that cognitively engaging activities (foreign language learning and computer games), even only in old age, have the potential to improve cognitive functions in older adults; Transfer effects: not investigated; Long-term effects: yes, after 3 months.
Berggren et al.[60]	To assess whether foreign language learning in older age is a promising avenue for combatting age-related cognitive decline.	n=160; age=65–75 years; intervention: in group, 11 weeks, 2 sessions of 150 min per week; study groups: language training (n=90); passive control (n=70); assessments: pre- and post-test.	Primary outcome: results demonstrate that an initial language course aimed at healthy older adults is unlikely to have any substantial effect on overall cognitive ability; Transfer effects: not investigated; Long-term effects: not investigated.
Ghavidel et al.[34]	To assess the efficacy of a WM training program on visuospatial and verbal WM in older female adults.	n=45; age=60–75; intervention: individual, 14 weeks, 2 sessions of 30–45 min per week; study groups: WM training (n=25), active control (n=20); assessments: pre- and post-test.	Primary outcome: the results support the feasibility of using CCT among elderly women and point to positive results of WM training in their visuospatial and verbal WM; Transfer effects: not investigated; Long-term effects: not investigated.
Guo et al.[62]	To investigate whether a musical instrument training program can improve cognitive function and neural efficiency on fMRI in musically naïve older adults.	n=53; age=61–85; intervention: group based, 16 weeks, 1 session of 60 min per week; study groups: Key-HIT program (n=27), active control (n=26); assessments: pre- and post-test.	Primary outcome: results provide important new insight into training-related plasticity, demonstrating that the Key-HIT program can improve verbal memory and neural efficiency in older adults; Transfer effects: verbal memory; Long-term effects: not investigated.

Continue…

Table 1. Continuation.

Authors	Objectives	Methods	Results found
Maraver et al.[38]	To examine the efficacy of an executive control training focusing on WM and inhibition in healthy older adults.	n=44; age=65.07±3.91; intervention: individual, 4 weeks, 3 sessions of 60 min per week; study groups: WM training and inhibition (n=22), active control (n=22); assessments: pre- and post-test.	Primary outcome: there were specific improvements between sessions, such as processing speed and executive control; Transfer effects: response inhibition; Long-term effects: not investigated.
Kazazi et al.[52]	To investigate the effect of CT on improving WM, selective attention and QoL of elderly people with normal cognitive function.	n=52; age=60+; intervention: group, 12 sessions, 2 sessions of 45 min per week; study groups: CCT ARAM (n=26), active control (n=26); assessments: pre- and post-test; follow-up: 3 months.	Primary outcome: when considering the results of this study, enhancement of specific cognitive domains (selective attention and WM) could improve overall cognition. Transfer effects: quality of life; Long-term effects: yes, after 3 months.

fMRI: functional magnetic resonance imaging; TIADL: timed instrumental activities of daily living; CWMS: Categorization Working Memory Span Task; WM: working memory; N-Back: rapid information updating task, typical for training and assessing WM; CCT: computerized cognitive training; Key-HIT: Keyboard harmonica instrument training; RON: Rise of Nations; BF: Brain Fitness; LE: low ecological (baixa conexão com atividades diárias); HE: high ecological(high connection with everyday activities); Gf: fluid intelligence; PI: proactive interference (reduced recall accuracy and slower reaction time due to previously relevant, but now irrelevant WM content); ARAM: Attentive Rehabilitation of Attention and the Memory; QoL: quality of life; ADLs: activities of daily living.

moderate-to-high score and good-to-excellent quality rating for the articles reviewed. Mean overall score for articles across all categories was 0.81 out of 1.0 in fulfilling Down and Black methodological quality requirements. The breakdown of scores by domain was as follows: reporting 0.95, external validity 0.51, bias/internal validity 0.62, confounding 0.99, and power 0.56 (Table 3).

DISCUSSION

The aim of this study was to investigate and evaluate the effects of WM training on the cognition of healthy elderly people, based on individual and group interventions reported in the literature. A total of 47 eligible studies with a wide range of objectives were selected for review.

As can be seen, the analyzed studies presented a variety of research methods and objectives related to WM training, among which the evaluation of the intervention effects on trained and untrained cognitive skills stands out[28-33,35,39,42,49-52,54,56,71,72]. Transfer effects were mentioned in 36 articles, representing a significance related to the benefits of WM training.

These results corroborate the outcomes identified in the meta-analysis by Karbach and Verhaeghen. The analyses presented by these authors showed that 100% of the evaluated studies whose focus was on WM training presented close or distant transference effects. In this systematic review, 76.5% described at least one observed effect. It should be noted that eight studies did not investigate transfer effects[34,48,50,53,58,60,61,63].

In contrast, three reviewed articles found no transfer effect from WM training[35,37,43]. This outcome was also found in other studies, such as the one by Goghari and Lawlor-Savage[72]. When comparing the effects of WM training with logic and planning training in groups of healthy elderly, the authors found that there was an improvement in the cognitive functions of both groups; however, transfer effects were not observed even in the training focused on WM. As described, the conclusions suggest that some variables interfered in the results, for example, the participants' high cognitive reserve[73].

Cognitive reserve is understood as the use of mechanisms for adaptation and flexibility of cognitive functions in the face of changes caused by the natural or pathological process of cognitive aging. Despite being a characteristic common to all people, some have greater cognitive reserve compared to others. This is due to different variables, the high level of education, and greater involvement in leisure activities, for example, which are associated with greater capacity for cognitive reserve.

Other important factors related to cognitive performance refer to neurogenesis (capacity to form new neurons) and neuroplasticity (formation of new synaptic connections). Like cognitive reserve, both depend on exposure to stimulating factors, such as CT[9].

The improvement in the performance of certain cognitive functions observed in the studies included in this review validates the hypotheses related to cognitive plasticity from training, since healthy elderly people achieved better results in performing activities after undergoing interventions. In this sense, some researchers highlighted the cognitive plasticity observed at the conclusion of their studies, including prefrontal neuroplasticity[13,24,34,41,46,49,51,59]

Table 2. Studies comparing older and younger adults.

Authors	Objectives	Methods	Results found
von Bastian et al.[70]	To investigate whether intensive WM training promotes enhancements in WM and reasoning performance in a YA and OA comparative setting.	n=57 OA, 62–77 years, n=66 YA, 19–36 years; intervention: individual, 4 weeks, 20 sessions of 10 min; study groups: WM training (n=27 OA, n=34 YA), active control (n=30 OA, n=32 YA); assessments: pre- and post-test.	Primary outcome: elderly and mature adults had better WM performance on the trained tasks and on an untrained task, but there was no distal transfer to reasoning. Transfer effects: complex amplitude; Long-term effects: not investigated.
Brehmer et al.[64]	To investigate training gains, transfer effects after and their maintenance after intensive WM CCT in YA and OA.	n=45 OA, 60–70 years, n=55 YA, 20–30 years; intervention: individual, 5 weeks, 5 sessions of 26 min per week; study groups: WM training (n=26 OA, n=29 YA), active control: low level WM (n=19 OA, n=26 YA), assessments: pre- and post-test; follow-up: after 3 months.	Primary outcome: training and transfer gains were slightly greater for YA than for OA on some tasks, but comparable across age groups on others; Transfer effects: distal transfer to sustained attention and activities of daily living; Long-term effects: Yes, after 3 months.
Heinzel et al.[66]	To investigate to what extent WM in OA can be improved by adapted WM training and to compare training gains between YA and AO.	n=30 OA, 60–75 years, n=30 YA, 22–30 years; intervention: individual, 4 weeks, 3 sessions of 45 min per week; study groups: WM training (n=15 OA, n=25 YA), passive control (n=15 OA, n=15 YA); assessments: pre- and post-test.	Primary outcome: the results indicate an improvement in central executive processing that may facilitate WM and dual-task coordination and point out that distal transfer is possible in the elderly; Transfer effects: short-term memory, episodic memory, and processing speed; Long-term effects: not investigated.
Sandberg et al.[68]	To investigate whether an intervention for executive functioning, addressing several basic processes (updating, shifting, and inhibition), can induce transfer effects in YA and OA.	n=30 OA and 29 YA; intervention: group based, 5 weeks, 3 sessions of 45 min per week; study groups: executive process training (n=15 OA, 69.73±5.02/n=16 YA, 26.25±4.01), passive control (n=15 OA, 68.8±4.8/n=13 YA, 24.62±3.4); assessments: pre- and post-test.	Primary outcome: training provided improvements in the lettering task and proximal transfer was observed in numerical updating and inhibition tasks in YA and elderly adults; Transfer effects: update and Inhibit; Long-term effects: not investigated.
Chan et al.[65]	To examine how visuospatial WM training improves finger movement sequential accuracy in YA and OA.	n=22 OA, age=70±4.01, n=26 YA, 21±1.37; intervention: individual, 10 days, 10 sessions of 60 min; study groups: WM training (n=12 OA, n=13 YA), active control (n=10 OA, n=13 YA); assessments: pre- and post-test.	Primary outcome: with CCT of visuospatial WM, there was an improvement in visuospatial WM and the ability to learn finger sequences with visual aids explicitly in YA and OA; Transfer effects: proximal transfer for all facets of WM in general; Long-term effects: not investigated.
Sandberg and Neely[69]	To examine long-term maintenance of training gains and transfer effects in YA and OA after an executive training program (Sandberg et al.,[68]).	n=24 OA and 19 YA; intervention: group based, 5 weeks, 3 sessions of 45 min per week; study groups: executive functions training (n=14 OA, 71.6±5/n=11 YA, 27.5±3), passive control (n=10 OA, 71.2±5.3/n=8 YA, 25.1±3.1); assessments: pre- and post-test; follow-up: 18 months.	Primary outcome: YA improved performance on two complex WM tasks immediately after training; Transfer effects: proximal transfer for a numerical update task; Long-term effects: yes, for a period of 18 months in early and late adulthood.
Rolle et al.[67]	To assess age-related differences in distributed attention and plasticity of this ability in response to CT in YA and OA groups.	n=40 OA, 61–75 years, n=42 YA, 20-28 years; intervention: individual, 2 weeks, 5 sessions of 30 min per week; study groups: spatial attention training (n=20 OA, n=21 YA), active control (n=20 OA, n=21 YA); assessments: pre- and post-test.	Primary outcome: training effects provide evidence that effective attentional allocation can be trained and improved regardless of age and result in the transfer of benefits to an WM task. Transfer effects: WM. Long-term effects: not investigated.

fMRI: functional magnetic resonance imaging; WM: working memory; N-Back: rapid information updating task, typical for training and assessing working memory; OA: older adults; YA: younger adults; CCT: computerized cognitive training.

Table 3. Results of the downs and black checklist for the present systematic review.

Downs and black checklist	n	Mean	Standard deviation	Minimum	Median	Maximum
Reporting score (converted)	47	10.38	0.64	9.00	10.00	1100
External validity score (converted)	47	1.55	0.62	1.00	1.00	3.00
Internal validity and outcome bias score (converted)	47	4.34	0.81	3.00	4.00	7.00
Confounding factors score (converted)	47	5.91	0.28	5.00	6.00	6.00
Power score (converted)	47	0.81	0.06	0.68	0.79	0.96
Overall score (converted)	47	10.38	0.64	9.00	10.00	11.00
Overall score (original, no conversion)	47	22.74	1.80	19.00	22.00	27.00

Regarding the long-term effects after the interventions, 12 studies showed associated results. Effects were noticed after 3[51,59,63,64], 4[58], 6[24,28,32,40], 8[13], 9[49], and 36 months[48]. While two studies did not identify long-term effects after 8[29] and 3[55] months of follow-up. The remaining studies included did not investigate the long-term effects of training.

Five recently published meta-analyses investigated the long-term effects of memory training in healthy older adults[14,16-19], but Hou et al.[18] reported that four of these reviews present important inconsistencies that prevent a specific conclusion on these effects, for example, with the absence of a methodological standard and limitations regarding the reporting of follow-up time of the analyzed studies, which represents a lack of clarity regarding the effects to be long term.

The most recent meta-analysis[18], exploring the objectives, methods, and results of 22 studies, concluded that there was maintenance of long-term effects after WM training, both for shorter periods (<6 months) and for longer periods (>6 months), showing similarities in the observed effects.

In short, the literature is not consistent in reporting transfer effects and long-term effects of WM training in elderly individuals. This literature review, as well as studies by Karbach and Verhaeghen[11] and Hou et al.[18], reported both follow-up effects and untrained skills, while studies by Schwaighofer et al.[19], Teixeira-Santos et al.[16], Sala et al.[14], and Nguyen et al.[17] showed no significant long-term benefits and close or distant transfer effects.

Individual or group interventions

Regarding the methods adopted, there was a prevalence of individual interventions, among which 27 had only elderly people as participants and 7 compared young adults and elderly people. The other studies (13) conducted strategies in groups. No significant differences were observed in the results of the two intervention modalities, with transfer effects and long-term effects in both individual and group interventions.

The benefits associated with individual cognitive intervention are described by Justo-Henriques et al.[74]. According to the authors, individual sessions allow the customization of activities and a greater approach to the participant, which promotes greater engagement. In addition, when performing an individual intervention, the facilitator is able to recognize the specific demands of the individual and focus on training the most compromised skills, favoring the achievement of benefits after the intervention.

Cognitive group training allows for social interactions, which, as mentioned by Ordonez et al.[75], can alleviate social isolation and the perception of loneliness. Engaging in group activities generates benefits for quality of life, well-being, and mental and cognitive health and is even capable of reducing the chances of developing or worsening dementia[76].

Comparison between young adults and seniors

Seven individual WM training studies compared the performance of younger and older adults. The benefits of memory training for both younger and older subjects were reported across all studies; however, training in various executive processes induced fewer transfer effects to the untrained cognitive abilities of older participants.

Although, as already mentioned, based on the results obtained by other studies, the elderly benefit from transfer effects to untrained cognitive skills, theories explain why these effects are more expressive in younger people[77]. The concepts of brain reserve and cognitive reserve are part of this explanation.

While the cognitive reserve is intended for functional adaptations and flexibilities, the brain reserve is related to individual anatomical characteristics. It is these reserves that allow the elderly to compensate for the deficits caused by the aging process or a pathology. When recruiting neural resources, the elderly person may be able to perform tasks in the same way as a young person; however, in tasks that require greater neuronal activation, due to high complexity, compensatory resources tend not to be sufficient, causing differences in performance of young and old[77].

It is also possible to find in the literature hypotheses that the elderly show more significant improvements in cognitive performance after training compared to younger adults[78-80]. The researchers attribute this outcome to the already existing high-performance capacity of young people, which limits the expansion and achievement of even better results.

The differences in the intensity of the transference effects for young and old submitted to WM training found in this review corroborate most of the reviews and meta-analyses carried out with this theme[78-80]. However, a difference was found with the results of the most recent meta-analysis, in which significant transfer effects were found in the elderly compared to the younger ones[11].

Overall, the interventions involving older adults only showed positive effects on cognitive performance, albeit in the form of WM training gains for the target cognitive ability or transfer effects of this type of training, as well as other types of WM-related CT. The studies also reported transfer effects of the training performed to everyday functions in older adults, with consequent improvements in quality of life.

Positive effects were also reported by the studies comparing the performance of older adults with young adults, including the possibility of promoting far-transfer effects in older adults, although contrasting with reported difficulty inducing these effects through training of different executive processes.

Thus, it was concluded that WM training, as well as different types of WM-related CT, can contribute to the maintenance and/or improvement of cognition in older people, recruiting their brain plasticity to promote mental health and prevent cognitive problems which can negatively impact their quality of life.

Limitations of the study include the difficulty performing a more comprehensive review of the wide variety of studies, published within the time window, investigating WM training and directly or indirectly related cognitive skills to determine the efficacy of nonpharmacological interventions aimed at enhancing cognitive performance of older adults.

Therefore, future studies with interventions focusing on specific aspects of WM and executive functions should be conducted in both healthy and cognitively impaired young-old and old-old.

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Neuropsychological findings in migraine: a systematic review

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ABSTRACT. Patients with migraine often experience cognitive dysfunction during a migraine attack, but they have also been reported to complain about cognitive impairment after an attack and during the interictal period. **Objective:** The aim of this study was to determine what neuropsychological test methods are used to assess cognitive functioning in migraine patients and to examine the neuropsychological findings in adult (≥18 years) migraineurs compared to adult (≥18 years) healthy controls (HC). **Methods:** A systematic review was conducted on the literature published between 2012 and the present. The search results were screened and additional studies identified in the lists of references in the selected articles. A total of 16 articles met the inclusion criteria. **Results:** The 16 articles included in the review compared chronic migraineurs (CM), migraineurs with (MwA) and without aura (MwoA), and migraineurs without aura classification (MIG) to HC. A total of 45 neuropsychological assessment methods were identified. CM and MwA were found to perform significantly worse than HC in executive function, attention, and visual functioning. Additionally, both MwA and MwoA performed significantly worse than HC in memory functions. CM and both MwA and MwoA also performed significantly worse than HC in general cognitive functioning. Surprisingly, MIG performed significantly better than HC in several cognitive domains, including executive, motor, and language functioning and general cognitive functioning. **Conclusions:** This systematic review mostly concurs with the results of an earlier systematic review on the topic from 2012, but with the important addition that different migraine diagnostic groups should be assessed separately.

Keywords: Adult; Cognition; Migraine Disorders; Neuropsychological Tests.

ACHADOS NEUROPSICOLÓGICOS NA ENXAQUECA: UMA REVISÃO SISTEMÁTICA

RESUMO. Pacientes com enxaqueca frequentemente apresentam disfunção cognitiva durante uma crise, mas também foram relatadas queixas de comprometimento cognitivo após uma crise e durante o período interictal. **Objetivo:** Determinar quais métodos de testes neuropsicológicos são usados para avaliar o funcionamento cognitivo em pacientes com enxaqueca e examinar os achados neuropsicológicos em adultos (≥ 18 anos) com enxaqueca em comparação com adultos (≥ 18 anos) controles saudáveis (CS). **Métodos:** Foi realizada uma revisão sistemática da literatura publicada entre 2012 e o presente. Os resultados da pesquisa foram selecionados e estudos adicionais identificados nas listas de referências nos artigos selecionados. Dezesseis artigos preencheram os critérios de inclusão. **Resultados:** Os 16 artigos incluídos na revisão compararam enxaqueca crônica (EC), enxaqueca com (EcA) e sem aura (EsA), e enxaqueca sem classificação de aura (E) em CS. Foram identificados 45 métodos de avaliação neuropsicológica. Indivíduos com EC e EcA apresentaram desempenho significativamente pior do que CS em função executiva, atenção e funcionamento visual. Além disso, tanto a EcA quanto a EsA tiveram desempenho significativamente pior do que em CS nas funções de memória. A EC, a EcA e a EsA também tiveram desempenho significativamente pior do que CS no funcionamento cognitivo geral. Surpreendentemente, a E teve um desempenho significativamente melhor do que os CS em vários domínios cognitivos, incluindo o funcionamento executivo, motor e de linguagem e o funcionamento cognitivo geral. **Conclusões:** Esta revisão sistemática concorda principalmente com os resultados de uma revisão sistemática anterior sobre o tema de 2012, mas com o importante adendo de que diferentes grupos diagnósticos de enxaqueca devem ser avaliados separadamente.

Palavras-chave: Adulto; Cognição; Transtornos de Enxaqueca; Testes Neuropsicológicos.

INTRODUCTION

Migraine is a primary headache disease causing moderate-to-severe pain attacks[1]. It differs from tension-type headache in that migraine pain has a unilateral localisation; the pain is pulsating in quality;

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and the intensity of pain varies from moderate to severe. Attacks may last from a few hours to up to 3 days and may be associated with nausea and/or vomiting. Another common symptom of migraine is sensitivity to lights or sounds during attacks[1]. Migraine is classified as having aura symptoms (migraine with aura) if the symptoms listed above are accompanied with fully reversible visual, sensory, speech and/or language, motor, brainstem, or retinal aura. Migraine is diagnosed as chronic when the patient has more than 15 headache days per month and 8 or more of these headaches meet the migraine criteria[1].

In a large population study in the United States, 11.7% of participants over the age of 12 years suffered from migraine[2]. The prevalence of migraine has been reported to be highest in middle life (age 35–45 years), and it is roughly twice or even three times more common in women than in men[2,3]. According to the 2016 Global Burden of Disease Study, it is one of the leading causes of disability globally[4]. Several triggering factors are known to provoke an attack: stress and relaxation after stress, normal female hormonal cycle and changes in it, irregular meals, alcohol, certain odours or foods, low levels of magnesium in brain tissue, or altered levels of signal substances, such as serotonin (5-HT)[5].

In addition to pain and other symptoms, migraine patients have consistently reported cognitive dysfunction during migraine attacks. A 2018 systematic review on cognitive functioning during a migraine attack seems to confirm that cognitive dysfunctions do indeed occur in both the headache phase and the postdrome phase of migraine[6]. The most reported cognitive dysfunctions during a migraine attack were related to concentration problems and difficulties in attention. Lower intellectual capacity or "fog" was also reported[6].

Abnormalities in white matter are common in long-standing and highly frequent migraine, and it seems that they are a result rather than the cause of migraine[7,8]. However, Evans et al.[7] reported that clinically meaningful abnormalities requiring intervention in the migraineur's central nervous system were relatively rare. Kruit et al.[8], in contrast, found that especially migraineurs with aura had a higher prevalence of subclinical infarcts in the posterior circulation and that migraineurs in general had a higher prevalence of brainstem hyperintense lesions. However, in the absence of longitudinal assessments, it is still unclear whether these imaged lesions and abnormalities have relevant functional correlates and whether they can explain possible dysfunctions in a migraineur's cognitive functioning.

If migraine can cause abnormalities in brain tissue[5,7,8], then it is reasonable to assume that migraineurs might perform worse than healthy non-migraineurs on neuropsychological assessment, even during the interictal period. Evidence to this effect would contribute to a better understanding of migraine and the burden it places on the people affected. The most recent systematic review on the effect of migraine on cognition interictally was published in 2012[9]. In this review, de Araújo et al.[9] reported that adult migraineurs performed worse than healthy controls (HC) in the following cognitive domains: memory, attention, information processing speed, and executive function. In memory functions, decline was detected in recognition memory[10], verbal and visual memory[11,12], and working memory[13]. In attention, migraineurs showed declined performance compared to HC in sustained attention[10,11], concentration[14], and verbally supported attention[12]. Additionally, Hooker and Raskin[10] and Zeitlin and Oddy[15] reported decline in information processing speed, while Calandre et al.[16] reported that migraineurs performed worse than HC in visual-motor processing. In executive functions, Meyer et al.[14] reported that migraineurs' capacity to solve problems and judgment changes was declined compared to HC. Furthermore, Mongini et al.[13] reported that migraineurs' ability to plan their actions was declined compared to HC. However, de Araújo et al.[9] did not report their results according to different migraine diagnoses, and therefore, the effects of chronicity and aura symptoms remained unclear. The systematic review in 2012 was also unable to ascertain whether these findings were directly associated with migraine. Therefore, it encouraged further studies with greater methodological refinement[9].

The possible impacts of migraine on cognitive functioning warrant closer investigation, as this could give a clearer picture of the underlying causes of possible cognitive decline. This is especially important in later years of life when cognitive decline can be a symptom of dementia. The effects of migraine on cognitive functions outside attacks have been studied from at least the 1980s[15], but controversy continues to surround the issue.

This study reviews the literature published during the past decade (2012–2021) on the effects of migraine on cognition. Neuropsychological methods play a key part in diagnosing and identifying changes in cognitive functioning. However, there are no global standards on what tests should be used to assess migraineurs' cognitive functioning; as a result, multiple different methods are used. This review focuses on neuropsychological findings in adult (≥18 years) migraineurs. We have two research questions:

- What neuropsychological test methods are used to assess cognitive functioning in migraine patients? and

- What the neuropsychological findings in migraineurs are compared to HC?

METHODS

This systematic review was conducted according to the guidelines for Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2015 statement)[17]. The search was conducted on 13 February 2021, in the following databases: Cinahl, Pubmed MEDLINE, PsycArticles, Ovid PsycINFO, Scopus, and Web of Science. The search terms used were *migraine* combined with *cognition* or *cognitive* and *neuropsychological assessment* or *evaluation* or *test*. The search was limited to the period from 2012 to the present. No language limitations were applied. Detailed search strategies for all the databases are presented in Supplementary material.

The following inclusion criteria were applied:

- studies on patients with migraine (episodic, chronic, and with or without aura) were included if;
- the studies compared adult (≥18 years) migraine patients' cognitive functioning to adult (≥18 years) HC;
- migraine patients' cognitive functioning was assessed in the interictal period; and
- cognitive functioning was assessed with neuropsychological test methods. Single case studies and non-English articles were excluded.

Cluster headache and other types of headache patients were also excluded. Additionally, the reference lists of the articles retrieved from the database were screened for additional studies. The quality of the studies included was appraised with the AXIS Scale[18]. The quality assessment is provided in Supplementary material (Table S1).

RESULTS

The database search yielded 545 articles, of which 159 duplicates were removed. Additionally, 20 articles were retrieved from the reference lists. Out of the 406 articles screened based on title and abstract, 373 were excluded because they did not meet the inclusion criteria. The remaining 33 full texts were assessed for eligibility. A further 17 articles were judged not to meet the inclusion criteria, leaving 16 articles for this systematic review. The exclusion reasons and number of articles excluded based on these reasons are presented in the PRISMA flowchart (Figure 1).

The following data were retrieved from the articles included in the review: patient's diagnostic statuses and diagnostic criteria, sample size, age at examination, gender, neuropsychological assessment methods, and results on the relation of migraine and neuropsychological functioning. The information extracted from the articles is presented in Table 1.

The articles reviewed are also described in Table 1[19-34]. The articles compared HC to patients with different migraine statuses: migraine without aura (MwoA),

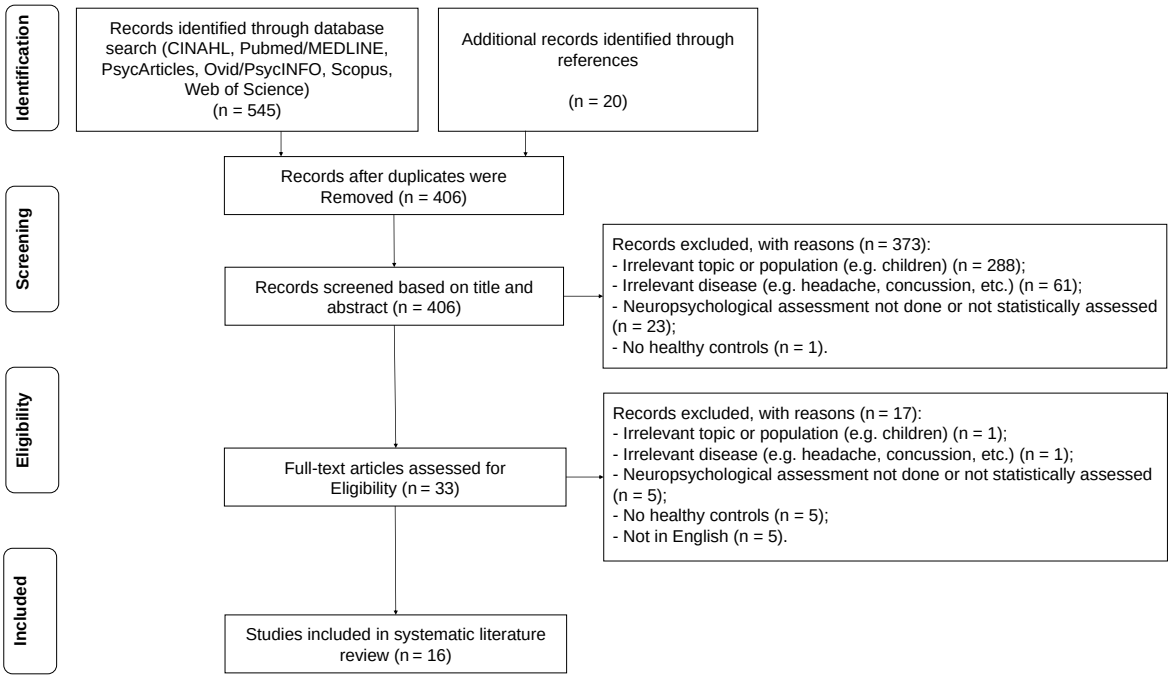

Figure 1. PRISMA flowchart of the systematic literature search.

Table 1. Description of the studies reviewed and the neuropsychological findings comparing migraineurs and healthy controls.

Study	Sample size and migraine diagnosis	Age at examination mean (sd)	Gender (male/ female, n)	Neuropsychological assessment methods	Results on the relation of migraine and neuropsychological functioning
Baschi et al., 2019[19]	Total: n=42 MwoA: n=21 HC: n=21	29.0 (64.3) 27.9 (3.2)	18/24 9/12 9/12	Corsi Test, Buschke Selective Reminding Test, Trail-Making Test (TMT) A and B	MwoA performed significantly better than HC only in tasks evaluating visuospatial memory (short-term p=0.002; long-term p=0.001).
Dresler et al., 2012[24]	Total: n=55 (130)* MIG: n=24 HC: n=31	37.4 (NA) 38.4 (NA)	21/34 5/19 16/15	TMT, Go/No-go Task and Stroop Task	MIG differed significantly from HC only in the Stroop interference task (p=0.04).
Ferreira et al., 2018[27]	Total: n=60 CM: n=30 HC: n=30	33.7 (11.2) 33.7 (9.7)	2/58 1/29 1/29	Montreal Cognitive Assessment (MoCA), Verbal Fluency Test, Stroop Test, Color Trails Test, Wechsler Adult Intelligence Scale (WAIS-III) Digit Span (digits forward), Vocabulary and Matrix Reasoning; Rey Auditory Verbal Learning Test (RAVLT)	CM performed worse than HC in MoCA (p=0.00), Verbal Fluency (p=0.00), Clock Drawing Test (p=0.00), Stroop Test (p=0.01), WAIS-III Digit Span (p=0.00), and WAIS-III Matrix Reasoning (p=0.01). In a linear regression model, CM continued to be an independent factor predicting lower performance compared to HC in Verbal Fluency, Clock Drawing Test, and Stroop Test.
Gil-Gouveia et al., 2016[20]	Total: n=48 MwoA: n=24 HC: n=24	33.3 (7.2)	12/36 6/18 6/18	Finger Tapping, TMT, Stroop Test, Wechsler Memory Scale (WMS-III) – Reverse Digit Span, Phonemic Verbal Fluency, the Aachen Aphasia Test, naming of five compound nouns.	All patients underwent neuropsychological tests twice (average time between tests was 45 days, sd 13.6 days). No significant differences were found between MwoA and HC in performance between first and second evaluation or in test performances between evaluations.
Han et al., 2019[21]	Total: n=64 MwoA: n=32 HC: n=32	38.0 (8.9) 39.1 (11.4)	26/38 12/20 14/18	Mini-Mental State Examination (MMSE), Stroop Test, Shape Trail Test (STT), Attentional Networks Test (ANT)	Significant differences were found only in Stroop III (p=0.03) and STT B (p=0.001). MwoA performed worse than HC. In ANT, MwoA demonstrated significantly longer response times in executive control tasks (p=0.01).
Huang et al., 2017[29]	Total: n=58 MwA; n=10 MwoA: n=24 HC: n=24	36.1 (10.1) 36.1 (13.0)	12/46 6/28 6/18	MoCA, Rey-Osterrieth Complex Figure Test (ROCFT), Digit Symbol Substitution Test (DSST)	Migraineurs performed significantly worse in MoCA total (p=0.007) and in language (p=0.005), executive functions (p=0.042), memory (p=0.006), orientation (p=0.012), and calculation tasks (p=0.018). Migraineurs also performed worse than HC in ROCFT recall (p=0.012).
Le Pira et al., 2014[30]	Total: n=60 MwA: n=12 MwoA: n=32 HC: n=16	42.1 (10.2) 36.7 (9.7) 35.8 (12.6)	11/49 1/11 7/25 3/13	Frontal Assessment Battery (FAB), TMT, Controlled Oral Word Association Test (COWAT), Stroop Test, Boston Scanning Test (BST)	In FAB, MwA performed significantly worse than MwoA (p=0.003) and HC (p=0.0001). In BST, HC performed significantly better than MwA (p=0.0001) and MwoA (p=0.001). In COWAT, a significant difference in performance was reported between HC and MwoA (p=0.001).
Lo Buono et al., 2019[31]	Total: n=150 MwA: n=50 MwoA: n=50 HC: n=50	41.1 (14.1) 38.3 (11.8) 38.2 (11.3)	NA NA NA NA	Attentive Matrices (AT), TMT, RAVLT, Semantic and Phonemic Verbal Fluency	Migraineurs performed worse than HC in RAVLT delayed memory (MwA: p=0.001; MwoA: p=<0.001) and in TMT-B compared to HC (MwA: p=0.005; MwoA: p=<0.001). MwoA performed significantly worse in Semantic Verbal Fluency than HC (p=0.02).
Martins et al., 2012[25]	Total: n=428*(478) MIG: n=61 HC: n=367	61.9 (7.6) 66.8 (9.0)	159/269 5/56 154/213	MMSE, California Verbal Learning Test, WMS-III – visual reproduction and faces I, TMT, Semantic and Phonemic Verbal Fluency, Stroop Test, Digit Span, Symbol Search, Wechsler Abbreviated Scale of Intelligence (WASI) – vocabulary, matrix reasoning, information, Famous Faces Test.	MIG were found to have a significantly lower performance in Symbol Search Test compared to HC (p<0.001). No other statistically significant differences were found between MIG and HC. MIG were significantly younger than non-migraine headache patients and HC and scores from neuropsychological tests were not adjusted by age.

Continue...

Table 1. Continuation.

Study	Sample size and migraine diagnosis	Age at examination mean (sd)	Gender (male/ female, n)	Neuropsychological assessment methods	Results on the relation of migraine and neuropsychological functioning
Baena et al., 2018[32]	Total: n=2466 (4208)* MwA: n=435 MwoA: n=804 HC: n=1227	48.1 (7.2) 49.5 (7.9) 55.3 (9.4)	1075/ 1391 82/353 216/588 777/450	Consortium to Establish a Registry for Alzheimer's Disease Word List Memory Test (CERAD-WLMT), Semantic Fluency Test (SFT), and TMT-B	In CERAD-WLMT, both migraine groups performed significantly worse than HC (p<0.001). After adjusting for gender, age, race, education level, and physical illnesses, no significant differences were found. In SFT, no significant differences were found. In TMT-B, MwA (p=0.005) performed worse than HC. After adjusting, MwoA performed significantly worse than HC (p=0.01; p=0.03).
Padilla et al., 2016[33]	Total: n=63 MwA: n=24 MwoA: n=16 HC: n=23	25.0 (5.8) 27.0 (6.8) 25.0 (4.7) 24.0 (5.0)	17/46 5/19 4/12 8/15	Complutense Verbal Learning Test (TAVEC), ROCFT, Grober and Buschke Free and Cued Selective Reminding Test (FCSRT)	In the ROCFT direct and percentile copy strategy, both migraine groups performed significantly worse than HC (p>0.001). After merging the two migraine groups, the study found significant differences in the ROCFT direct and percentile copy strategy and in direct and percentile recall between migraineurs and HC, with migraineurs performing worse (p=0.001).
Santangelo et al., 2016[22]	Total: n=144 MwoA: n=72 HC: n=72	34.9 (11.2) 33.8 (11.9)	15/129 9/63 6/66	MoCA	Migraineurs performed significantly lower than HC on the total MoCA score (p<0.001) and on attention (p<0.001), memory (p<0.001), visuospatial (p<0.001), and executive domains (p=0.001).
Santangelo et al., 2018[23]	Total: n=175 MwoA: n=91 HC: n=84	33.8 (10.5) 32.3 (10.4)	34/141 16/75 18/66	MoCA, Memory for Intentions Screening Test (MIST)	Migraineurs had significantly lower MoCA scores than HC (p=0.003). In MIST, migraineurs achieved lower scores on time-based (p<0.001) and event-based (p=0.018) tasks than HC.
Wen et al., 2016[26]	Total: n=6420 (6708)* MIG: n=1021 HC: n=5399	63.8 (11.1) 65.9 (11.4)	2675/3645 191/830 2584/2815	MMSE, 15-word Learning Test, Letter–Digit Substitution Test, Stroop Test, Verbal Fluency Test, Purdue Pegboard Test	MwA had the highest mean difference in general cognition compared to HC in MMSE. Migraineurs as a group performed better than HC on the Stroop colour-naming and colour–word interference subtasks. Migraineurs also scored higher on the Verbal Fluency Test and Purdue Pegboard Test. No p-values were presented.
Yetkin-Ozden et al, 2015[34]	Total: n=111 MwA: n=21 MwoA: n=53 HC: n=37	35.3 (12.0) 38.9 (10.5) 36.1 (11.6)	22/89 13/61 9/28	Benton Face Recognition Test (BFRT), Line Orientation Test (LOT)	Migraineurs showed significantly lower performance in both BFRT (p=0.027) and LOT scores (p=0.014) compared to HC. Additionally, MwoA showed significantly lower performance in BFRT than MwA (p=0.031).
Zucca, et al., 2020[28]	Total: n=93 CM: n=37 EM: n=27 HC: n=29	46.1 (11.3) 45.1 (12.2) 42.9 (14.8)	30/63 9/28 9/18 12/17	Wisconsin Card Sorting Test (WCST)	Migraineurs presented worse performance when compared to HC in accuracy score (p=0.012), global monitoring (p=0.015), monetary gains (p=0.022), and control sensitivity (p=0.027). Also, comparing CM to EM patients, CM performed significantly worse in accuracy score (p<0.001), free-choice improvement (p=0.004), global monitoring (p=0.001), monetary gains (p=0.001), and control sensitivity (p<0.001).

CM: chronic migraine; EM: episodic migraine; HC: healthy controls; MIG: migraine (aura not classified); MwA: migraine with aura; MwoA: migraine without aura; NA: not available; *Other participants also included.

migraine with aura (MwA), migraine without the classification of aura symptoms (MIG), chronic migraine (CM), and episodic migraine (EM). MwoA was compared to HC in five studies[19-23], but there were no studies that compared only MwA to HC. Three studies compared MIG to HC[24-26], and two studies compared CM or EM to HC[27,28]. Six studies included patients with both MwA and MwoA and HC[29-34].

The mean quality of the studies included was 16.1 when evaluated with the AXIS Scale[18]. Sample sizes ranged from 42 to 6,420 participants. Most of the studies had 175 participants or fewer. Participants' mean age ranged from 27.0 to 48.1 years in MwA patients, from 25.0 to 49.5 years in MwoA patients, from 37.4 to 63.8 years in MIG patients, and from 33.7 to 46.1 years in CM patients. The mean age of HC ranged from 24.0 to 66.8 years. One study also included EM patients, whose mean age was 45.1 years[28]. All studies except Lo Buono et al.[31] reported the gender distribution of the participants. In all studies, females accounted for more than half of the participants: the proportion of female migraineurs varied from 57.1 to 99.7%. The gender distribution for HC was similar: the proportion of female participants varied from 46.7% to 96.6%.

Migraine and migraine status were mainly diagnosed using the *International Classification of Headache Disorders* (*ICHD*) third edition (beta version, 2013)[19-23,27,29,31,33] or second edition (2004)[24,26,30,32,34-36]. Zucca et al.[28] used the *ICHD-III* (2018)[1] and Martins et al.[25] used the ID-Migraine[37] to diagnose migraine and migraine status.

All neuropsychological test methods used in the articles reviewed are presented according to cognitive domain in Table 2[19-34,38-70]. In the 16 articles, the cognitive performance of migraineurs and HC was assessed

Table 2. Neuropsychological test methods used to assess cognition according to cognitive domain.

Cognitive domain	Neuropsychological test	Articles in which the test method was used
Executive functions and attention	The Attentional Networks Test (ANT)[38]	Han et al., 2019[21]
	The Attentive Matrices (AT)[39]	Lo Buono et al., 2019[31]
	The Boston Scanning test[40]	Le Pira et al., 2014[30]
	The Color Trail Test[41]	Ferreira et al., 2018[27]
	The Digit Symbol Substitution Test (DSST)[29]	Huang et al., 2017[29]
	The Frontal Assessment Battery (FAB)[42]	Le Pira et al., 2014[30]
	The Go/No-go Task[43]	Dresler et al., 2012[24]
	The Letter-Digit Substitution Test[44]	Wen et al., 2016[26]
	The Memory for Intentions Screening Test (MIST)[45]	Santangelo et al., 2018[23]
	The Rey-Osterrieth Complex Figure Test (ROCFT)[46,47]	Huang et al., 2017[29]; Padilla et al., 2016[33]
	The Shape Trail Test (STT)[21]	Han et al., 2019[21]
	The Stroop Test[48]	Dresler et al., 2012[24]; Ferreira et al., 2018[27]; Gil-Gouveia et al., 2016[20]; Han et al., 2019[21]; Le Pira et al., 2014[30]; Martins et al., 2012[25]; Wen et al., 2016[26]
	The Trail-Making Test A and B[49]	Baschi et al., 2019[19]; Dresler et al., 2012[24]; Gil-Gouveia et al., 2016[20]; Le Pira et al., 2014[30]; Lo Buono et al., 2019[31]; Martins et al., 2012[25]; Baena et al., 2018[32]
	The Wechsler Adult Intelligence Scale (WAIS-III) – Digit Span, forward[50]	Ferreira et al., 2018[27]; Martins et al., 2012[25]
	The Wechsler Memory Scale III (WMS-III) – The Reverse Digit Span[51]	Gil-Gouveia et al., 2016[20]
	The Wisconsin Card Sorting Test (WCST)[52]	Zucca et al., 2020[28]
Memory	The Grober and Buschke Free and Cued Selective Reminding Test[53]	Padilla et al., 2016[33]
Visual memory	The Corsi Test[54]	Baschi et al., 2019[19]

Continue...

Table 2. Continuation.

Cognitive domain	Neuropsychological test	Articles in which the test method was used
	The Wechsler Memory Scale III (WMS-III) – Visual Reproduction[50]	Martins et al., 2012[25]
Verbal memory	The 15-Word Learning Test[26]	Wen et al., 2016[26]
	The Buschke Selective Reminding Test[55]	Baschi et al., 2019[19]
	The California Verbal Learning Test (CVLT)[56]	Martins et al., 2012[25]
	The Complutense Verbal Learning Test (TAVEC)[57]	Padilla et al., 2016[33]
	The Consortium to Establish a Registry for Alzheimer's Disease Word List Memory Test (CERAD-WLMT)[58]	Baena et al., 2018[32]
	The Rey Auditory Verbal Learning Test (RAVLT)[59]	Ferreira et al., 2018[27]; Lo Buono et al., 2019[31]
Language function	The Aachen Aphasia Test, naming of five compound nouns[60]	Gil-Gouveia et al., 2016[20]
	The Controlled Oral Word Association Test (COWAT)[61]	Le Pira et al., 2014[30]
	The Phonemic Verbal Fluency[62]	Gil-Gouveia et al., 2016[20]
	The Semantic Fluency Test[63]	Baena et al., 2018[32]
	The Semantic and Phonemic Verbal Fluency[25,31]	Lo Buono et al., 2019[31]; Martins et al., 2012[25]
	The Verbal Fluency Test[26,27]	Ferreira et al., 2018[27]; Wen et al., 2016[26]
Language function	The Wechsler Abbreviated Scale of Intelligence (WASI) – Information[64]	Martins et al., 2012[25]
	The Wechsler Abbreviated Scale of Intelligence (WASI) – Vocabulary[64]	Martins et al., 2012[25]
	The Wechsler Adult Intelligence Scale (WAIS-III) – Vocabulary[50]	Ferreira et al., 2018[27]
Visual function	The Line Orientation Test (LOT)[65]	Yetkin-Ozden et al., 2015[34]
	The Wechsler Abbreviated Scale of Intelligence (WASI) – Matrix Reasoning[64]	Martins et al., 2012[25]
	The Wechsler Adult Intelligence Scale (WAIS-III) – Matrix Reasoning[50]	Ferreira et al., 2018[27]; Martins et al., 2012[25]
	The Wechsler Adult Intelligence Scale III (WAIS-III) – Symbol Search[50]	Martins et al., 2012[25]
Facial recognition	The Benton face recognition test (BFRT)[66]	Yetkin-Ozden et al., 2015[34]
	The Famous Faces Test[25]	Martins et al., 2012[25]
	The Wechsler Memory Scale III (WMS-III) – Faces 1[51]	Martins et al., 2012[25]
Motor function	The Finger Tapping Test[67]	Gil-Gouveia et al., 2016[20]
	The Purdue pegboard Test[68]	Wen et al., 2016[26]
General screening tests	Mini-Mental State Examination (MMSE)[69]	Han et al., 2019[21]; Martins et al., 2012[25]; Wen et al., 2016[26]
	Montreal Cognitive Assessment (MoCA)[70]	Ferreira et al., 2018[27]; Huang et al., 2017[29]; Santangelo et al., 2016[22]; Santangelo et al., 2018[23]

with a total of 45 different neuropsychological test methods, addressing different cognitive domains. These neuropsychological test methods are divided into the following cognitive domains: executive functions and attention, memory, language functions, visual functions, and motor functions. Memory functioning tests were further divided into general memory, visual memory, and verbal memory functioning. Also, a subcategory of facial recognition was added in the visual functions category. Some studies furthermore applied general cognition screening tests. Arithmetic functions were not assessed in any of the studies.

In addition to descriptive facts about the articles included in the review, Table 1 presents the main neuropsychological findings for each article. Overall, the articles reported contradictory findings on all migraine groups compared to HC. The clearest differences were seen in executive functions, attention, and verbal memory, where especially MwA performed worse than HC. For CM, the clearest differences compared to HC were reported in executive functions and attention[27,28]. Even though some differences were also reported in other cognitive domains, no firm conclusions can be drawn about the performance of CM compared to HC in these domains. Across the various fields of cognition, almost all articles reported no significant differences between MIG and HCs. In contrast, MIG actually performed significantly better than HC in executive, motor, and language functioning and, in general, cognitive functioning[25,26].

Comparisons of MwA to HC also yielded contradictory results. The clearest differences were reported in executive functions, attention, and verbal memory. No significant differences were reported between MwA and HC in language functions[30-32]. A significantly worse performance was reported for MwA than HC in both visual functioning and general cognitive functioning[29,34]. Additionally, it was reported that MwA performed significantly worse than MwoA in executive and visual functions[34]. Comparisons of MwoA and HC yielded no clear conclusions on any of the cognitive domains, except general cognitive functioning[21-23].

DISCUSSION

The aim of this systematic review was to determine what neuropsychological test methods are used to assess cognitive functioning in migraine patients and to explore the neuropsychological findings in migraineurs compared to HC. The review included 16 articles which compared adult (≥18 years) CM, EM, MIG, MwA, and/or MwoA to adult (≥18 years) HC using neuropsychological test methods.

The articles used a wide range and a large number of neuropsychological test methods: a total of 45 different tests were applied in the articles included in this systematic review. The fields of cognition that received the most attention were executive functioning and attention, which were studied in 14 articles with 16 different test methods[19-33]. The most commonly used methods were executive functioning and attention tests, the Stroop test, and the Trail-Making test. The least studied field of cognition was motor functioning, which was tested with two different tests[20,26].

The neuropsychological findings were quite diverse. The clearest differences were reported between CM and HC and between MwA and HC in executive functioning. In memory functioning, MwA were reported to perform significantly worse than HC in verbal memory[31,32], but the comparisons between MwoA and HC yielded less conclusive results[19,31,32]. All migraine groups were reported to perform worse than HC in visual functioning, but no firm conclusions can be drawn because of the sporadic results[27,34]. Additionally, migraineurs quite consistently performed worse than HC on general cognitive functioning[22,23,27,29]. For language and motor functioning, however, differences between migraine groups and HC were not reported consistently enough and possible differences were rarely reported. Surprisingly, MIG performed significantly better than HC in several cognitive domains: executive, motor, and language functioning and general cognitive functioning[25,26]. It is also notable that MwA were reported to perform significantly worse than MwoA in executive and visual functions[34].

In the most recent systematic review on the subject from 2012, de Araújo et al.[9] reported that migraineurs performed worse than HC in the following cognitive domains: memory, attention, information processing speed, and executive function. The results of this review seem to be quite closely in line with this, since the clearest differences were seen in executive functions, attention, and memory. However, de Araújo et al.[9] did not report the results according to different migraine diagnoses. It has been shown that the severity of abnormalities imaged in the brain can be affected by the length and frequency of the migraine disease and by the presence of aura symptoms[8]. Therefore, migraineurs who suffer from chronicity and aura symptoms might have more severe neuropsychological dysfunctions, and this is why we have chosen to report the results of neuropsychological assessments according to migraine diagnosis. This proved to be a justified decision as we found that MwA and MwoA differed from each other in two cognitive domains[34]. Furthermore, CM was reported to differ from EM in one cognitive domain[28]. Although differences between migraine groups are not commonly reported, these few differences underscore the importance of studying migraine groups separately.

This systematic review furthers our understanding of the effects of migraine on cognition and shows how the subject has been studied over the past decade. It provides evidence on which cognitive domains are potentially affected by migraine and sheds light on the neuropsychological test methods that could be used — and currently are being used — to assess migraineurs' cognition in the interictal phase. Drawing from several databases, the review comprises a reasonable number of articles that were selected based on titles, abstracts,

and full texts. This provides a strong foundation for drawing meaningful conclusions. Having said that, it is important to note that the large number of test methods used in the articles makes direct comparisons between the studies rather difficult. Even though all studies assessed migraineurs' cognition in a clinical setting, not all of the test methods used can be regarded as equally applicable. For example, the Mini-Mental State Examination (MMSE), which was used by Han and colleagues[21], Martins et al.[25], and Wen et al.[26], has been criticized for its lack of sensitivity to detect minor cognitive changes[71].

The participants in the studies included in the review differed in terms of their demographic characteristics. The age and gender distributions varied across the studies, and a few studies reported that their migraineurs and HC were not demographically matched. Martins et al.[25] reported that their migraineurs were significantly younger, lower educated, and scored higher on a depression scale than HC and that they did not adjust the test scores by age. In a few studies, migraineurs were also reported to score higher on anxiety and depression than HC[21,29,32]. Such differences are only to be expected as migraine has been found to be comorbid with several psychiatric conditions, especially affective and anxiety disorders and even bipolar disorder[72-74]. Some studies reported that psychiatric disorders – for example, anxiety – negatively impacted cognitive functioning[75,76]. It is also noteworthy that some studies had quite small sample sizes or varying sample sizes in different groups of participants, which limits the validity of correlation analysis[24,25,29,33,34]. More carefully selected participant groups and larger sample sizes are needed to obtain more accurate or comparable results.

The aim of this systematic review was to determine what neuropsychological test methods are being used to assess cognitive functioning in migraine patients and to examine the neuropsychological findings in adult migraineurs compared to HC. The finding suggests that CM might be at higher risk of cognitive dysfunction, especially in the domains of executive function, attention, and visual functioning. Similar results were reported for MwA, as MwA were found to perform worse than HC, especially in the domains of executive function, attention, memory, and visual function. It is also suggested that MwoA might be at higher risk of cognitive dysfunction, especially in memory functioning. Based on our systematic review, it is not possible to draw any firm conclusions regarding the cognitive functioning of MIG.

This review concurs with the results of an earlier systematic review on the topic but makes the important addition that different migraine diagnostic groups should be assessed separately. It also concludes that more research is needed on the neuropsychological findings associated with migraine and that, in this work, greater focus should be given to ensuring the demographic consistency of the participant groups, larger sample sizes, and a more careful choice of neuropsychological test methods in order to ensure statistical quality and comparability. Migraine is known to be one of the leading global causes of disability, a major burden on health care systems, and a source of substantial financial and social losses. It has profound adverse effects on the economy more generally and on the everyday lives and quality of lives of people who live with migraine. The possible impact of migraine on cognitive functioning warrants further research, especially in the case of aging migraineurs in later years of life, which is why it is important to continue to pursue a deeper understanding of the disease.

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Working memory assessment using Cambridge neuropsychological test automated battery can help in the diagnosis of mild cognitive impairment:

a systematic review and meta-analysis

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ABSTRACT. Mild cognitive impairment (MCI) is an interstitial state between normal aging and dementia. **Objective:** In this study, we investigated working memory (WM) profiles of MCI patients using the Cambridge Neuropsychological Test Automated Battery (CANTAB). We also examined the diagnostic accuracy and possible associated factors as secondary outcomes of the study. **Methods:** We conducted an electronic search on EMBASE, PubMed, and ScienceDirect databases. Studies with MCI participants and using CANTAB battery subtests for the assessment of WM were included. Meta-analysis was conducted using the CMA2 software. **Results:** Out of 1537 records, 14 studies were covered in this systematic review, and 7 of them were included in the meta-analysis. There was a significant difference between MCI patients and healthy controls in spatial working memory (SWM) (SDM: 0.535; 95%CI 11–96; p-value=0.014), spatial span (SSP) (SDM: 0.649 95%CI 0.297–0.100; p-value<0.01), and rapid visual information processing (RVP) (SDM: 0.52; 95%CI 0.386–0.654; p-value<0.01). WM function of MCI patients was associated with the cerebrospinal fluid (CSF) levels of tau-protein and amyloid-beta (Aβ). **Conclusions:** WM is an impaired cognitive domain in MCI. CANTAB WM subtests including SSP, SWM, and RVP are accurate enough to be used as a proper assessment tool for the diagnosis of MCI in clinical settings. Tau-protein and Aβ are associated with lower WM scores in MCI patients; however, sex, age, psychiatric disorders, apolipoprotein 4 allele, and functional activity scores cannot affect WM.

Keywords: Cognitive Dysfunction; Memory, Short-Term; Neuropsychological Tests; Systematic Review; Meta-Analysis.

A AVALIAÇÃO DA MEMÓRIA DE TRABALHO USANDO A BATERIA AUTOMATIZADA DO *CAMBRIDGE NEUROPSYCHOLOGICAL* TEST PODE AJUDAR NO DIAGNÓSTICO DE COMPROMETIMENTO COGNITIVO LEVE: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

RESUMO. O comprometimento cognitivo leve (CCL) é um estado intersticial entre o envelhecimento normal e a demência. **Objetivo:** Neste estudo, investigamos os perfis de memória de trabalho (MT) de pacientes com CCL usando a bateria automatizada de testes neuropsicológicos de Cambridge (*Cambridge Neuropsychological Test Automated Battery* – CANTAB). Também examinamos a acurácia diagnóstica e possíveis fatores associados como desfechos secundários do estudo. **Métodos:** Foi realizada uma busca eletrônica nas bases de dados EMBASE, PubMed e ScienceDirect. Foram incluídos estudos com participantes com CCL e utilizando subtestes da bateria CANTAB para avaliação da MT. A meta-análise foi realizada usando o software CMA2. **Resultados:** Dos 1.537 registros, esta revisão sistemática abordou 14 estudos, e 7 deles foram incluídos na meta-análise. Houve uma diferença significativa entre pacientes com CCL e controles saudáveis na memória de trabalho espacial (MTE) (DPM: 0,535; IC95% 11–96; valor p=0,014), spatial span (SSP) (SDM: 0,649; IC95% 0,297–0,100; valor p<0,01) e processamento rápido de informação visual (PRV) (DPM: 0,52; IC95% 0,386–0,654; valor p<0,01). A MT de pacientes com CCL foi associada com os níveis de proteína tau e beta-amiloide (Aβ) no líquido cefalorraquidiano (CSF). **Conclusões:** A MT é um domínio cognitivo prejudicado no CCL. Os subtestes CANTAB WM, incluindo SSP, MTE e PRV, são precisos o suficiente para serem usados como uma ferramenta de avaliação adequada para o diagnóstico de CCL em ambientes clínicos. A proteína Tau e Aβ estão associadas a pontuações de MT mais baixas em pacientes com CCL; entretanto, sexo, idade, transtornos psiquiátricos, alelo da apolipoproteína 4 e escores de atividade funcional não podem afetar a MT.

Palavras-chave: Disfunção Cognitiva; Memória de Curto Prazo; Testes Neuropsicológicos; Revisão Sistemática; Metanálise.

This study was conducted by the Neurosciences Research Center of Tabriz University of Medical Sciences, Tabriz, Iran.

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INTRODUCTION

Mild cognitive impairment (MCI) is known as a transitional state between normal aging and dementia in the age continuum in which patients experience memory loss more than healthy age-matched older adults, but do not fulfill defined criteria for dementia diagnosis[1]. Based on manifestations and disease course, MCI includes different subtypes: amnestic or non-amnestic MCI and single- or multiple-domain MCI[2]. The amnestic MCI is typically associated with an increased risk of conversion to Alzheimer's disease (AD); however, non-amnestic subtypes, which may progress to non-AD dementias, may also evolve to AD[3].

Several studies have estimated the prevalence of MCI from 12 to 18% in older people over the age of 60 years[4-8]. With the global increase in life expectancy, early diagnosis and precise application of disease-modifying treatments for MCI have turned into a priority for the health systems[9,10]. Previous studies following MCI patients for 6 years found that 80% of patients progress to AD with an annual rate of 10–15%[1,11], which is 10-fold higher than the conversion rate in the normal population[12].

Several cognitive domains such as learning, short- and long-term memory, social cognition, language, perceptual motor, complex attention, or executive functioning are characteristically affected by the pathogenesis of AD along with disease progression[13,14]. Working memory (WM) can be defined as a component of short-term memory with a restricted capacity that depends on central executive functions and attention, utilizing stored information and linking them to long-term memory[15]. Unlike short memory which provides short-term storage of information, WM has been proposed as a multicomponent structure that stores incoming information and operates them to a more complicated cognitive function[16-18]. WM is highly associated with daily functioning abilities[19] and has shown an explicit linear decreasing relationship with age[20,21] so it can be used as a measure for early diagnosis of dementia[22].

Previous studies have shown impairment of WM in the early stage of dementia[23-26], which makes it a good factor for early diagnosis of the disease and prevention of disease progression. Classic paper-pencil tests like Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) are widely being used for the assessment of MCI[27]; however, these tests have shown some serious drawbacks with standardization of administration, the accuracy of response measurement, and demographic factors, importantly years of education and illiteracy[28-31].

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computerized neuropsychological test with a game-like and non-verbal environment that assesses the different cognitive domains like memory, attention, executive functions, learning, and problem-solving[32]. Among various subtests of CANTAB, spatial span (SSP) and spatial working memory (SWM) account for the assessment of WM[33-35]. Also, rapid visual processing (RVP) accounts for sustained attention and target detection that has a small WM component that is sensitive to parietal and frontal lobe dysfunction[36].

In this systematic review and meta-analysis study, we aimed to study the WM function in MCI patients using CANTAB to determine the severity of WM impairment in MCI patients, as the primary outcome, and compare it with healthy matched older adults, to define the diagnostic accuracy of WM profiles of CANTAB in the detection of MCI. Also, as another secondary outcome, we investigated the associated factors of WM function in MCI patients.

METHODS

This study was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[37]. This systematic review was designed to assess the WM function in MCI patients using the CANTAB, and the meta-analysis was conducted to compare the differences between MCI and healthy participants in WM subtests of the CANTAB.

Search

Two independent researchers (Z.S. and A.N.) conducted a systematic literature search on EMBASE, PubMed, and ScienceDirect databases combining the keywords "Cognitive dysfunction, cognitive decline, cognitive impairment, mental deteriorations, mild cognitive impairment, CANTAB, Cambridge Neuropsychological Test Automated Battery, neuropsychological test, working memory, immediate memory, short-term memory," on December 16, 2020. For the sake of comprehensiveness, the references of each included study were checked for any additional related papers.

Study selection

Search results were imported to the EndNote reference manager. After deleting duplicated studies, two independent authors (Z.S. and A.N.) started screening and selecting papers by title/abstract in the first stage and full text in the second stage. In case of any conflicts, investigators tried to convince each other or ask for a third expert researcher's comment (M.T. or M.F.).

Inclusion criteria were as follows:

1. Original journal articles,

2. MCI diagnosis at the baseline based on the clinical criteria,
3. Using CANTAB subtests that evaluate WM, and
4. Studies in English.

Exclusion criteria were as follows:
1. Studies in other languages, and
2. Other types of articles such as review articles, editorials, letters,
3. Conference abstracts, and
4. Animal studies.

Data extraction

Data were extracted by two independent authors (Z.S. and A.N.) in a pre-specified format using a data extraction table, including the name of the first author of the study, publication year, study design, the overall number of participants as well as the number of patients in each group of the study, mean age, years of education, diagnostic criteria, MMSE score, mean and standard deviations (SD) of CANTAB WM subtests in MCI group and the healthy control group, and finally associated and non-associated factors with WM function. We could not examine amnesic and non-amnesic subtypes separately since they were not described in most of the included articles. The online version of Web Plot Digitizer was used for extracting the exact values from the graphs. Extracted data were reviewed by a third author (M.T. or M.F.) and, in case of any disagreements about results, it was determined between authors or by a judgment of a third author.

Risk of bias in individual studies

The risk of bias (RoB) and methodological quality were evaluated (by Z.S. and A.N. separately) with Joanna Briggs Institute (JBI) checklist that contains eight questions, evaluating inclusion criteria, detailed study subjects and setting, the validity of exposure, the standard measurement of the condition, and the outcome, identifying and dealing with confounding factors and statistical analysis[38].

Statistics

In this study, meta-analysis was performed using comprehensive meta-analysis (CMA) version 2.0. The confidence interval was considered at 95% and 0.05 level of significance for the p-value. Studies that used SWM total errors, SSP length, as well as A' or latency measures of RVP subtest of CANTAB in MCI patients and healthy control group were included in the quantitative analysis. The I^2 model was also utilized for assessing the level of heterogeneity among included studies. Whenever any of the studies had reported data for MCI by subgroups (subjective MCI, amnestic MCI, single-domain MCI, multiple-domain MCI), we merged them using an excel code. The mean, SD, and the number of the individuals in each group were imported into CMA, and both the random-effect model (REM) and fixed-effect model (FEM) were utilized for assessing the difference between the groups. Also, the results of the study were reported in funnel plots in Supplementary Material.

RESULTS

Search results and selection process

The electronic search identified 1,235 records through databases and 655 records added from other resources. After removing duplicates, 1,537 records were screened, and 1,434 records were excluded. Out of 66 studies that were assessed in the full-text stage, 14 studies were included in this systematic review, and 7 of them met our inclusion criteria for the meta-analysis. The PRISMA flow diagram is presented in Figure 1. Table 1[10,33,39-50] is a summary of the characteristics and findings of included studies.

Characteristics of the studies and participants

Five of included studies were cross-sectional and nine were cohorts. Only baseline data of the cohort studies are taken into account. In sum, 930 out of 1670 participants were diagnosed with MCI, and 527 were healthy controls. The mean age of the participants was between 55 and 75 years. The years of education varied from 7 to 14, and the male ratio varied between 8 and 56%.

MCI diagnosis

In this study, most of the researchers used MMSE for the diagnosis of MCI, and the rest of the studies used the other tests or criteria, such as Petersen criteria, MOCA, Rey Auditory Verbal Learning Test, and Dementia Rating Scale.

CANTAB tests for WM

Regarding the tests for WM in CANTAB, 11 of the included studies reported SWM, and 9 of them reported SSP for assessing WM. As mentioned before, RVP has a small WM component and was used in nine of our included studies. Only one study reported that used delayed matching to sample (DMS) subtest of CANTAB as an assessment tool for WM.

Factors associated with WM in MCI

In terms of factors associated with WM functions of MCI patients, sex, age, psychiatric disorders such as

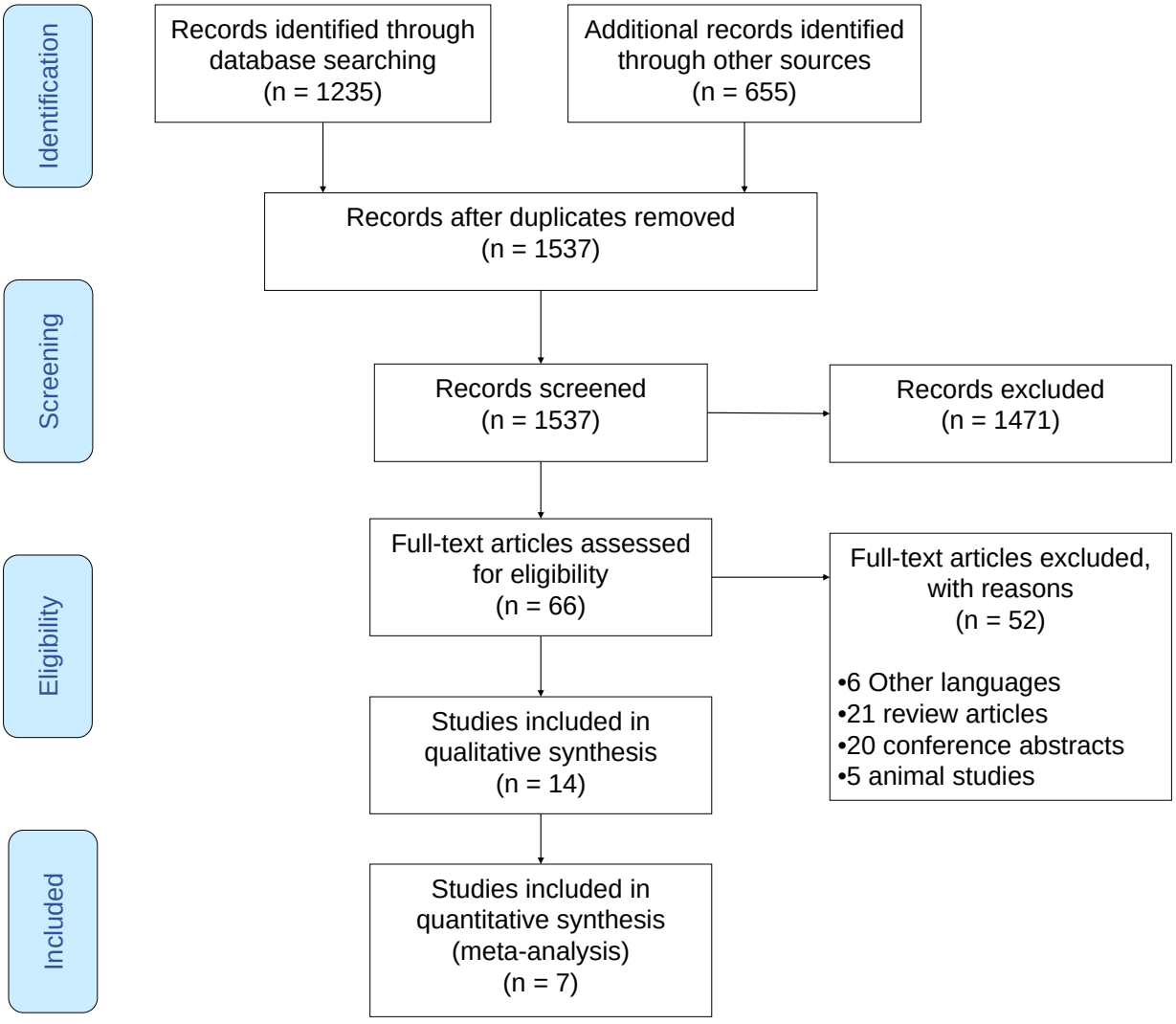

Figure 1. PRISMA flow diagram.

depression, apolipoprotein 4 (ApoE4), and functional activity scores were not significantly correlated to CANTAB WM scores, while a higher cerebrospinal fluid (CSF) levels of tau-protein and amyloid-beta (Aβ) were associated with a lower function in WM tests.

Meta-analysis

Out of 14 included studies, 3 of them did not include any healthy participants for control group and 4 others did not report our intended component of CANTAB subtests to be included in the quantitative synthesis; hence, they were excluded from the meta-analysis. Seven remaining studies were included in the meta-analysis. The forest plots of the meta-analyses are shown in Figures 2–4. The quantitative synthesis of studies using CANTAB subtests to assess WM showed a significant difference between MCI and healthy controls in SWM (REM SDM: 0.535; 95%CI 0.110–0.960; p=0.014, FEM SDM: 0.450; 95%CI 0.270–0.630; p<0.01; test for heterogeneity I^2: 81.28%; p<0.01), SSP (REM SDM: 0.649; 95%CI 0.297–1.000; p<0.01, FEM SDM: 0.510 95%CI 0.654–0.365; p<0.01; test for heterogeneity I^2: 82.76%; p<0.01), and RVP (REM SDM: 0.481; 95%CI 0.316–0.647; p<0.01, FEM SDM: 0.52; 95%CI 0.386–0.654; p<0.01; test for heterogeneity I^2: 46.49%; p=0.05). Also, RVP A' (REM SDM: 0.583; 95%CI 0.244–0.922; p<0.01, FEM SDM: 0.590; 95%CI 0.401–0.870; p<0.01; test for heterogeneity I^2: 67.87%; p=0.01) and RVP latency (REM and FEM SDM: 0.449; 95%CI 0.259–0.639; p<0.01; test for heterogeneity I^2: 0%; p=0.50) were significantly different between patients with MCI and healthy controls.

Table 1. Characteristics and summary of findings of included studies.

Author (year)	Study design	Sample size	Mean age	Education	Male ratio (%)	MMSE score	Eligibility criteria MCI	Eligibility criteria-control	CANTAB subtests for WM	MCI			Control			Associated factors	Non-associated factors
										Mean	SD	n	Mean	SD	n		
Nathan et al. 2017[40]	Cross-sectional	145	68.2±7.37	46.9% above 10 years of education	42.8	26.6±1.9 (24 to 30)	Age 55–90 years; subjective memory complaint verified by a family relative; at least 1 standard deviation deficit in a measure of episodic memory; an MMSE score of 24–30; a CDR scale score of 0.5 (with a score of 0.5 for the memory subscale); a clinical diagnosis of amnestic MCI, but preservation of general cognitive and functional performance to no meet clinical criteria for AD; GDS scale score <6; and Hachinski Modified Ischemic Scale score ≤4		SWM between errors	27.7	8.3					Aβ42, total tau, p-tau, hippocampal volume	Age, GDS, NPIQ, FAQ, MMSE, education, sex, APOE4
									SWM strategy	19.9	2.4						
									DMS % correct (all delays)	67.9	16.3						
									RVP A'	0.8	0.1	145					
Saunders and Summers et al. 2010[41]	Cross-sectional	131	Control: 69.32±5.83 S-MCI: 71.16±7.08 A-MCI: 71.18±7.02	Control: 13.56±3.14 S-MCI: 13.00±3.52 A-MCI:13.13±3.35	48.09	-	Memory problems, with a history of decline from a former level; preserved cognitive functioning; intact activities of daily living; no history of significant medical, neurological, or psychiatric condition; no history of major risk factors for vascular disease; and no history of alcohol abuse, sensory impairment, or impairment of hand mobility.	No cognitive complaints or medical history, participants with matched mean age and level of education	SWM total errors (S-MCI)	42.06	15.05	32	33.68	13.08	25	Age, WTAR (a-MCI), DRS II (a-MCI), BNT (a-MCI), RAVLT trial 5 recall (a-MCI), RAVLT delayed (a-MCI)	Education, sex, WTAR (S-MCI), WAIS-II FSIQ, GDS, PAL, DRS II (S-MCI), BNT (S-MCI), RAVLT trial 5 recall (S-MCI), RAVLT delayed (S-MCI)
									SWM total errors (A-MCI)	51.82	15.15	60					
									SSP length (S-MCI)	5.20	0.69	32	5.80	0.76			
									SSP length (A-MCI)	4.96	0.64	60					
									RVP A' (S-MCI)	0.86	0.05	32	0.93	0.04			
									RVP A' (A-MCI)	0.87	0.05	6					
									RVP latency (S-MCI)	530.70	123.75	32	447.50	77.51			
									RVP latency (A-MCI)	519.68	123.57	60					
Egerházi, et al. 2017[42]	Cross sectional	40	55±6	-	47.5	28±0.6	No neurological symptoms or other physical disorders, amnestic MCI diagnosis according to the criteria of Petersen, CDR= 0.5, mild short-term memory loss, with symptoms insufficient for the diagnosis of dementia according to the criteria of the DSM-IV, MMSE≥26, normal CT/MRI, No medication intake		SWM (Z-score)	-0.8871			-	-	-	-	-
									SSP (Z-score)	-0.755			-	-	-		
									RVP (Z-score)	-2.101		25	-	-	-		
Collie et al. 2002[39]	cohort	46	Control: 65.94±5.37 MCI: 67.82±7.75	Control: 12.37 ±3.78 MCI: 11.64±3.86	45.65	28.12±1.42	Age >50 years, no psychiatric and neurological diagnosis. Exclusion criteria at this stage included a history of respiratory, circulatory, or endocrine disease, personal or family history of psychiatric illness, head injury or substance abuse. MCI based on CERAD neuropsychological battery		SWM Total errors	33.33	15.81	23	25.19	12.24	23	CERAD (word list recall and learning)	Age, sex, education, MMSE, depression, CERAD, APOE4, CFQ, WMS-R, state and trait anxiety test, and NART
									SWM Strategy score	17.04	3.24	23	15.15	2.57	23		
									SSP task score	4.74	1.05	23	5.38	0.90	23		
Facal et al. 2014[43]	Cross sectional	145	MDA-MCI: 70.34±9.49 SDA-MCI: 67.62±9.40 Control: 67.36±9.09	MDA-MCI: 9.54±3.77 SDA-MCI: 9.23±4.10 CONTROL: 10.22±5.05	37.93	MDA-MCI: 22.86±1.65 SDA-MCI: 27.00±1.81	MMSE >20, no history of clinical stroke, traumatic brain injury, motor sensory defects, alcohol, or drug abuse/dependence, not diagnosed with any significant medical or psychiatric illnesses, GDS <10.		SSP Correct items (MDA-MCI)	21.76	7.09	44	25.86	6.80	58	MMSE, WAIS vocabulary, memory complaints, CAMCOG (language, attention) CVLT	Age, education, occupational, complexity, vocabulary, frequency of reading, leisure and cultural activities, social participation
									SSP Correct items (SDA-MCI)	26.00	6.71	43					

Continue...

Table 1. Continuation.

Author (year)	Study design	Sample size	Mean age	Education	Male ratio (%)	MMSE score	Eligibility criteria MCI	Eligibility criteria-control	CANTAB subtests for WM	MCI			Control			Associated factors	Non-associated factors
										Mean	SD	n	Mean	SD	n		
Juncos-Rabadán et al. 2014[44]	Cross sectional	170	MDA-MCI: 71.06±8.36 SDA-MCI: 68.96±8.60 MDNA-MCI: 66.78±8.56 Healthy control: 68.16±8.75	MDA-MCI: 10.18±4.09 SDA-MCI: 9.52±4.08 MDNA-MCI: 7.96±3.77 Healthy control: 9.35±4.62	-	MDA -MCI: 23.40±1.58 SDA -MCI: 27.50±1.50 MDNA-MCI: 24.53±2.35	No prior diagnosis of dementia, psychiatric or neurological disorders, severe illness, deafness or blindness, not receiving chemotherapy, not consumers of substances or alcohol, informant-corroborated memory complaints, performance of 1.5 SDs below age norms on the Spanish version of (CVLT), no significant or minimal impact on activities of daily living assessed by the Lawton and Brody Index, not demented according the NINCDS-ADRDA and DMS-IV criteria. Normal or corrected-to-normal vision and hearing and visual acuity	Scored higher than the cutoff point in memory, general cognitive functioning, and specific cognitive tests, no history of clinical stroke, traumatic brain injury, motor-sensory defects, alcohol or drug abuse/ dependence, and no diagnosis of any significant medical or psychiatric illnesses. Normal or corrected-to-normal vision and hearing and visual acuity	SSP length (MDA-MCI)	4.40	0.83	32	4.77	0.67	54	Memory complaints (informant), MMSE, CVLT Language, Attention, calculation, Praxis	Age, education, Visual acuity
									SSP length (SDA-MCI)	4.65	0.80	57					
									SSP length (MDNA-MCI)	4.45	0.83	32					
									SSP total errors (MDA-MCI)	11.93	3.97	32	11.68	3.97			
									SSP total errors (SDA-MCI)	11.60	3.96	57					
									SSP total errors (MDNA-MCI)	11.66	5.25	32					
									SSP time to last response (MDA-MCI)	9063.22	4845.18	32	6429.49	1666.14			
									SSP time to last response (SDA-MCI)	6698.75	2526.20	57					
									SSP time to last response (MDNA-MCI)	7892.75	2674.63	32					
Summers and Saunders et al. 2012[33]	cohort	106	Control: 69.36±5.8 Stable MCI: 71.04±7.1 Progressed MCI:* 73.80±7.9	Control: 13.64±3.1 MCI: 12.55±3.0 Progressed: 14.60±3.5	46.25	-	Memory problems with a history of decline; preserved cognitive functioning; intact activities of daily living; no history of significant medical, neurological, or psychiatric condition; no history of major risk factors for vascular disease; and no history of alcohol abuse, sensory impairment, or impairment to hand mobility	No cognitive complaints or medical history of significance, control group was matched to the mean age level of education of the MCI groups.	SSP length (Stable MCI)	4.84	0.69	25	5.84	-0.75	25	WTAR	Age, education, FSIQ, DRS, sex, RAVLT, BNT
									SSP length (progressed)	4.70	0.82	10					
									SWM total errors (stable MCI)	50.24	18.46	25	32.92	12.95			
									SWM total errors (progressed)	45.90	9.18	10					
									RVP A'(stable MCI)	0.864	0.04	25	0.939	0.04			
									RVP A' (progressed)	0.820	0.05	10					
Klekociuk and Summers et al. 2014[45]	cohort	118	60–90	-	38.98	-	No previous medical, neurological, or psychological conditions, no evidence of dementia, AEMSS score ≥9, preserved activities of daily living, subclinical impairment as a performance 1.28 standard deviations or greater below age-appropriate normative references.	No previous medical, neurological, or psychological conditions, no evidence of dementia, AEMSS score ≥9, preserved activities of daily living. No evidence of subclinical impairment.	SSP length (a-MCI)	5.55	0.91	22	5.20	0.84	49	RAVLT, DRS-2, FSIQ, digit span, WAIS–III, LNS	Age, education, sex, HADS Depression
									SSP length (na-MCI)	4.72	0.74	25					
									SSP length (a-MCI+)	4.68	0.72	22					
									SWM total errors (a-MCI)	20.73	17.78	22	29.16	18.37			
									SWM total errors (na-MCI)	30.52	17.31	25					
									SWM total errors (a-MCI+)	38.18	17.08	22					
									SWM strategy (a-MCI)	29.64	6.87	22	30.41	6.88			
									SWM strategy (na-MCI)	33.52	5.85	25					
									SWM strategy (a-MCI+)	33.23	6.02	22					
									RVP latency (a-MCI)	407.08	90.50	22	469.34	9.30			
									RVP latency (na-MCI)	542.48	109.6	25					
									RVP latency (a-MCI +)	522.95	155.29	22					

Continue...

Table 1. Continuation.

Author (year)	Study design	Sample size	Mean age	Education	Male ratio (%)	MMSE score	Eligibility criteria MCI	Eligibility criteria-control	CANTAB subtests for WM	MCI			Control			Associated factors	Non-associated factors
										Mean	SD	n	Mean	SD	n		
Cacciamani et al. 201[84]6	cohort	25	MCI-AD: 68.58±6.65 MCI-ambiguous: 68.69±7.75	MCI-AD†: 10±3.94 MCI-ambiguous: 9±4.01	40	27.04±0.31	Age between 55 and 80 years, presence of subjective memory complaints, presence of memory impairment as documented by scoring at least 1 SD below cutoff point on the Logical Memory II subscale (delayed recall) from the WMS; Preserved or slightly impaired functional abilities on FAQ, not responding to diagnostic criteria for dementia, MMSE≥24, CDR score of 0.5, GDS <6, Hachinski Modified Ischemic scale ≤4, at least 5 years of formal education		SWM Strategy (overall MCI)	37.44	0.72	25		-		Total-tau, phospho-tau	Age, sex, education, FAQ score, Aβ42, CDR, MMSE, FAQ, GDS, Hachinski Modified Ischemic Scale, Logical Memory II, Mental Deterioration Battery, RAVLT
									SWM strategy (MCI-AD)	38.17	0.95	12					
									SWM strategy (MCI-ambiguous)	36.77	1.06	13					
									SWM errors (overall MCI)	53.96	4.25	25					
									SWM errors (MCI-AD)	59.92	5.73	12					
									SWM errors (MCI-ambiguous)	48.46	6.04	13					
									RVP A' (overall MCI)	0.81	0.02	25					
									RVP A' (MCI-AD)	0.81	0.03	12					
									RVP A' (MCI-ambiguous)	0.82	0.01	12					
Reijs et al. 2017[10]	cohort	263	68.3±9.1	10.4±4.5	56	25.5±3.9	Memory clinic referral for the evaluation of cognitive complaints, age >60 years, a MMSE-score >19, one or more cognitive impairments on neuropsychological tests according to Petersen's criteria, and no clinical diagnosis of dementia.	Age >40, MMSE >the 10th percentile according to age- and education-adjusted local norms, no cognitive impairment on neuropsychological tests	SWM errors	29.6	8.8	73	19.2	10.0	46	Age, sex, education, MMSE, CDR, Aβ42, t-tau, wordlist learning and delayed recall and recognition, animal fluency	FAQ
Klekociuk and Summers et al. 2014[47]	cohort	122	a-MCI: 70.61±7.99 na-MCI: 70.58±5.97 a-MCI+‡: 69.26±6.56 Control: 72.66±6.52	a-MCI: 14.43±3.16 na-MCI: 14.92±3.52 a-MCI+: 12.48±3.53 Control: 14.20±3.74	39.34	-	Presence of cognitive complaints (e.g., memory, attention); preserved general cognition (as assessed by the DRS-2; self-reported capacity to maintain independent daily functioning (confirmed by an informant); no history of major medical, neurological, or psychiatric illness); no history of major risk factors for vascular disease and no history of sensory impairment or impairment to hand mobility.		SWM total errors)a-MCI(	20.29	17.77	23	29.42	18.52	50	WTAR (FSIQ), DRS-2, Digit Span (forward and backward)	Hospital Anxiety and Depression Scale, LNS, Age, education, HADS, Letter-Number Sequencing total, Digit Symbol Coding
									SWM total errors)na-MCI(	32.04	18.83	26					
									SWM total errors)a-MCI+(	36.63	18.96	23					
									SSP length (a-MCI)	5.52	0.91	23	5.19	0.84			
									SSP length (na-MCI)	4.73	0.71	26					
									SSP length (a-MCI+)	4.74	0.71	23					
									RVP latency (a-MCI)	482.92	112.31	23	468.04	89.73			
									RVP latency (na-MCI)	545.36	108.20	26					
									RVP latency (a-MCI+)	519.02	152.07	23					
									RVP A' (a-MCI)	0.90	0.047	23	0.902	0.042			
									RVP A' (na-MCI)	0.87	0.05	26					
									RVP A' (a-MCI+)	0.85	0.047	23					

Continue...

Table 1. Continuation.

Author (year)	Study design	Sample size	Mean age	Education	Male ratio (%)	MMSE score	Eligibility criteria MCI	Eligibility criteria-control	CANTAB subtests for WM	MCI			Control			Associated factors	Non-associated factors
										Mean	SD	n	Mean	SD	n		
Saunders and Summers et al. 2011[48]	cohort	106	Control: 69.19±5.75 na-MCI: 71.41±7.22 a-MCI: 70.96±6.85	Control: 13.50±3.09 na-MCI: 13.17±3.50 a-MCI: 13.04±3.39	-	-	Memory problems with a history of decline; preserved cognitive functioning; intact activities of daily living; no history of significant medical, neurological, or psychiatric condition; no history of major risk factors for vascular disease; no history of alcohol abuse, sensory impairment, or impairment to hand mobility		SWM strategy (a-MCI)	37.61	23.56	52	35.42	15.29	26	RAVLT trial 5, DRS-2 AEMSS, RAVLT, GDS, BNT	Age, education, WTAR, FSIQ
									SWM strategy (na-MCI)	38.23	10.71	29					
									SWM errors (a-MCI)	50.50	14.56	52	33.39	12.84			
									SWM total errors (na-MCI)	43.59	14.75	29					
									SSP length (a-MCI)	4.90	0.57	52	5.82	0.76			
									SSP length (na-MCI)	5.22	0.69	29					
									RVP latency (a-MCI)	513.33	126.19	52	445	76.48			
									RVP mean latency (na-MCI)	529.58	125.63	29					
									RVP A'(a-MCI)	0.87	0.07	52	0.93	0.05			
									RVP A'(na-MCI)	0.85	0.05	29					
Stonsaovapak et al. 2020[49]	cohort	45	MCI: 68.39±8.37 Control: 68.39±8.37	-	8.88	-	MCI diagnosis based on the criteria of the MCI Working Group of the European Consortium on Alzheimer's disease, age between 45 and 90 years, with a TMSE score of >23, (MoCA)-Thai score of <25		SWM between errors	53.48	13.10	23	51.45	14.81	22		age, sex, educational, TMSE score, MoCA
									SWM total errors	55.39	13.31		52.64	15.51			
									RVP mean latency	2.77	0.12		2.72	0.11			
									RVP total hits	10.61	5.23		13.68	4.57			
Campos-Magdaleno et al. 2021[50]	cohort	208	Control: 64.26±8.83 MCI-stable: 70.94±7.54 MCI-worsened: 75.44±7.14	Control: 10.28±4.71 MCI-stable: 9.15±3.40 MCI-worsened: 9.30±4.79	35.13	Control: 28.34±1.34 MCI-stable: 25.13±2.89 MCI-worsened: 24.04±2.53	No previous diagnosis of MCI or dementia, clinical stroke, traumatic brain injury, motor-sensory defects, alcohol or drug abuse/dependence, or any neurological or psychiatric disease. Self-reported, informant corroborated concerns about cognition, 1.5 SDs below age and education norms in one or more cognitive domains in CAMCOG-R except for memory, assessed by CVLT, no significant or minimal impact on activities of daily living	No previous diagnosis of neurologic disorders, normal adults in general functioning and specific domain tests, attending primary care health centers with self-reported cognitive concerns; confirmation of these concerns by the short Spanish version of the questionnaire for subjective memory complaints	SSP (MCI-stable)	4.5	2.82	32	5.00	3.84	149	age, Lawton-Brody, SCC, Praxis CAMCOG-R, MMSE, CVLT	Gender, education, CCI
									SSP (MCI-worsened)	3.9	3.27	27					

*In this study, "Progressed" is used for the participants who were classified at baseline as a-MCI or na-MCI but were reclassified as a-MCI following the 20-month assessment; †Subjects with mild cognitive impairment and Alzheimer's disease like CSF profiles; ‡MCI+ defined as multiple domains amnestic mild cognitive impairment in this study; CANTAB: Cambridge Neuropsychological Test Automated Battery; MMSE: Mini-Mental State Examination; WM: working memory; MCI: mild cognitive impairment; SWM: spatial working memory; SSP: spatial span; RVP: rapid visual information processing; DMS: delayed matching to sample; S-MCI: subjective MCI; A-MCI: amnestic MCI; NPIQ: Neuropsychiatric Inventory Questionnaire; FAQ: Functional Activities Questionnaire; APOE: apolipoprotein; Aβ: amyloid-beta; SDA-MCI: single-domain MCI; CFQ: Cognitive Failures Questionnaire; MDA-MCI: multiple-domain amnestic MCI; MNDA-MCI: multiple-domain non-amnestic MCI; GDS: Geriatric Depression Scale; BNT: Boston Naming Test; TMSE: Thai Mental State Examination; MoCA: Montreal Cognitive Assessment; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CAMCOG: Cambridge Cognitive Examination; CVLT: California Verbal Learning Test; DRS: dementia rating scale; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey Complex Figure Test and Recognition Trial; FSIQ: Full Scale Intelligence Quotient; WTAR: Wechsler test of adult reading. CCI: Charlson Comorbidity Index; DSP: Digit Span; WAIS–III: Wechsler Adult Intelligence Scale, 3rd edition; LNS: Letter–Number Sequencing; MMSE: Mini Mental State Examination; CDR: Clinical dementia rating; FAQ: the Functional Assessment Questionnaire; WMS: Wechsler Memory Scale; SMCQ: subjective memory complaints questionnaire; SD: standard deviation, NINCDS-ADRDA: the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; TMSE: Thai mental state examination; MOANS: Mayo Older American Normative; AEMSS: age- and education-corrected MOANS scaled scores (AEMSS) score.

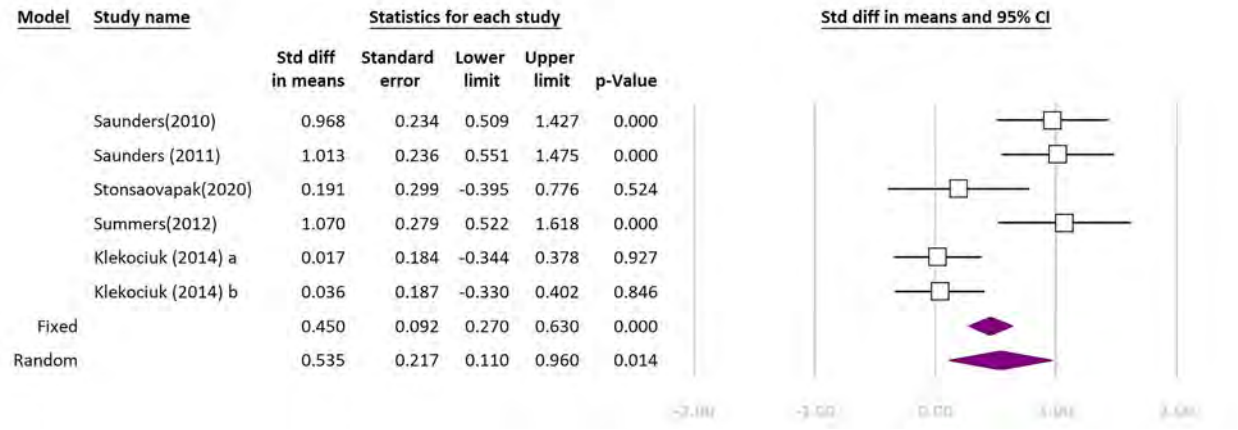

Figure 2. Meta-analysis of comparing patients with mild cognitive impairment and healthy controls based on "total errors" measure of spatial working memory (SWM) test of Cambridge Neuropsychological Test Automated Battery. The purple indicator is the final result. (Test for heterogeneity: I^2: 81.28%; p<0.01).

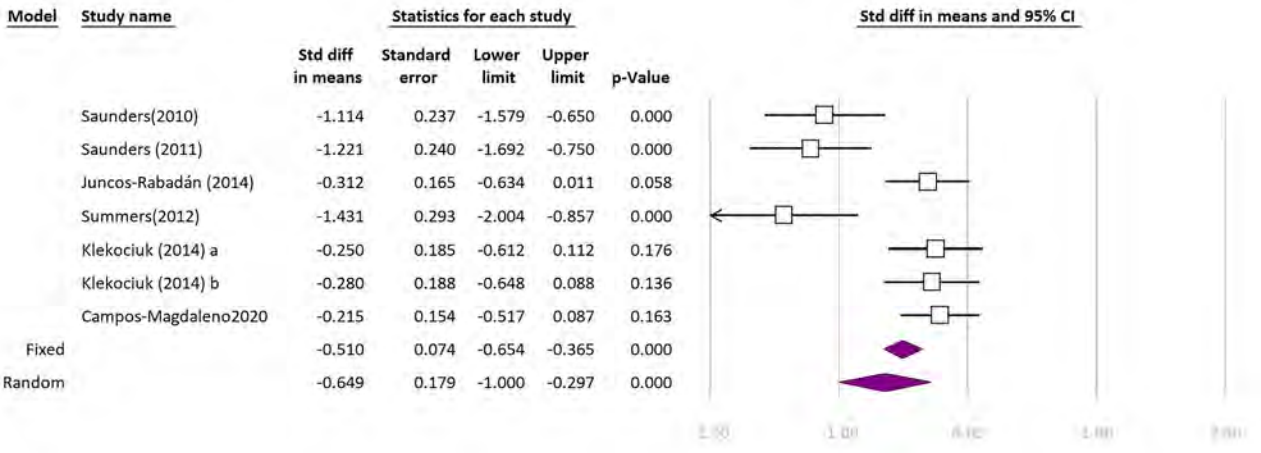

Figure 3. Meta-analysis of comparing patients with mild cognitive impairment and healthy controls based on "length" measure of spatial span (SSP) test of Cambridge Neuropsychological Test Automated Battery. The purple indicator is the final result. (Test for heterogeneity: I^2: 82.76%; p<0.01).

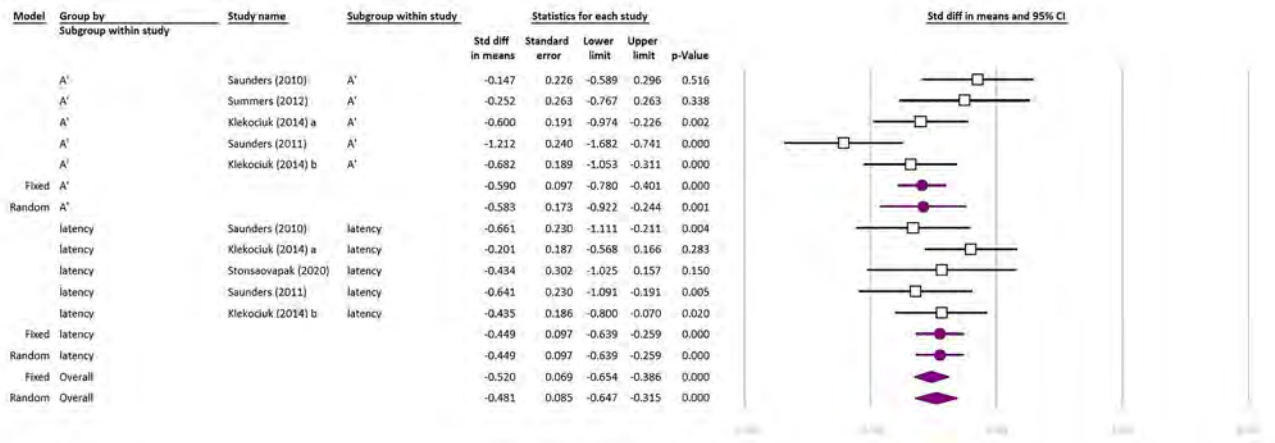

Figure 4. Meta-analysis of comparing patients with mild cognitive impairment and healthy controls based on "A' and mean latency" measures of Rapid Visual Processing (RVP) test of Cambridge Neuropsychological Test Automated Battery. The purple indicators are the final results. (Test for heterogeneity: overall I^2: 46.49%; p-value=0.05; A' I^2: 67.87 %; p=0.01; Latency I^2: 0%; p=0.50).

Risk of bias

The results of the RoB assessments are shown in Table 2 [10,33,39-50]. There was not any exposure studied in our systematic review; so, the third question of the checklist, which assessed the validity of the exposure measurement, was not applicable. Furthermore, we only considered MMSE, Petersen, and MoCA as standard index tests for MCI diagnosis. Because of that, the overall rate of standard measurement of conditions was low. Besides, only 35.7% of the studies mentioned the setting properly. Briefly, there were no considerable levels of bias in most of the included studies.

DISCUSSION

This study assessed the WM function of patients with MCI and compared it between MCI patients and healthy people using the CANTAB. Also, influencing factors on WM were considered. SWM, SSP, and RVP were the most commonly used subtests of CANTAB for assessing the WM. The results of quantitative synthesis revealed a significant difference between healthy controls and patients with MCI regarding the CANTAB-based WM assessments. Also, the available evidence suggested a significant correlation between CSF levels of tau-protein and Aβ with WM function in patients with MCI.

One of the preclinically deteriorated domains in AD and MCI is WM[21,51,52]. WM comprises a cognitive spectrum from attention allocation to specific stimuli to complex decision-making. Some studies have suggested WM as an early predictor of AD[53]. Regardless of the method of assessment, WM function is found to significantly deteriorate in MCI[24,54]. WM is subdivided into verbal and visual components[55]. Emrani et al. found that the visual component of WM is more sensitive than verbal WM, for distinguishing between MCI patients and healthy older adults[56]. Align with the aforementioned study, our quantitative synthesis reveals that the WM of MCI patients based on SWM, SSP, and RVP is impaired significantly, so it can be suggested as a proper diagnostic evaluation for MCI.

CANTAB is a novel neuropsychological battery for evaluating cognitive state. This battery has shown promising outcomes in the diagnosis of cognitive function in healthy older adults, MCI, AD, or any other possible diseases that may compromise cognition[32,57]. It has several benefits over traditional paper-pencil tests, such as reducing the risk of human error and data noise, recording reaction times precisely, lowering data storing problems, easing task scoring, and having access to normative comparison[32,58]. Also, CANTAB has a non-verbal structure that makes it more convenient for people with different languages[59,60]. Regarding the

Table 2. Results of risk of bias assessment.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Nathan et al., 2017[40]	Yes	No	NA	Yes	Yes	Yes	Yes	Yes
Saunders and Summers, 2010[41]	Yes	No	NA	No	Yes	No	Yes	Yes
Égerházi et al., 2007[42]	No	No	NA	Yes	Yes	Yes	Yes	No
Collie et al., 2002[39]	Yes	No	NA	Yes	Yes	Yes	Yes	Yes
Facal et al., 2014[43]	Yes	No	NA	Yes	Yes	Yes	Yes	Yes
Juncos-Rabadán et al., 2014[44]	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes
Summers and Saunders, 2012[33]	Yes	No	NA	No	Yes	No	Yes	Yes
Klekociuk and Summers, 2014[45]	Yes	Yes	NA	No	Yes	Yes	Yes	Yes
Cacciamani et al., 2017[46]	Yes	No	NA	Yes	Yes	Yes	Yes	Yes
Reijs et al., 2017[10]	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes
Klekociuk and Summers, 2014[47]	Yes	Yes	NA	No	Yes	Yes	Yes	Yes
Saunders and Summers, 2011[48]	Yes	No	NA	No	Yes	Yes	Yes	Yes
Stonsaovapak et al. 2020[49]	No	No	NA	No	Yes	Yes	Yes	Yes
Campos-Magdaleno et al., 2020[50]	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes
Overall	85.7%	35.7%	NA	57.1%	100%	85.7%	100%	92.8%

NA: not applicable.

disadvantages, CANTAB is a time-consuming test, and providing the test instruments, imposes an extra cost to the clinicians, which limits its usage in resource-limited settings. The accuracy of WM tests of CANTAB battery in distinguishing between MCI patients and healthy older adults was studied in our review and CANTAB has shown to be a proper battery for MCI diagnosis.

As a secondary outcome of the study, we assessed related factors with WM function in MCI patients. Aging is one of the confirmed predictors of cognitive decline[61]. Although WM function is found to be affected by age[62], in most of our included studies, age was not associated with the WM scores of the patients. This may be because most of the participants in our study were older people while there is a need for the participation of patients with a wider age range to survey the age differences.

The relation between CSF biomarkers and cognitive state is one of the interest areas for research. Soldan et al. in a cohort study investigated the performance of cognitively healthy adults on CANTAB-PAL and found that it was associated with CSF p-tau levels[63]. This study suggested that the AD-related CSF biomarker can predict specific cognitive dysfunctions. In our included studies, Aβ and tau-protein were associated biomarkers with WM functions of MCI patients. On the contrary, ApoE4, which is one of the most studied genetic factors associated with human cognition and one of the well-known predictors of AD[64], was not associated with WM function of MCI patients, as reported in two studies[39,40].

This study is a novel and unprecedented review of WM assessment of MCI patients with CANTAB. One of the challenges related to this study was that the included studies did not report the sensitivity and specificity of CANTAB for the diagnosis of WM deficits in MCI patients. This should be considered in future studies. The other related limitation was that the included studies used heterogeneous criteria for baseline diagnosis of MCI; thus, the results cannot be generalized to all of the considered populations. Nevertheless, a comprehensive review of available evidence with a systematic approach was the main strength of this study.

This study reveals that WM is an impaired cognitive domain at MCI. Based on our assessment, WM subtests of CANTAB, including SWM, SSP, and RVP, can pinpoint deficits in MCI patients, so CANTAB-based WM assessment can help the clinicians in the diagnosis of MCI. Also, WM functions of MCI patients are associated with some of the AD-associated biomarkers, such as tau-protein and Aβ. There is a need for future well-designed studies on this topic to reach a comprehensive conclusion in terms of both diagnostic accuracies of WM profiles of CANTAB battery and factors that can affect the WM in MCI patients.

Authors' contributions. ZS, MF: These two authors contributed equally to this work and both of them should be considered as shared co-first authorship. ZS: formal analysis, investigation, project administration, resources, writing – original draft. MF: formal analysis, investigation, project administration, resources, writing – original draft. AN: formal analysis, investigation, project administration, resources, writing – original draft. MT: conceptualization, validation, writing – review & editing.

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Original Article

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Prevalence of cognitive impairment in Brazilian indigenous community from Amazonas

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ABSTRACT. Studies on the prevalence of dementia in the indigenous population are still scarce worldwide. In the few available studies, prevalence evidence varies from low to very high, with early onset of the disease and high mortality rate after the initial diagnosis. Still, little is known about the rate of dementia in indigenous populations from low- and middle-income countries, where the dementia prevalence in the general population is estimated to increase significantly in the next decades. **Objective:** This study aimed to determine the prevalence of cognitive impairment and associated factors in Brazilian indigenous people of the Mura ethnicity in Amazonas, Brazil. **Methods:** A total of 217 indigenous individuals aged 50 years and older from Amazonas, Brazil, were submitted to cognitive assessment. Attention, memory, verbal fluency, visuospatial performance, and mood state composed the cognitive impairment diagnosis. **Results:** The prevalence of cognitive impairment was 43.3% (95%CI 36.6–49.7) and varied according to age [OR=1.03 (95%CI 1.00–1.06)], education [OR=0.74 (95%CI 0.62–0.87)], body mass index [OR=0.91 (95%CI 0.83–0.98)], and income [OR=0.52 (95%CI 0.27–0.99)]. **Conclusions:** Cognitive impairment had an early onset in an indigenous community, and its prevalence was greater in older individuals with low education and low family income. These findings highlight the importance of implementing public indigenous health policies focusing on health professional training for early cognitive impairment detection.

Keywords: Cognitive Dysfunction; Dementia; Population Groups; Epidemiology; Prevalence.

PREVALÊNCIA DE COMPROMETIMENTO COGNITIVO EM INDÍGENAS BRASILEIROS DO AMAZONAS

RESUMO. No mundo, estudos sobre a prevalência de demência em idosos indígenas são insuficientes, porém nas evidências disponíveis, a prevalência varia de baixa a muito alta, com início precoce da doença e elevada taxa de mortalidade após o diagnóstico inicial. As evidências em países de baixa e média renda são escassas, e neles a prevalência de demência aumentará significativamente nas próximas décadas. **Objetivo:** Determinar a prevalência de déficit cognitivo e fatores associados em indígenas brasileiros da etnia Mura no Amazonas, Brasil. **Métodos:** Duzentos e dezessete indígenas com 50 anos ou mais do Amazonas, Brasil, foram submetidos a avaliação cognitiva. Atenção, memória, fluência verbal, desempenho visuoespacial e estado de humor compuseram o diagnóstico de déficit cognitivo. **Resultados:** A prevalência de déficit cognitivo foi de 43,3% (intervalo de confiança — IC95% 36,6–49,7) e variou de acordo com a idade [*odds ratio* — OR=1,03 (IC95% 1,00–1,06)], educação [OR=0,74 (IC95% 0,62–0,87)], índice de massa corporal [OR=0,91 (IC95% 0,83–0,98)] e renda [OR=0,52 (IC95% 0,27–0,99)]. **Conclusões:** O comprometimento cognitivo teve início precoce na comunidade indígena, sendo sua prevalência maior em idosos com baixa escolaridade e baixa renda familiar. Esses achados destacam a importância da implementação de políticas públicas de saúde indígena, com foco na formação de profissionais de saúde, para a detecção precoce do déficit cognitivo.

Palavras-chave: Disfunção Cognitiva; Demência; Grupos Populacionais; Epidemiologia; Prevalência.

This study was conducted by the Department of Medical-Surgical Nursing, School of Nursing, Universidade de São Paulo, São Paulo SP, Brazil.

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INTRODUCTION

Almost 70% of the 130 million people expected to develop dementia by 2050 are living in low- and middle-income countries[1]. The global estimated prevalence of dementia is 5–7%, with higher rates in low- and middle-income countries and illiterate older adults[2,3]. The prevalence of cognitive impairment no dementia (CIND) varies widely, ranging from 3 to 27%[4-7], and in Brazil, it ranges from 19.5 to 34.8% [8,9]. Unlike dementia, in mild cognitive impairment (MCI) and CIND, the patient can keep independence in functional abilities[10]. MCI clinical diagnosis is based on evidence of cognitive decline reported by patient or informant or clinician over time, objective evidence of impairment in one or more cognitive domains, preservation of independence in functional abilities, and not demented[10,11]. The concept of CIND is a broader definition of impairment that encompasses subjects who meet criteria for MCI and others who are cognitively impaired but do not meet all the criteria for MCI[11].

These projections may be underestimated when considering minority groups, such as indigenous population, who are disproportionately impacted by diseases worldwide[12,13]. Despite recent efforts to increase the inclusion of minority groups, indigenous populations are still underrepresented in dementia research, posing a challenge to understand the real impact of dementia across all race, ethnic, and social groups[12,13].

Indigenous populations are growing rapidly, and approximately 370 million individuals are estimated to be worldwide[14]. The advancement of urbanization, changes in dietary habits, and the aging of indigenous population have contributed to increase the prevalence of hypertension, diabetes mellitus (DM), obesity, metabolic syndrome, and alcoholism[15-17]. These conditions represent important risk factor for atherosclerosis, which plays a pivotal role in the etiology of cognitive impairment and dementia[18].

Despite that, the evidence regarding dementia in that population is scarce[19,20]. A recent systematic review revealed that dementia prevalence in the indigenous population range from 0.5 to 26.8% in individuals from high-income countries[21]. Early onset and high mortality represent the main features of dementia in indigenous[21]. Moreover, age, low educational level, and poor health conditions are the major modifiable risk factors reported[21].

Poverty, low educational levels, limited access to health system resources, and lack of population understanding about dementia pose additional vulnerability to cognitive disorders in the indigenous population from low- and middle-income countries[22]. However, fundamental questions remain regarding the dementia prevalence in those individuals, arising the critical need to understand how dementia affects indigenous communities in low- and middle-income countries[3]. The absence of such knowledge limits health policy maker actions and compromises the implementation of preventive measures to reduce the global disparities in dementia. The aim of this study was to determine the prevalence of cognitive impairment and associated factors in a Brazilian indigenous people of the Mura ethnicity in Amazonas, Brazil.

METHODS

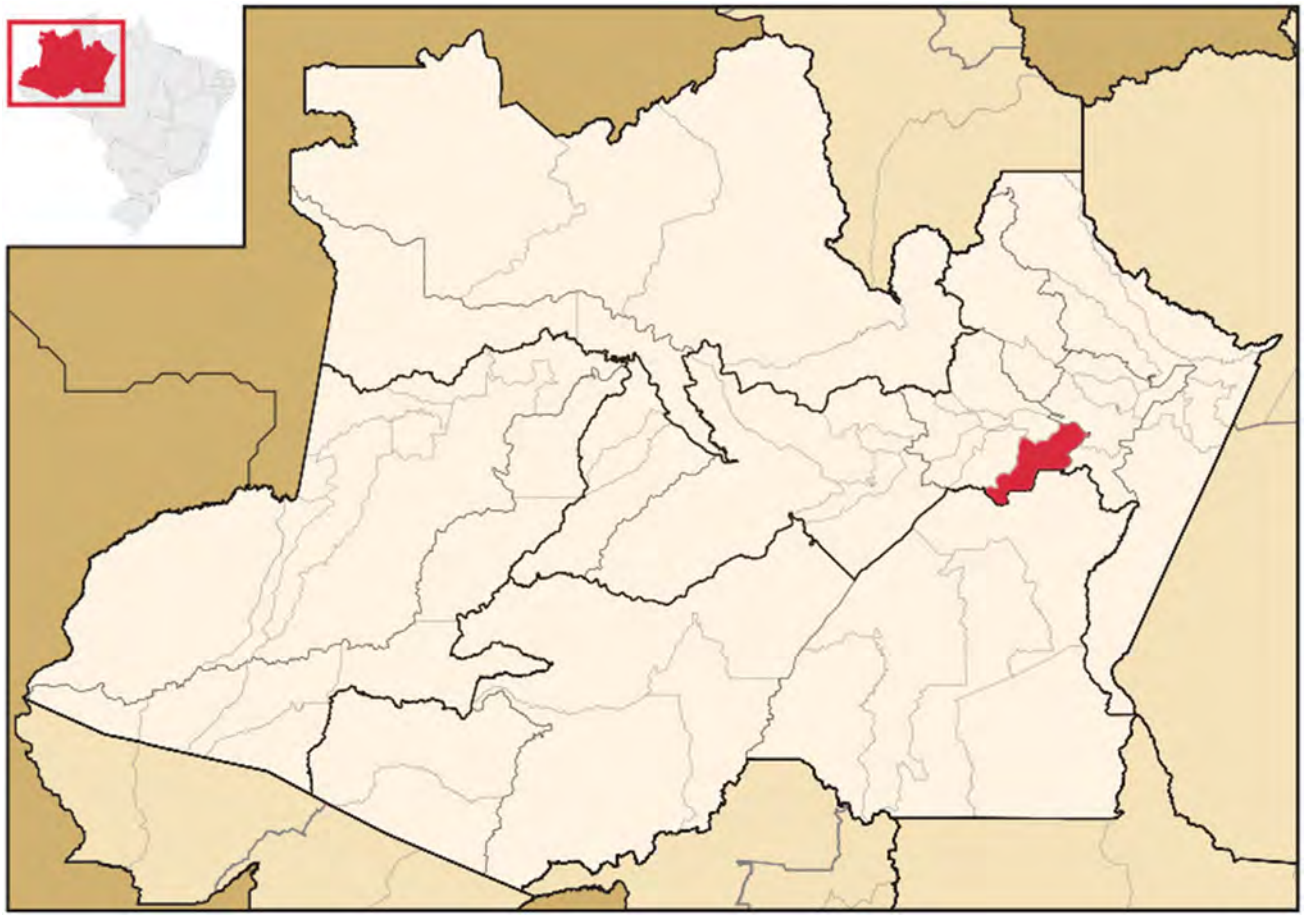
Study design and setting

A cross-sectional observational study was carried out in the village of Pantaleão, which is 218 km from Manaus, located in Amazonas, Northern Brazil (Figure 1). Autazes inhabitants are distributed among three ethnic groups: the Apurinã, Munduruku, and Mura. In the last census in 2013, Mura represented the most populous ethnicity, with 8,103 indigenous people and 12.8% of older adults[23].

After authorization from the National Foundation of Indians (FUNAI), the official Brazilian organization for indigenous population, a survey was conducted with those inhabitants aged ≥50 years with the assistance of local organizations, members of the community, and health care workers. Given the absence of reliable data on the number of dwellers aged ≥50 years, the snowball (referral) sampling technique was employed, whereby participants and other members of the community helped identify potential participants known to them to increase the sample size. A total of 245 indigenous individuals were identified. Data collection was carried out in a single phase, entailing an interview conducted at the household by a nurse trained in applying the tests. Testing took, on average, 70 min and included informed consent, the sociodemographic questioner, anthropometric data, cognitive and mood assessment, and subjective cognitive decline. The Research Ethics Committee of the School of Nursing of the University of São Paulo (nº 1.105.424), the National Research Ethics Committee, and the FUNAI (CONEP, nº 1.308.120) approved the study.

Participants

The study included individuals who self-identified as indigenous, lived, or worked in the village of Pantaleão and spoke Portuguese besides the native language. Dwellers out of town or who had deceased during the data



Source: SIASI/SESAI/MS (2013).

Figure 1. Geographical location of the municipality of Autazes in Manaus, Amazonas. SIASI/SESAI/MS (2013).

collection period were excluded, as they were individuals who refused to participate. None of the participants showed visual or hearing deficits precluding cognitive assessment, psychoactive medication, and had a history of stroke in the past 3 months. The final sample comprised 217 indigenous subjects of both genders (n=126 women; 58.1%), with a mean age of 64.2 (range 50–100) years.

Cognitive assessment

All participants were submitted to the following neuropsychological tests: the Mini-Mental State Examination (MMSE) recommended for use in Brazil[24]; the Brief Cognitive Screening Battery (BCSB) involving immediate and delayed recall (after 5 min), often printed drawings (e.g., shoe, house, comb, plane, turtle, book, spoon, tree, and bucket) scoring 10 points each[25]; the Digit Span Forward (DSF) and Digit Span Backward (DSB) entail the repetition of six sequences, each containing two and seven digits, to be repeated by the participant in the order readout (DSF) and reverse order (DSB), scoring 6 points in maximum; the Semantic Verbal Fluency Test (Animals and Fruits)[26]; and the Stick Design Test[27], which involves reproducing four different drawings (i.e., square, a triangle with a shaft, rafters, and rake) shown previously, using four matchsticks. All of these tests have been validated for use in the Brazilian population and possess discriminatory sensitivity for identifying cognitive impairment in individuals with low educational level[24-28].

Subjective cognitive decline

The memory complaint scale comprises seven questions assessing the frequency of memory complaints and the degree they impact daily activities. Responses are graded in increasing intensity (0, 1, and 2), yielding the following classification: no memory complaints (0–2 points), mild memory complaints (3–6 points), moderate memory complaints (7–10 points), and severe memory complaints (11–14 points)[29].

Mood and depressive symptoms

The mood was measured by the Faces Scale of Andrews[30], a visual scale containing seven figures of stylized faces

representing expressions ranging from extreme happiness to extreme unhappiness, with 1: very happy; 2: happy; 3: somewhat happy; 4: regular; 5: somewhat unhappy; 6: unhappy; and 7: very unhappy. The lower the rating, the greater the degree of psychological well-being, where score ≥4 indicates impaired well-being. Depressive symptoms were assessed using the short version of the Geriatric Depression Scale (GDS), comprising 15 questions (yes/no) on depression symptoms. A score ≥6 indicates a positive screen for depression and requires further examination[31].

Criteria for cognitive impairment diagnosis

Cognitive assessment, subjective cognitive decline, and mood data were independently reviewed by two neurologists to reach a consensus diagnosis, based on the criteria established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and International Classification of Diseases (ICD-10) for dementia diagnosis[32]. The consensus diagnosis was used to classify participants into "with cognitive impairment" and "without cognitive impairment." This classification was based on the following criteria:

1. Score on MMSE ≤14 for illiterate subjects and ≤19 for literate subjects (mean minus two standard deviations based on the normative data)[33];
2. Score ≤9 on verbal fluency or ≤7 on delayed recall of BCSB[24-28,33];
3. Analysis of performance on the other cognitive tests, according to case-by-case observation; and
4. The instruments assessing subjective cognitive decline, mood, and depression symptoms were also considered in the classification.

A third specialist reviewed disparities on the consensus diagnosis. Due to the unavailability of several participants' relatives, functional assessment for daily living activities of indigenous older adults was not determined, and therefore, discrimination between MCI and dementia was not performed.

Statistical analysis

Data were normally distributed. An analysis of variance (ANOVA) was used for repeated samples with Greenhouse correction in the absence of sphericity in the distribution pattern of the variables. Multiple comparisons (post-hoc) were made using the Bonferroni test. Student's t-test and chi-square test were used to compare means and frequencies, respectively. To characterize the sample, classic descriptive analysis procedures were used with average, standard deviation, and absolute and relative frequency calculations. The association between the prevalence of cognitive impairment and factors such as sex, age, education, income, arterial hypertension, DM, smoking, alcoholism, body mass index (BMI), and mood changes was analyzed using odds ratio (OR) measures. The significance level was 5% with a 95% confidence interval.

RESULTS

Description of sociodemographic, habits, and medical history

Participants were predominantly female, aged 50–100 years, self-identified indigenous, widowed or in a stable union, and had low educational level (0–15 years) and economic status. The majority of the population (92.7%) belong to low economic status (D and E classes), with a family income mean of R$ 639.78 (160–180 range in US$). Regarding medical history, most participants were not in the use of medications, had no chronic diseases, and were within the ideal limit for BMI. There was no significant difference between the groups for sociodemographic characteristics or medical history (Table 1).

Cognitive impairment and associated factors

The prevalence of cognitive impairment was 43.3% in the total sample. The odds of cognitive impairment varied across age, education, and BMI (Table 2). In participants aged ≥50 years, every year of age increased the odds of cognitive impairment by 3% (OR=1.03), whereas every year of education reduced the odds by 26% (OR=0.74). In participants aged ≥60 years and those aged ≥65 years, every year of age increased the odds of cognitive impairment by 9% (OR=1.09) and each year of education reduced this chance by 29% (OR=0.71; Table 2). Moreover, BMI and family income reduced the odds of cognitive impairment by 10% (OR=0.90) and 48%, respectively, in individuals aged ≥60 years (Table 2).

DISCUSSION

This study revealed that almost half of the indigenous people over 50 years of age had signs of cognitive impairment, indicating a relatively higher prevalence and earlier onset, compared to the rates found in other indigenous populations[21]. Age and education levels were the main factors associated with cognitive impairment.

It is noteworthy that prevalence encompassed individuals with MCI and dementia. They were not discriminated against in our study due to the difficulties of having the participants' proxy evaluating their functional ability for daily activities. Comparing our findings

Table 1. Sociodemographic characteristics and medical history for total sample and according to cognitive impairment.

Variables		Cognitive impairment			p
		Total sample n=217	Yes n=94	No n=123	
		Mean (±SD) or n (%)	Mean (±SD) or n (%)	Mean (±SD) or n (%)	
Age, years		64.2 (10.2)	65.0 (11.5)	63.7 (9.1)	0.384
Age group	50–59	81 (37.3)	38 (40.4)	43 (35.0)	0.524
	60–64	44 (20.3)	16 (17.0)	28 (22.8)	
	≥65	92 (42.4)	40 (42.6)	52 (42.2)	
Education		1.3 (2.1)	1.1 (1.9)	1.5 (2.3)	0.164
Illiterate (% yes)		128 (59.0)	62 (66.0)	66 (53.7)	0.072
Gender (% female)		126 (58.1)	59 (46.8)	67 (53.2)	0.220
Indigenous (% yes)		216 (99.5)	94 (43.5)	122 (56.5)	0.567
Marital status	Single	14 (6.5)	6 (42.9)	8 (57.1)	0.062
	Married	63 (29.0)	22 (34.9)	41 (65.1)	
	Divorced	5 (2.3)	-	5 (100)	
	Others	135 (62.2)	66 (48.9)	69 (51.1)	
Retired (% yes)		116 (53.5)	52 (44.8)	64 (55.2)	0.631
Economic class	C2	6 (2.8)	3 (50)	3 (50)	0.525
	D-E	211(97.2)	91(43.1)	120(56.9)	
Medical history (% yes)	Medication	38 (17.5)	14 (36.8)	24 (63.2)	0.375
	Diabetes mellitus	43 (19.8)	17 (39.5)	26 (60.5)	0.576
	Hypertension	72 (33.2)	28 (38.9)	44 (61.1)	0.353
	Stroke	17 (7.8)	6 (35.3)	11 (64.7)	0.487
	Epilepsy	1 (0.5)	0 (0)	1 (100)	0.567
	Alcoholism	8 (3.7)	2 (25.0)	6 (75.0)	0.471
	Smoking	6 (2.8)	2 (33.3)	4 (66.7)	0.700
Body mass index	Underweight	6 (2.8)	2 (33.3)	4 (66.7)	0.732
	Normal	103 (47.5)	49 (47.6)	54 (52.4)	
	Overweight	80 (36.9)	32 (40.0)	48 (60.0)	
	Class I obesity	18 (8.3)	7 (38.9)	11 (61.1)	
	Class II obesity	7 (3.2)	2 (28.6)	5 (71.4)	

SD: standard deviation.

with previous studies in indigenous older adults[34-36], the prevalence detected was higher in the Mura indigenous participants. Smith et al.[36] found a prevalence of cognitive impairment of 40.2% (26.8% with dementia and 13.4% with CIND) in older adults aged 65 years and over. Radford et al.[35] found a prevalence of cognitive impairment of 38.7% (21.0% with dementia and 17.7% with CIND) among individuals aged 60 years and above, while Giudice et al.[34] reported a prevalence of 35.3% (21.0% with dementia and 14.3% with CIND) in older adults aged ≥45 years. In contrast, other authors have found a low prevalence (0.4–7.5%) in indigenous

Table 2. Prevalence of cognitive impairment and associated factors.

Yes	Prevalence of cognitive impairment					
	Total sample n (%) [95%CI]		≥60 years n (%) [95%CI]		≥65 years n (%) [95%CI]	
	94 (43.3) [36.6–49.72]		59 (43.7) [35.63–52.13]		47 (51.1) [41.04–61.05]	
Associated factors	[95%CI]	OR	[95%CI]	OR	[95%CI]	OR
Sex (female)	0.86–2.6	1.5	0.86–3.40	1.71	0.96–5.08	2.20
Diabetes mellitus	0.81–3.14	1.6	0.59–2.84	1.29	0.46–3.14	1.20
Hypertension	0.52–1.63	0.92	0.39–1.60	0.79	0.30–1.64	0.71
Alcoholism	0.02–1.49	0.18	0.01–2.25	0.12	0.01–5.21	0.23
Smoking	0.26–6.76	1.33	0.08–21.11	1.29	0.06–15.77	0.96
Age	1.00–1.06*	1.03	1.04–1.15*	1.09	1.02–1.18*	1.09
Education	0.62–0.87*	0.74	0.53–0.91*	0.71	0.49–0.94*	0.71
Income	0.42–1.05	0.67	0.27–0.99*	0.52	0.27–1.27	0.59
Body mass index	0.83–0.96*	0.90	0.83–0.98*	0.91	0.84–1.03	0.93
Mood	0.81–3.14	1.60	0.86–3.40	1.71	0.96–5.08	2.20

OR: odds ratio; CI: confidence interval; *significant association.

populations from Canada, Australia, and Guam[37-41]. However, these studies involved older adults with greater education[6,8,36] or diagnosed according to clinical criteria[37-41] without citing the use of neuropsychological tests, in contrast to this study.

Regarding associated factors, the odds of cognitive impairment were higher in older participants, proving up to three times higher in older adults over 65 years than in younger participants. Moreover, approximately 58% of the participants with cognitive impairment were <65 years old. Among them, 40.4% were aged 50–59 years, suggesting earlier cognitive impairment onset than the general population, which is approximately 70 years old for MCI in the United States and over 60 years old in Brazil[42]. A recent systematic review corroborates our findings reporting that age was the main non-modifiable risk factor for cognitive impairment in the indigenous population[21]. Furthermore, CIND and dementia were detected in indigenous individuals aged 45–65 years[34-36,38,40], supporting that early cognitive impairment occurs in the indigenous population.

Education was another factor found to influence the prevalence of cognitive impairment in the indigenous population of the village of Pantaleão. For participants aged 50 years and over, each year of schooling decreases cognitive impairment by 26%. Moreover, the rate of cognitive impairment tended to be higher among illiterate than educated individuals. Low education has been reported as one of the main risk factors for dementia, particularly in developing countries, including those in Latin America and Brazil[2,3]. Older adults with 8 years of education or less are approximately twice as likely to develop dementia than higher educated individuals[2].

The current explanation for the low education impact on increasing the risk of dementia is grounded in the cognitive reserve theoretical model[43,44]. According to this model, some people can better tolerate the brain structural and biochemical changes by recruiting compensatory or preexisting brain mechanisms intrinsically related to educational and occupational activities[43,44]. Individuals with low levels of education tend to use the brain for processing differently than individuals with high levels of education[43,44]. Inter-individual variability, efficiency, and flexibility in the primary brain networks invoked in a task performance are the theoretical model explaining differences of cognitive performance in individuals with low education and from diverse ethnic groups[43,44]. Smaller cognitive reserve, low schooling, and temporary exposure to a health demand anticipate, in years, a

clinical manifestation of dementia[45]. In this sense, the high prevalence of cognitive impairment observed in mid-life and older adults indigenous may be related to low cognitive reserve due to illiteracy and low educational level. However, the educational level is not the only or even the best cognitive reserve indicator in any population[43,44], especially in those from diverse ethnic backgrounds. The influence of culture and environment on neural activity, cognitive network, and cognitive reserve's neural basis is still a topic of ongoing research[43,44]. Therefore, future studies investigating clinical and biological indicators of cognitive reserve are necessary to elucidate the factors associated with the high prevalence of cognitive impairment in indigenous populations.

BMI and family income also affected the odds of cognitive impairment in the indigenous participants. Cognitive impairment odds were reduced by 10% for every point on the BMI, while each family income unit reduced the odds of cognitive impairment by 48% in older adults aged ≥60 years. Corroborating this finding, Giudice et al.[34] observed that low BMI was associated with greater cognitive decline in Aboriginals over a follow-up period of 5 years. Some participants presented lower-than-expected BMI in this study, which may have influenced the cognitive impairment odds. Regarding income influence, the lower the socioeconomic level, the higher the dementia prevalence in non-indigenous older adults in a Brazilian study[19]. Many authors hold that, in indigenous communities, the poor living conditions, low family income, poor housing, and limited access to health services represent important factors contributing to the cognitive impairment risk[43]. Although other indicators assessing socioeconomic level were not objectively assessed, the poor living conditions of the dwellers of Pantaleão were evident during the interviews, most of which were conducted at participants' homes. The majority of houses were wooden, arranged in streets and plots, many backing onto streams. A water supply system existed, but well water was predominantly used and basic sanitation deficient. Many homes housed multiple families, where this overcrowding exacerbated disorganization and poor hygiene. Most dwellers were unemployed, living on government welfare (pension or benefits).

In contrast to previous studies, no association between chronic noncommunicable diseases (NCDs) and the cognitive impairment prevalence rates was observed[15,17,19]. High rates of hypertension, DM, and dyslipidemia have been described in indigenous populations, with and without cognitive impairment[15,17,19]. Therefore, low percentages of diabetes, hypertension, and obesity observed in the current sample may explain the lack of association[15,17,19].

Limitations and final considerations

First, the sample comprised indigenous from a single village in the State of Amazonas. Further evidence from other ethnicities and rural communities can complement the current findings. Additionally, longitudinal studies with systematic participants follow-up, based on regular cognitive and clinical assessments, including the evaluation of dementia diagnosis, dementia biomarkers, such as tau protein and beta-amyloid, can discriminate cases into CIND and dementia, as well as enable identification of reversible dementia cases and factors that increase the risk of developing dementia in the indigenous population.

The use of traditional neuropsychological tests may also be a limitation. The cognitive tests applied in this study were already used by participants from Mamirauá and Amanã Sustainable Development Reserves, located about 600 km west of Manaus (Amazonas) in the Brazilian Amazonian region[33]. Moreover, they were featured by visual tasks and present low educational level influence. However, those tests were not validated for cognitive impairment diagnosis in the indigenous population. In interpreting our findings, a lack of adapted tests for the indigenous culture should be considered. Finally, functional assessment should be employed in future studies to better discriminate those with CIND from those with dementia.

Despite the limitations, the current evidence contributes to understanding the health disparities in low- and middle-income countries by providing evidence about cognitive impairment in Mura indigenous population in Brazil and the related factors.

An indigenous community from Amazonas, Brazil, presented high cognitive impairment prevalence, featured by early onset and associated with age, low educational level, BMI, and income. By showing the indigenous vulnerability to cognitive disorders, the current findings highlight the critical need to expand the investigation of dementia in underrepresented populations to adequately plan global strategies to face the dementia burden worldwide.

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Authors' contributions

APC: conceptualization, investigation, methodology, resources, writing – original draft. SMDB: data curation, formal analysis, methodology, supervision, writing – review & editing. RN: data curation, formal analysis, methodology, supervision, writing – review & editing. CCB: data curation, formal analysis, methodology, resources, writing – review & editing. FCS: data curation, formal analysis, methodology, resources, writing – review & editing. JNST: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, writing – original draft, writing-original draft.

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Original Article

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Can timed up and go subtasks predict functional decline in older adults with cognitive impairment?

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ABSTRACT. Even in the early stages of cognitive impairment, older people can present important motor alterations. However, there are no studies that have investigated Timed Up and Go (TUG) and its subtasks in predicting impairment of functional capacity over time in this population. **Objectives:** The aim of this study was to verify if the TUG test and its subtasks can predict functional decline over 32 months in older adults with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD). **Methods:** This is a prospective 32-month follow-up study, including at baseline 78 older adults (MCI: n=40; AD: n=38). The TUG and its subtasks (e.g., sit-to-stand, walking forward, turn, walking back, and turn-to-sit) were performed at baseline using the Qualisys Motion system. Functional capacity was assessed at baseline and after 32 months. **Results:** After follow-up, the sample had 45 older adults (MCI: n=25; AD: n=20). Of these, 28 declined functional capacity (MCI: n=13; AD: n=15). No TUG variable significantly predicted (p>0.05) functional decline in both groups, by univariate logistic regression analysis with the covariate gender. **Conclusions:** Although older adults with MCI and mild AD declined functional capacity, the TUG test and its subtasks could not predict this decline over 32 months.

Keywords: Alzheimer Disease; Mobility Limitation; Aged; Cognitive Dysfunction; Functional Status.

AS SUBTAREFAS DO *TIMED UP AND GO* PODEM PREDIZER O DECLÍNIO FUNCIONAL EM IDOSOS COM COMPROMETIMENTO COGNITIVO?

RESUMO. Mesmo nos estágios iniciais do comprometimento cognitivo, os idosos podem apresentar alterações motoras importantes. No entanto, não há estudos que tenham investigado o *timed up and go* (TUG) e suas subtarefas como preditores do comprometimento da capacidade funcional ao longo do tempo nessa população. **Objetivos:** O objetivo deste estudo foi verificar se o teste *timed up and go* (TUG) e suas subtarefas podem predizer o declínio funcional ao longo de 32 meses em idosos com comprometimento cognitivo leve (CCL) e doença de Alzheimer leve (DA). **Métodos:** Este é um estudo prospectivo de acompanhamento de 32 meses, que incluiu no início do estudo 78 idosos (CCL: n=40; DA: n=38). O TUG e suas subtarefas (sentar para levantar, caminhar para frente, virar, caminhar para trás e girar para sentar) foram realizados na linha de base pelo sistema Qualisys Motion. A capacidade funcional foi avaliada no início e após 32 meses. **Resultados:** Depois do seguimento, a amostra foi composta de 45 idosos (CCL: n=25; DA: n=20). Destes, 28 tiveram a capacidade funcional diminuída (CCL: n=13; DA: n=15). Nenhuma variável do TUG previu declínio funcional significativamente estatístico (p>0,05) em nenhum dos grupos, por meio da análise de regressão logística univariada com a covariável sexo. **Conclusões:** Embora os idosos com CCL e DA leve tenham tido sua capacidade funcional diminuída, o teste TUG e suas subtarefas não puderam prever esse declínio em 32 meses.

Palavras-chave: Doença de Alzheimer; Limitação da Mobilidade; Idoso; Disfunção Cognitiva; Estado Funcional.

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia among older adults, causing impairment in cognitive abilities, which interferes with the functional capacity of the individual[1,2]. Another common clinical condition in aging is mild cognitive impairment (MCI), also known as minor neurocognitive disorder[2].

This study was conducted by the Laboratório de Pesquisa em Saúde do Idoso, Departamento de Fisioterapia, Universidade Federal de São Carlos, São Carlos, SP, Brazil.

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The MCI is a transitional phase between natural aging and dementia. About 20% of older adults are diagnosed with MCI in developing countries, with an annual progression rate to dementia between 30% and 40%[3]. Identification, assessment, and early intervention in these older adults with impairments in functional capacity are essential[2].

One of the ways to predict functional decline in older adults is the Timed Up and Go (TUG) test[4,5]. The TUG subtasks characterize a set of actions performed in one's routine, fundamental for independent mobility[6]. Although the TUG is widely used in clinical practice, there is a lack of studies to verify if the test can predict functional capacity decline in older adults with MCI and mild phases of AD. Execution times greater than 12.47 s present a greater risk of falls in the elderly[7].

Most studies use TUG to analyze the variable time and a few other kinematic and kinetic variables that are able to assess balance. In addition, the analysis of partial times in their different subtasks allows greater accuracy and sensitivity to small changes in functional capacity[8]. Mirelman et al. found that older adults with MCI present a TUG performance with greater irregularity of gait step, lower trunk movement during transition subtasks, and lower axial rotation in the turn subtask compared to cognitively preserved individuals[9]. However, no studies were found that associated functional capacity and performance of TUG subtasks in older adults with MCI and AD, especially in the mild phase. This information could be useful for improving knowledge about cognitive impairment, functional capacity, prevention measures, and screening for declining functional capacity in older adults with cognitive impairment.

This study is justified by the fact that, although some studies show that even in the early stages of cognitive impairment, older people already present important motor alterations[10], so far there are no studies that have investigated TUG and its subtasks in predicting impairment of functional capacity over time in a population with cognitive impairment. This information would be important, since the TUG subtasks can be performed and reproduced even in older people with difficulty in understanding, such as the older people with MCI and AD in the light phase[11]. Thus, the objective of the present study was to verify if the analysis of the TUG test and its subtasks is capable of predicting the decline of functional capacity over 32 months in older adults with MCI and mild AD.

METHODS

Study design and participants

From a longitudinal analytical study, the functional capacity of mildly aged older adults with MCI and mild AD was investigated at two assessment times (M1=initial; M2=after 32 months). The project was approved by the Federal University of São Carlos (UFSCar) Research Ethics Committee (CAAE: 72774317.7.0000.5504). The study was carried out at the Research Laboratory of Older Adults Health (LaPeSI), UFSCar (São Carlos, São Paulo state, Brazil). Survey participants and caregivers who needed follow-up consultations were given detailed information about the study, including all procedures that would be performed. After clarifying the doubts, the signing of the Free and Informed Consent Form was requested.

The recruitment process took place between January and September 2015 and was widely disseminated throughout the city. To calculate the sample size, the rule of at least 10 cases of the outcome (success or failure, depending on which was rarer) for each independent variable used in the linear regression model was used[12]. Elderly people with cognitive complaints and diagnoses of AD were invited to participate in an initial assessment. The eligibility criteria of the sample were individuals aged 60 years and over, not institutionalized, and with the possibility of telephone contact.

After recruitment, the eligible volunteers participated in an evaluation to confirm the diagnosis of MCI or mild AD, in partnership with a neurologist and professor. Inclusion criteria were individuals who were able to walk alone for at least 10 m without aid devices, who were willing to participate in the proposed assessments, and who were admitted to one of the groups. Exclusion criteria were the presence of stroke with motor sequelae, neurological disorders that interfered in cognition other than MCI and AD, or mobility (Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis), severe and uncorrected audiovisual disorders that made communication difficult during the tests, and older adults with moderate or advanced AD at the initial moment.

For the diagnosis of MCI in the evaluation or confirmation of this diagnosis prior to the study, the following criteria were used:

- cognitive complaint corroborated by the person or by an informant (a person who stayed with the older person for at least half the day, four times a week);
- objective cognitive decline, scoring a score of 0.5 by the Clinical Assessment of Dementia (CDR)[13];
- normal general cognitive function for the level of education, assessed by the Mini-Mental State Examination (MMSE)[14];
- preserved functionality, assessed by the Pfeffer Scale[15]; and
- unaltered cognition or functionality to meet dementia criteria[15].

AD diagnosis prior to the study was confirmed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR)[16]. Through the CDR, only those with a score of 1, indicating the mild stage[12], were included in the group.

Measures

The first evaluation took place between January and September 2015. We use the following instruments:

- Anamnesis, composed of a questionnaire with sociodemographic and clinical characteristics, such as age, gender, falls in the last year[17], years of study, use of drugs, body mass index (kg/m^2), and presence of diseases. Volunteers could also count on the informant's help to answer these questions;
- Geriatric Depression Scale (cutoff score of 5 points to screen risk of depressive symptoms)[18]; and
- Minnesota Leisure-Time Physical Activity Questionnaire (assessment of the level of energy expenditure)[19].

Volunteers were instructed to come in comfortable clothes and their usual closed shoes. Mobility was assessed by the TUG through the Qualysis Pro Reflex Motion Analysis System, consisting of seven 1280×1024 (1.3 megapixel) resolution cameras, and with an adapted chair[10]. The test involved, after the "go" command, getting up from the chair, walking 3 m, bounded by a cone at their usual speed, going back to the chair, and sitting down. The volunteers were instructed to start and end the test with the trunk leaning on the chair. Paused and standardized instructions were given along the test[10]. The TUG was subdivided into five subtasks: sit-to-stand, walking forward, turn, walking back, and turn-to-sit[20-22] (Figure 1). The detection of TUG subtasks was performed according to the procedures demonstrated by Ansai et al.[11], being performed by a single evaluator (intra-evaluator reliability above 0.72 in total). Data were captured by the Qualisys Track Manager acquisition software and transferred to the Visual-3D software for processing. The collection frequency was 120 Hz[22]. MATLAB software was used to detect, separate, and analyze TUG subtasks.

In TUG (total performance), the time spent using a stopwatch and the number of steps were analyzed. A step was considered when the heel was removed from the ground until it touched the ground again[23]. Regarding performances on TUG subtasks, time, trunk range of motion (pitch axis, i.e., flexion/extension), and average velocities of trunk (pitch axis) during the sit-to-stand subtask were analyzed. Data collected from walking forward and walking back subtasks were gait speed (GS), time, and length of the first step and number of steps. In the turn subtask, time, average velocity of trunk (yaw axis, i.e., rotation), and number of steps were collected. The same variables of the sit-to-stand and turn subtasks were analyzed in the turn-to-sit subtask[10,23].

To assess functional capacity, the Pfeffer Scale[15] of 10 items was used, showing a degree of independence for performing instrumental Activities of Daily Living (ADL). The minimum score is 0, and the maximum is 30 points. The higher the number of points, the greater the dependence of the older adult, considering the presence of impairment in functional capacity from a score of 5[15].

The second assessment took place after 32 months, between September 2017 and May 2018. At this time, the functional capacity was assessed through the Pfeffer Scale and the Intercurrence Questionnaire was applied, in which the individual was asked about the occurrence of falls and other events during follow-ups, such as the number of hospitalizations, physical activity, physical therapy, and new diagnoses.

Figure 1. Performance on the subtasks of the timed up and go test in the Qualysis Pro Reflex system.

Statistical analysis

Initially, a descriptive analysis of the data and a point and interval estimate of the parameters of interest were performed. For the analysis, a significance level of α=0.05 was adopted. Statistical tests were performed using the SPSS software (version 22.0). The Kolmogorov-Smirnov normality test was applied to all continuous variables to verify data distribution. Confirming the hypothesis of normality, the independent t-test was used to verify the difference between older adults with declining functional capacity (final Pfeffer – initial Pfeffer>0) and those with no decline in functional capacity (final Pfeffer – initial Pfeffer≤0) in both groups. The chi-square test was used to verify differences in sociodemographic characteristics. In addition, univariate logistic regression analysis was used to identify whether the TUG test, as well as its subtasks (variables available in Table 1), would be a good predictor of functional decline (final Pfeffer – initial Pfeffer>0). The confounding variable used was gender in univariate logistic regression models.

RESULTS

At baseline, we contacted 82 potentially eligible volunteers. Of these, four were excluded from the sample by presenting visual disturbance severe and uncorrected, AD in the moderate phase, motor sequel of stroke, and inability to ambulate alone. Thus, the initial sample consisted of 78 older adults, including 40 with MCI and 38 with mild AD.

In the second phase of the study, after 32 months, all 78 volunteers were again invited to participate. Of these, 11 people died, 10 were loss of contact, and 12 gave up participating in the survey, resulting in sample loss of 33 volunteers. Thus, the final sample consisted of 45 volunteers, i.e., 25 MCI and 20 AD (Figure 2).

Regardless of the group to which they belonged, volunteers were classified with and without functional decline, based on the analysis of functional capacity by Pfeffer[15]. In all, 28 volunteers scored higher than the initial assessment, characterizing a decline in functional capacity during the time segment studied (MCI=13; AD=15). Table 1 presents the sociodemographic and clinical characteristics of the sample, separated by groups and the presence of functional decline.

The groups with MCI, regardless of whether or not they had impaired functional capacity, were predominantly female volunteers (91.7% no functional decline and 84.6% with functional decline; MMSE no functional decline n=8 [M2=26.25±1.75], with functional decline

Table 1. Sociodemographic and clinical characteristics of sample at the baseline.

Characteristics	MCI Group			AD Group			MCI×AD
	No functional decline (n=12)	With functional decline (n=13)	p-value	No functional decline (n=5)	With functional decline (n=15)	p-value	p-value
Age, M±SD	72.3±4.3	76.1±8.3	0.169*	78.6±4.8	77.8±6.5	0.806*	0.067
Women, n (%)	11 (91.7)	11 (84.6)	0.588†	1 (20.0)	7 (46.7)	0.292†	0.001‡
Body mass index (kg/m^2), M±SD	30.8±5.0	29.8±3.6	0.597*	26.8±4.7	27.2±5.5	0.886*	0.030‡
Years of schooling, M±SD	6.6±3.9	5.0±3.0	0.270*	5.8±2.4	5.7±5.3	0.969*	0.926
Total number of drugs, M±SD	7.3±4.6	8.0±6.9	0.757*	7.4±3.3	9.5±6.9	0.517*	0.415
History of falls at baseline, n (%)	7 (58.3)	7 (53.8)	0.581†	2 (40.0)	9 (60.0)	0.791†	0.634
Falls during 30 months, n (%)	5 (41.7)	10 (76.9)	0.108†	3 (60.0)	11 (73.3)	0.778†	0.402
GDS (0–15), M±SD	2.8±2.4	4.1±2.3	0.184*	3.0±1.8	2.6±2.5	0.755*	0.266
MMSE (0–30), M±SD	24.5±2.2	23.6±3.3	0.199*	19.0±8.7	17.4±4.7	0.434*	0.000‡
Minnesota (total score), M±SD	2281.4±2813.0	1188.4±953.3	0.241*	490.8±943.9	988.1±1266.8	0.878*	0.114
Pfeffer at baseline (absolute number) (0–30), M±SD	4.0±6.0	1.8±2.1	0.169*	13.2±11.6	12.3±10.5	0.806*	0.000‡

M±SD: mean±standard deviation; n (%): number of individuals (percentage); MCI: mild cognitive impairment; AD: Alzheimer's disease; kg/m^2: kilogram/meter squared; GDS: Geriatric Depression Scale; MMSE: Mini-Mental State Examination; Minnesota: Minnesota Leisure Time Activities Questionnaire; *Analyzed by the independent t-test; †Analyzed by chi-square test; ‡p<0.05 (differences between subgroups for each group analyzed by the independent t-test or chi-square test).

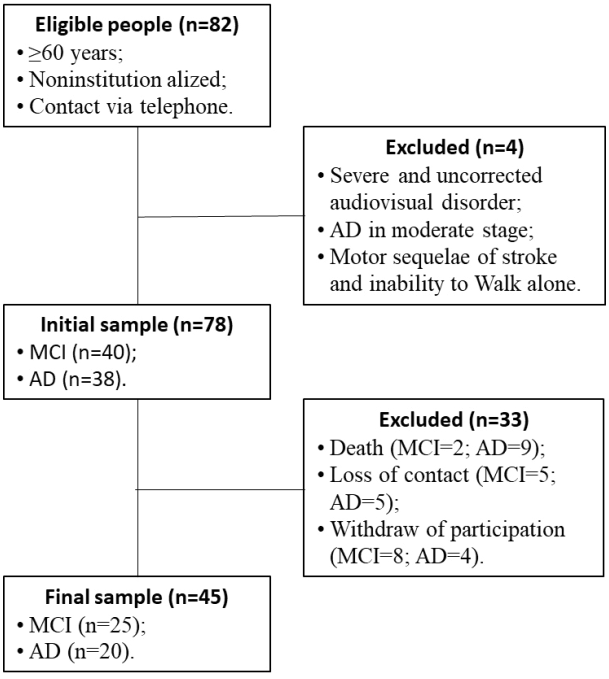
n=9 [M2=22.44±5.57, p=0.085]). There was no statistically significant difference regarding sociodemographic variables and clinical characteristics between the MCI subgroups with and without functional decline, and the same was true for the AD group (Table 1).

Regarding the performance of the volunteers in TUG and its subtasks, it was observed that in the sit-to-stand subtask, both groups had similar averages regarding the duration of trunk acceleration movement. In the turn subtask, the volunteers with MCI performed the step-in terms of time, average speed, and number of steps with better performance compared to the AD group. In the walking back subtask, the values for the groups regarding walking speed and first step time were similar, and the length of the steps was equal. In the turn subtask, the MCI group also obtained values that demonstrate better performance compared to the AD group (Table 2).

In the logistic regression analysis, no mobility variable was significantly associated with functional decline, neither in the MCI nor in the AD groups (Table 3).

DISCUSSION

TUG and its subtasks did not allow greater precision in the evaluation of older adults with MCI or in mild phase of AD, rejecting the initial hypothesis of the present study that TUG could be a more sensitive test for small functional changes in this population. However, studies investigating whether alterations in physical tests, especially TUG, may predict functional alterations in older adults with cognitive impairment have not yet been found in the literature.



MCI: mild cognitive impairment; AD: Alzheimer's disease.

Figure 2. Flowchart of the sample.

In a cohort study with older adults after anatomical lesions and requiring only minor outpatient procedures, it was observed that the use of TUG in older adults can help to identify individuals with bone frailty and at risk of functional decline[24]. Another study identified that the time to perform TUG was similar between older people with preserved cognition and MCI, but the quality to perform the test was different. This shows that there are motor-cognitive interactions already in individuals with MCI, i.e., at-risk stages for the development of dementia[25]. Zidan et al. verified that TUG is superior to the GS test in predicting multiple geriatric outcomes, including a decline of functional capacity, being able to predict the decline in health, the difficulty of performing ADL, and falls in community-dwelling older adults[26].

In this study, although there was no significant difference in the relationship between TUG and functional capacity, it was possible to observe that the older adults who showed a decline in functional capacity over the 32 months had different performance in the sit-to-stand, walking back, and turn subtasks. In the sit-to-stand subtask, the mean achievement speed was higher in both groups that declined functional capacity. The sit-to-stand subtask is crucial for survival. Therefore, it is important to know that when it is compromised, it can interfere with the performance of ADL. This result may be partly explained by the association between cognitive impairment and lower limb function of the volunteers. The ability to get up from the chair involves complex factors where it is necessary to move the center of mass forward while still sitting, acceleration in the posteroanterior and vertical planes, push-off, and finally stabilization once the position standing is reached[8].

In the walking back subtask, the step length was shorter when compared to the older adults who did not decline in terms of functional capacity, especially in the AD group. The aging process associated with the presence of neurodegenerative diseases, such as AD, aggravates gait automatism and increases balance deficit. In the mild phase of AD, the modulation of the locomotor pattern is increased, making gait more cautious[26,27]. Impairment in balance causes this caution to occur during walking, decreasing the length of the step and longer stay in double support, especially when they are preparing to perform a more complex activity such as, in the case of the present study, turn to sit down. These strategies adhered to by the older adults aim to reduce risks and maintain safety while walking[26,27].

Fear of falling can restrict individuals' activities, leading them to a decline in functional capacity accompanied by decreased quality of life.

In the turn subtask, it was observed that the volunteers with mild AD who had declined in functional capacity took longer to perform it. With aging, gait demands more attention and resources, reflecting the need for different cognitive mechanisms for its proper control and performance[10]. Thus, it seems that the greater the cognitive impairment, the greater the demand to perform a given task, directly interfering with functional capacity. When observing the performance of TUG, the total number of steps was higher in individuals who reduced functional capacity, regardless of the group to which they belonged. All these findings are in agreement with the study by Mirelman et al. who found that individuals with cognitive impairment show greater irregularity of gait step, lower trunk movement during transition subtasks, and lower axial rotation during the turn subtask compared to cognitively preserved individuals[9].

Subtle motor impairments are present in the transition from mild to moderate phases and worse performance in performing basic ADL in advanced AD[27]. Progress from explicit memory deficit to processing memory would explain the initial decline in the performance of

Table 2. Timed up and go performance and its subtasks.

		MCI group			AD group			MCI×AD
	Variable, M±SD	No functional decline (n=12)	With functional decline (n=13)	p-value	No functional decline (n=5)	With functional decline (n=15)	p-value	p-value
Timed up and go performance	Total time (s)	14.2 (5.6)	12.7 (2.8)	0.419	15.9 (3.2)	14.0 (7.8)	0.618	0.372
	Number of steps	16.5 (2.9)	19.1 (6.3)	0.216	17.4 (4.1)	19.2 (5.8)	0.537	0.602
Sit-to-stand subtask	Time (s)	0.9 (0.4)	0.9 (0.2)	0.707	1.1 (0.3)	0.9 (0.4)	0.317	0.276
	Trunk range of motion, pitch axis (°)	20.5 (4.9)	24.7 (5.1)	0.057	18.6 (2.9)	20.8 (9.7)	0.624	0.198
	Trunk – average velocity, pitch axis (°/s)	44.2 (11.9)	47.7 (12.1)	0.478	29.7 (10.6)	35.2 (18.3)	0.533	0.004*
Walking forward subtask	First step – length (m)	0.2 (0.1)	0.2 (0.1)	0.602	0.2 (0.1)	0.3 (0.8)	0.439	0.134
	Number of steps	5.7 (2.5)	5.2 (1.2)	0.554	5.9 (1.0)	7.2 (5.9)	0.649	0.160
	First step – time (s)	0.6 (0.1)	0.6 (0.0)	0.690	0.7 (0.1)	0.6 (0.2)	0.554	0.593
	Gait speed (m/s)	0.4 (0.2)	0.5 (0.1)	0.843	0.3 (0.8)	0.3 (0.1)	0.281	0.001*
Turn subtask	Time (s)	2.3 (1.1)	2.0 (0.6)	0.433	2.1 (0.6)	3.2 (2.8)	0.396	0.085
	Trunk – average velocity, yaw axis (°/s)	73.2 (28.5)	74.9 (18.3)	0.854	62.8 (14.8)	43.5 (31.0)	0.204	0.001*
	Number of steps	4.5 (1.8)	4.2 (1.3)	0.594	4.2 (0.8)	4.7 (2.2)	0.656	0.452
Walking back subtask	First step – length (m)	0.3 (0.1)	0.3 (0.1)	0.700	0.2 (0.1)	0.1 (0.2)	0.458	0.211
	Number of steps	4.6 (2.5)	4.4 (1.3)	0.805	4.6 (0.9)	4.8 (1.8)	0.811	0.424
	First step – time (s)	0.7 (0.1)	0.6 (0.1)	0.730	0.6 (0.1)	1.8 (3.1)	0.419	0.116
	Gait speed (m/s)	0.6 (0.2)	0.6 (0.1)	0.783	0.5 (0.1)	0.9 (1.2)	0.468	0.495
Turn-to-sit subtask	Average velocity, pitch axis (°/s)	38.9 (9.7)	35.9 (10.7)	0.494	26.5 (5.4)	21.3 (20.2)	0.587	0.002*
	Average velocity, yaw axis (°/s)	42.4 (16.9)	43.2 (12.8)	0.902	36.3 (8.7)	28.3 (15.3)	0.287	0.008*
	Time (s)	2.4 (1.6)	2.0 (0.6)	0.431	2.5 (0.5)	2.7 (1.8)	0.796	0.087
	Trunk range of motion, pitch axis (°)	50.8 (5.6)	53.0 (7.8)	0.452	47.6 (7.5)	45.3 (17.8)	0.784	0.096
	Number of steps	3.9 (0.9)	3.7 (0.8)	0.763	4.5 (0.5)	3.9 (2.1)	0.561	0.451

M±SD: mean±standard deviation; MCI: mild cognitive impairment; AD: Alzheimer's disease; °: degree; s: seconds; m: meter; p>0.05 for all analyses by the independent t-test (both in the MCI group and the AD group).

instrumental ADL in people in the mild phase of DA. As the disease progresses, impairments in other cognitive abilities occur that further compromise basic activities[27]. The Pfeffer Scale used in this study evaluates items related to instrumental activities, while the TUG is a physical and mobility test. This fact may partly explain our results, where functional decline assessed by TUG was not sensitive to predict functional decline assessed by Pfeffer.

The final study sample consisted of 45 older adults, which was represented by the majority of females. According to Elahi and Miller, it is the gender that is most susceptible to the acquisition of dementia syndromes, such as MCI and AD[28]. In addition, other factors consistent with the literature were found, such as: a) prevalence of low level of education in the functionally declining group[29], and b) higher hospitalization rate in the groups with functional decline, which may be correlated with the increase in the number of falls from M1 to M2 of all groups, except MCI, which did not decline functionally[30]. The number of volunteers who performed physical activities in the group that did not decline functionally was lower than the group that declined functionally, although they were advised to remain physically active[31].

An important point to note is that the present study was followed up for 32 months, which was not the case with other studies found in the literature. Considering the follow-up time, a greater impairment of functional capacity was expected, especially in the group with the highest cognitive impairment.

This study is limited by the small sample size due to outcomes over time and the fact that we used the MMSE only as a cognitive assessment instrument. It also has a

Table 3. Univariate mobility predictors of functional decline in participants with mild cognitive impairment and Alzheimer's disease, by the logistic regression analysis.

Measures		MCI group (n=25)		AD group (n=20)	
		OR (95%CI)	p-value	OR (95%CI)	p-value
Timed up and go performance – Total time (s)		0.914 (0.745–1.121)	0.389	0.982 (0.843–1.145)	0.820
Sit-to-stand subtask	Time (s)	0.564 (0.049–6.434	0.645	0.387 (0.026–5.757)	0.490
	Trunk range of motion, pitch axis (°)	1.198 (0.985–1.458)	0.071	1.029 (0.902–1.173)	0.674
	Trunk – average velocity, pitch axis (º/s)	1.032 (0.959–1.110)	0.402	1.014 (0.945–1.088)	0.702
Walking forward subtask	First step – length (m)	0.249 (0.001–108.118)	0.654	1.031 (0.723–1.470)	0.866
	Number of steps	0.860 (0.550–1.345)	0.509	1.148 (0.777–1.695)	0.488
	First step – time (s)	0.068 (0.000–194.213)	0.508	0.075 (0.000–75.308)	0.463
	Gait speed (m/s)	2.126 (0.026–171.993)	0.736	0.000 (0.000–83.329)	0.163
Turn subtask	Time (s)	0.641 (0.246–1.667)	0.361	1.594 (0.668–3.806)	0.294
	Trunk – average velocity, yaw axis (°/s)	1.005 (0.970–1.041)	0.768	0.943 (0.872–1.020)	0.144
	Number of steps	0.839 (0.492–1.431)	0.520	1.136 (0.652–1.981)	0.652
Walking back subtask	First step – length (m)	0.322 (0.001–115.496)	0.706	34.542 (0.002–701132,955)	0.484
	Number of steps	0.950 (0.629–1.436)	0.808	1.396 (0.635–3.069)	0.407
	First step – time (s)	0.315 (0.001–67.252)	0.673	4.677 (0.022–1006.629)	0.573
	Gait speed (m/s)	1.617 (0.027–95.097)	0.817	0.236 (0.003–20.101)	0.524
Turn-to-sit subtask	Average velocity, pitch axis (°/s)	0.961 (0.878–1.052)	0.390	0.936 (0.810–1.083)	0.374
	Average velocity, yaw axis (°/s)	1.011 (0.951–1.074)	0.729	0.928 (0.834–1.033)	0.173
	Time (s)	0.605 (0.262–1.401)	0.241	1.143 (0.599–2.182)	0.685
	Trunk range of motion, pitch axis (°)	1.039 (0.915–1.180)	0.554	0.986 (0.916–1.062)	0.708
	Number of steps	0.732 (0.258–2.072)	0.556	0.905 (0.448–1.827)	0.780

MCI: mild cognitive impairment; AD: Alzheimer's disease; °: degree; s: seconds; m: meter; p>0.05 for all analyses (both in the MCI Group and the AD Group); OR: odds ratio; CI: confidence interval, adjusted by gender.

limitation in the fact that Pfeffer is a scale that applies to the caregiver in relation to the older adult; besides that, as previously mentioned, it evaluates the instrumental activities and not the functional capacity in general. However, it is important to note that the caregiver who responded to the instrument was the person who spent most of the time with the volunteer. In addition, Pfeffer is a scale widely used in clinical practice, and further investigations with these instruments may contribute to the knowledge of professionals who use it. It was also possible to observe a significant limitation of the absence of studies that discuss about the prediction of functional decline related to tests in older adults, mainly with MCI and AD. In contrast, as a strong point, it is important to emphasize that this is a longitudinal study and the first to address whether the TUG subtasks are related to functional decline.

Further longitudinal follow-up studies observing older adults with MCI and AD may provide clinical information on each TUG subtask, especially on the impact of these consequences on the individual's functional capacity.

Authors' contributions. MMS: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, software, visualization, writing – original draft, writing – review & editing. JHA: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing. DCPS: data curation, formal analysis, investigation, methodology, validation, visualization, writing – original draft, writing – review & editing. PGR: data curation, formal analysis, investigation, methodology, software, supervision, validation, visualization, writing – original draft, writing – review & editing. ACMT: data curation, formal analysis, funding acquisition, investigation, methodology, resources, software, validation, visualization, writing – original draft, writing – review & editing. LPA: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing.

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Original Article

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Lower extremities task of pressing an "accelerator" or a "brake": association with traffic accidents in older drivers – a preliminary study

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ABSTRACT. Traffic accidents by older drivers are a social urgent problem. The National Police Agency (NPA) in Japan has institutionalized the *Cognitive Function Test* (NPA test) for renewal of a driver's license for older adults. However, driving ability cannot be simply evaluated by usual cognitive tests on the desk. **Objective:** It is important to add an on-road test, but if not possible, we can use simulators. Before doing simulators, it is important to use the right foot to control the accelerator and brake pedals. We applied the Posner paradigm (visual attention test) for lower extremities. **Methods:** The participants were older adults. They and their families had anxiety about their driving. The 66 participants (44 men and 22 women) were divided into groups with and without experience of a traffic accident, and the following tests were examined: General cognitive and executive function tests, the NPA test, and an original Lower Extremity Reaction Test. Each participant was asked to press the "brake" or "accelerator" pedal by the right foot as quickly as possible in response to a traffic situation shown on the screen. **Results:** Compared to participants with favorable reactions to the Lower Extremity Reaction Test, those with poor reaction time tended to have more traffic accidents (OR=6.82), rather than the result of the NPA test. **Conclusions** The results suggest that the probability of having a traffic accident can be better evaluated using the Lower Extremity Reaction Test.

Keywords: Aging; Automobile Driving; Attention.

A TAREFA DAS EXTREMIDADES INFERIORES DE PRESSIONAR UM "ACELERADOR" OU UM "FREIO": ASSOCIAÇÃO COM ACIDENTES DE TRÂNSITO EM MOTORISTAS MAIS VELHOS – UM ESTUDO PRELIMINAR

RESUMO. Os acidentes de trânsito por motoristas idosos são um problema social urgente. A Agência Nacional de Polícia (*National Police Agency* – NPA) no Japão institucionalizou o Teste de Função Cognitiva (teste NPA) para renovação de carteira de motorista para idosos. No entanto, a capacidade de dirigir não pode ser avaliada simplesmente por testes cognitivos usuais escritos. **Objetivo:** É importante adicionar um teste em estrada, mas se não for possível, simuladores podem ser utilizados. Antes de fazer simulações, é importante usar o pé direito para controlar os pedais do acelerador e do freio. Aplicamos o paradigma de Posner (teste de atenção visual) para extremidades inferiores. **Métodos:** Os participantes eram idosos. Eles e suas famílias tinham ansiedade sobre a condução de veículos. Os 66 participantes (44 homens e 22 mulheres) foram divididos em grupos com e sem experiência de acidente de trânsito, e foram examinados os seguintes testes: testes cognitivos gerais e funções executivas, o teste NPA, e um Teste de Reação de Extremidade Inferior original. Cada participante foi solicitado a pressionar o pedal de "freio" ou "acelerador" com o pé direito o mais rápido possível em resposta a uma situação de trânsito mostrada na tela. **Resultados:** Comparados aos participantes com reações favoráveis ao Teste de Reação de Extremidade Inferior, aqueles com tempo de reação ruim tenderam a ter mais acidentes de trânsito (OR=6,82) do que o resultado do teste NPA. **Conclusões:** s resultados sugerem que a probabilidade de ocorrência de um acidente de trânsito pode ser melhor avaliada por meio do Teste de Reação da Extremidade Inferior.

Palavras-chave: Envelhecimento; Condução de Veículo; Atenção.

This study was conducted by the Group of Geriatric Behavioral Neurology Project, New Industry Creation Hatchery Center, Tohoku University, Sendai, Japan.

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INTRODUCTION

Traffic accidents by older drivers are a social urgent problem and there is a need to develop reliable measures of driving ability.

People with mild cognitive impairment (MCI) or early dementia show driving disability. Di et al.[1] used machine learning to predict incident MCI and dementia using monthly driving data from in-vehicle recording devices. Babulal et al.[2] examined whether driving behavior can predict preclinical Alzheimer's disease (AD). Driving can be used as a novel neurobehavioral marker to identify the presence of preclinical AD. A couple of systematic reviews concluded that all cognitive domains apart from language reported to show a moderate association with on-road driving outcome in mild dementia[3], we are still far from a widely accepted approach of driving ability evaluation in this increasing population[4].

However, a real-world driving test cannot be performed in Japan for license testing in all drivers, although driving simulation and neuropsychological tests are used for evaluating driving ability.

The National Police Agency (NPA) in Japan has standardized a *Cognitive Function Test* (NPA test) for renewal of a driver's license for adults aged ≥75 years. It consists of time orientation, figure naming and recall after interference, and clock drawing. When a driver is identified as Class 1 (suspected decrease of cognitive function), they have to submit a medical certificate. The guidelines require evaluations of dementia, such as AD or vascular dementia; higher brain functions including aphasia, apraxia, visuospatial function, and executive function; and the Clinical Dementia Rating (CDR)[3,4] and suspected MCI. However, we think driving ability cannot be evaluated simply by testing of cognitive function based on the belief that these abilities are equivalent, as in the NPA test.

In driving a car, it is important to use the right foot in different ways to control the accelerator and brake pedals. These pedals have conflicting functions and are located in a place where a driver cannot confirm the pedals visually. The upper extremities are used to control the wheel, but even if a driver visually confirms a risk and intends to control the wheel, the risk cannot be avoided without appropriate use of the right foot.

For example, the Trail-Making Test (TMT) is a well-known measure of executive function, but a version of this test for the foot is not common[5]. The nerves of the foot are located furthest from the brain and are easily affected by aging. In patients with cerebrovascular disease, vascular Parkinsonism may be present even if there is no clear decrease in cognitive functions that control use of the upper extremities and language. AD with cerebrovascular disease is the main form of dementia in Japan, followed by vascular dementia[6,7]. Thus, many people with very mild symptoms may be living in the community.

This background raises the question of the best test for detection of reduced function of the lower extremities for driving. The Posner paradigm is used as a visual attention task for the upper extremities[8,9]. This is a simple test, in which an examinee is requested to push the right or left button on a computer screen when a light is shown on the right or left side with hands, respectively. As a pre-cue, we prepared a valid condition, in which the light is shown in the same place as that in a real test, and an invalid condition. Healthy persons can react to lights on the right and left equally since they suspect a faint when the light is shown on the right side as a pre-cue. Thus, they have no difference in reaction time between the valid and invalid conditions. However, some patients with cognitive dysfunction, especially AD, have a delayed reaction because they are affected by the invalid conditions provided as a pre-cue[9]. This is a disorder of attention shifting, which is a visual attention characteristic.

We thought that this principle may be applicable to a test of the lower extremities. When a red signal is shown, an examinee should press the brake, whereas with a green signal, the examinee should press the accelerator, but should press the brake if a child is seen, even when the light is green. This is a high-level task in which a signal color and a child need to be recognized at the same time to operate the brake or accelerator appropriately. Here, we define this procedure as the "Lower Extremity Reaction Test." After accumulation of data for accidents in a database of community medicine, we examined the relationships of these data with the results of the NPA test. Our hypothesis was that scores on the Lower Extremity Reaction Test would predict traffic accidents more effectively than those on the NPA test.

METHODS

Participants and classification

This was a consecutive outpatient study. The participants were older adults who visited an amnesia clinic in Town A. In Japan, patients who are diagnosed with dementia are required to return their driver licenses, and we use this rule to provide appropriate guidance. The participants had visited the clinic for the first time before diagnosis, at a time when they and their families had anxiety about their driving.

All participants were older adults who had got driving licenses before 40 years or more, and they all drive their cars 1–2 times a week. All participants were

assessed by a neurologist (K.M.) for the functional capacity in lower limbs, and no participants revealed weakness of muscle strength, sensory disturbance, and coordination problem. Their ADL levels were good and did not have orthopedic problems.

Inclusion criteria

The participants were required to have a driver's license and to have driven their cars in the local area over the past 2 years. Since they had passed the test for renewal of the driver license, other than the NPA test, we judged that they had no problem with near visual acuity.

Exclusion criteria

Older adults with paralysis or sensory deficit confirmed in a neurological test were excluded.

Older adults who take dementia medication such as a cholinesterase inhibitor, a drug for improvement of cerebral circulation and metabolism, an antiepileptic drug, an antidepressant, or another drug that may affect cerebral circulation and metabolism were excluded from the study.

A total of 66 participants (men: 44, women: 22) were divided into groups with and without experience of a traffic accident (the accident group vs. the nonaccident group), and correlations with the following test results were examined.

Ethical considerations

Written informed consent was obtained from all participants and their families before the study was conducted. The study was performed after obtaining approval from the Ethical Committee of Tohoku University School of Medicine.

Tests conducted in the study

Questionnaire survey on traffic accidents

Traffic accidents, including property damage accidents, were evaluated based on self-reporting and information from families of the participants. According to the Japanese Road Traffic Act 2, traffic accidents are defined as accidents causing injury (or death) or property damage accidents.

Neuropsychological tests

General cognitive function and executive function test

The Mini-Mental State Examination (MMSE) was used as a general cognitive function test, and the TMT-A and Digit Symbol (DS) test (120 s) were used as executive function tests.

National police agency test

The NPA test was performed to categorize the participants into Classes 1, 2, and 3. Class 1 shows suspected decrease of cognitive function (grossly correspond to dementia), Class 2 indicates possible decrease of cognitive function (grossly correspond to MCI), and Class 3 notes no cognitive impairment.

Original lower extremity reaction test

The Posner paradigm as a visual attention task[8,9] for the upper extremities was adapted to the lower extremities. A computer designed for persons with a disability of the upper extremities was used, since this has two pedals placed side by side for use with the lower extremities. Each participant was asked to press the "brake" or "accelerator" pedal as quickly as possible in response to a traffic situation indicated by each of four images shown on the screen (Figure 1).

The reaction times of the lower extremity were measured and correct and incorrect reactions were recorded. The following information was given to the participants:

- Pedals are positioned on the right and left sides under a desk with a computer screen, as the "accelerator" and "brake," respectively. The pedals under the desk cannot be seen.
- Only the right foot should be used to push the accelerator or the brake.

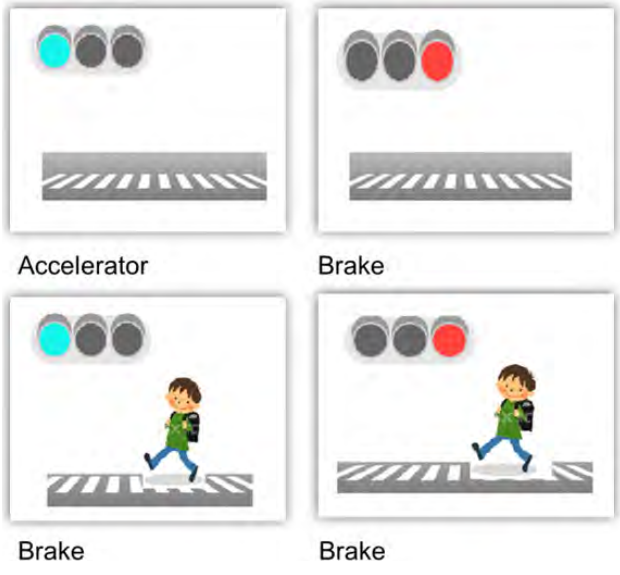

Figure 1. A computer designed for persons with a disability of the upper extremities was used, since this has two pedals placed side by side for use with the lower extremities. Each participant sitting position was asked to press the "brake" or "accelerator" pedal as quickly as possible in response to a traffic situation indicated by each of four images shown on the screen.

- After a red or green light is shown on the computer screen, the brake or accelerator should be pressed as quickly as possible, using the right foot (simple condition).
- A more complex condition will be used to simulate a driving situation as closely as possible. For example, if a child is seen, even when the light is green, the brake should be pressed.

Statistical analyses

Demographics

The demographics (together with the results of Analysis 1) of the two groups are summarized.

Relationships between the lower extremity reaction test and others

To examine how the results of the Lower Extremity Reaction Test are related to function, the number of correct actions and average reaction time (s) were defined as objective variables. Spearman rank-correlation coefficients were then calculated for these variables with age, scores on the MMSE, TMT-A, DS, and NPA tests.

Difference between the accident group and the nonaccident group

The test scores are compared between the accident group and the nonaccident group. The Mann-Whitney U test was performed for both groups without logistic analysis.

Prediction of traffic accidents using the lower extremity reaction test and the National Police Agency test

A crossover analysis was performed to examine the relationship of traffic accidents based on the classification using the NPA test and the reaction time measured under complex conditions in the Lower Extremity Reaction Test, using a chi-square test and calculation of the odds ratio.

Logistic analysis of traffic accidents was also performed, using all measures as forced entry, and that of the number of correct actions and reaction time as explanatory variables.

The SPSS software was used for statistical analysis.

RESULTS

Demographics

The demographics (together with the results of Analysis 1, see below) of the two groups are shown in Table 1.

There was no significant difference in age, years of education, and total score on the MMSE[10] between the groups.

Relationships between the lower extremity reaction test and other tests

Table 2 shows the results of Analysis 1.

Difference between the accident group and nonaccident group

Table 1 shows the results of Analysis 2.

Prediction of traffic accidents using the lower extremity reaction test and the National Police Agency test

Figure 2 illustrates the results of Analysis 3.

Participants with a poor reaction time had experienced more traffic accidents, compared to those with a favorable reaction. The relationship between reaction

Table 1. Demographics and differences between accident and nonaccident groups.

		Accident	Nonaccident	t-test, chi-square test, Mann-Whitney U test	p-value
Participants (men/women)		32 (24/8)	36 (20/16)	2.8	0.94*
Age (years)		77.6 (5.9)	75.2 (7.0)	1.5	0.14†
Education (years)		11.3 (2.3)	11.6 (2.5)	-0.56	0.58†
MMSE (score)		19.1 (5.7)	20.5 (6.2)	328.0	0.45
Trail-making test, s		81.0 (34.4)	66.0 (38.4)	208.0	0.046
Digit Symbol (120 s)		32.5 (13.6)	48.3 (18.3)	37.0	0.045
NPA test: Class I/Class II/Class III		16/12/4	13/13/10	2.7	0.26*
Lower extremity reaction test	Correction	23.6 (8.2)	27.9 (3.6)	363.5	0.008
	Reaction time	1.17 (0.41)	1.03 (0.66)	351.0	0.006

*Chi-square test. †t-test. MMSE: Mini-Mental State Examination; NPA: National Police Agency.

Table 2. Relationships between the lower extremity reaction test and other tests.

	Number of correct actions		Average reaction time	
	rs	p-value	rs	p-value
Age	-0.30	0.012	0.17	0.170
NPA test	0.34	0.005	-0.55	<0.001
MMSE	0.54	<0.001	-0.52	<0.001
Trail-making test A	-0.49	<0.001	0.35	0.013
Digit symbol (120 s)	0.63	<0.001	-0.68	<0.001

NPA: National Police Agency; MMSE: Mini-Mental State Examination.

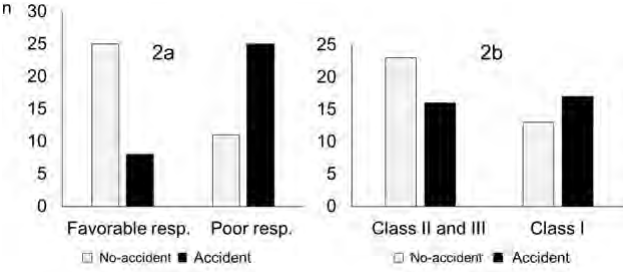

Figure 2. Participants with a poor reaction time had experienced more traffic accidents, compared to those with a favorable reaction [chi-square value=9.89, p=0.017 (two-sided), odds ratio (OR)=5.00]. **A.** The relationship between reaction time and experience of traffic accidents for participants with correct reactions. Compared to participants with favorable reactions, those with poor reaction time tended to have more traffic accidents [chi-square=13.40, p=0.0003 (two-sided), OR=6.82]. **B.** The results for the NPA test showed that older participants in Class 1 also tended to have traffic accidents more than those in Classes 2 and 3 [chi-square=1.7, p=0.20 (two-sided), OR=1.88]; however, the Lower Extremity Reaction Test gave a higher odds ratio.

time and experience of traffic accidents for participants with correct reactions is shown in Figure 2A. Compared to participants with favorable reactions, those with poor reaction time tended to have more traffic accidents. The results for the NPA test (Figure 2B) showed that older participants in Class 1 also tended to have traffic accidents more than those in Classes 2 and 3; however, the Lower Extremity Reaction Test gave a higher odds ratio.

The results of logistic analysis forced entry of all measures showed all negative findings. However, by focusing the number of correct reactions and the reaction time as variables, only the number of correct reactions had a significant correlation with the probability of having a traffic accident. We have entered all measures shown in Table 1.

DISCUSSION

Summary of results

We developed an original Lower Extremity Reaction Test for asking participants to press the "brake" or "accelerator" pedal by the right foot as quickly as possible in response to a traffic situation shown on the screen. Compared to participants with favorable reactions to the Lower Extremity Reaction Test, those with poor reaction time tended to have more traffic accidents, rather than the result of the NPA test.

Relationships between the lower extremity reaction test and other tests

The results for the Lower Extremity Reaction Test were correlated with general and executive function, which suggests a high validity of the test. There was no correlation with age, which indicates that the results of the test are not affected by visual acuity or motor response, which are normally decreased by aging.

Markers of traffic accidents: National Police Agency test versus lower extremity reaction

Participants with experience of a traffic accident had a significantly lower average reaction time(s) on the Lower Extremity Reaction Test, even after multivariate adjustment. The odds ratios suggest that the probability of having a traffic accident can be partially predicted by a neuropsychological test with use of the upper extremities, but that this probability cannot be fully determined without evaluation of use of the right foot for pressing the accelerator or brake.

Pedal operation

In a study by Hasegawa et al.[11], participants using a driving simulator were required to stop a vehicle as quickly as possible when a red signal was presented on a monitor. In most trials, the vehicle stopped when the brake pedal was applied in a normal manner. In a few trials, however, stepping on the brake pedal resulted in sudden acceleration of the vehicle (unintended acceleration). These results suggest that there are age-related differences in error detection and correction abilities in unexpected situations, due to incorrect pedal manipulation. During a situation of unintended acceleration, the ability to correct pedal stepping declined in older subjects; however, there was no significant age-related decline in the quickness of performing regular and simple pedal stepping.

Neurological basis of safe driving

A recent review[12] indicated that widespread brain networks, including the occipital, parietal, frontal, and

cerebellar regions, are required for safe driving. These networks are vulnerable in AD pathology that shows extensive neocortical brain damage, and early pathological changes in the posterior temporo-parietal regions are responsible for impaired driving in the early stage of AD. Using a driving simulator and functional magnetic resonance imaging, Choi et al.[12] determined the overall effective connectivity between brain areas related to driving. In both hemispheres, visual attention, inhibitory control movement, and episodic memory retrieval pathways were prominent. The activation of these pathways indicates that driving requires multidomain executive function, in addition to vision. Moreover, pathway activation is influenced by driving experience and familiarity of the driver. An interesting finding of Choi et al. was the prominence of the inhibitory control movement pathway in both hemispheres[12]. Research on inhibitory control has mainly been conducted using go/no-go tasks[13], and there are no reports associated with driving. Inhibitory control is a multidomain executive function critical for flexible responsivity to changing task demands and thus is an essential component of adaptive behavioral regulation.

Limitations

The participants in this study were patients who visited an amnesia clinic for the first time; therefore, there is a possibility that patients with dementia were included. Generally speaking, older drivers in Japan do not want to be diagnosed by medical doctors, since their driving licenses should be returned to the police office once diagnosed with dementia. Our participants had also this behavior and not all of them had medical diagnosis. This is a limitation of this study and had added a description of these in the revise manuscript. In the future, it will be required to perform tests for older adults classified as healthy (CDR 0) or with possible dementia (CDR 0.5), as determined by using CDR evaluation. This study also includes the first use of the Posner cueing task for the lower extremities, and there are no standard values for this test. Results for CDR 0 subjects would provide these values.

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Authors' Contributions: KM: conceptualization, methodology, project administration, supervision, writing – original draft, and writing – review & editing; KK: data curation.

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Original Article

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Three verbal fluency tasks:
normative data and convergent validity in Argentines over 50 years

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ABSTRACT. Verbal fluency tasks are frequently used in neuropsychological assessment, standing out for their easy application and good sensitivity to early cognitive impairment. However, in Argentina, the availability of updated norms is limited, especially for the action fluency variant. There is also little evidence of validity. **Objectives:** The aim of this study was to obtain Argentine norms for three verbal fluency tasks and to analyze their convergent validity. **Methods:** Using a nonprobability sampling method, 303 Argentines from a nonclinical population (age mean=66.8, 50–91 years) were recruited to participate in this study. Those with medical conditions that could compromise neuropsychological performance were excluded. Three verbal fluency tasks (i.e., phonological, semantic, and action), the Montreal Cognitive Assessment (MoCA) test, and the Digit Span-WAIS III test were administered. Correlations and multiple regressions were subsequently performed. **Results:** Education and age significantly explained 11.8% of the variance in phonological fluency, 15.8% of the variance in semantic fluency, and 20.2% of the variance in action fluency. Hence, the normative data varied according to educational level and age group, with normal performance limit values between 9 and 14 for phonological fluency, 11 and 18 for semantic fluency, and 8 and 17 for action fluency. Positive correlations were obtained between all verbal fluency tasks, as well as between the MoCA test and the Digit Span test. **Conclusions:** This study supports the applicability of three verbal fluency tasks in an Argentine context by providing age- and education-corrected norms and acceptable evidence of convergent validity.

Keywords: Neuropsychological Tests; Language; Speech; Argentina; Reproducibility of Results; Verbal Fluency.

TRÊS TAREFAS DE FLUÊNCIA VERBAL: DADOS NORMATIVOS E VALIDADE CONVERGENTE EM ARGENTINOS COM MAIS DE 50 ANOS

RESUMO. As tarefas de fluência verbal são frequentemente utilizadas na avaliação neuropsicológica, destacando-se pela facilidade de aplicação e boa sensibilidade ao comprometimento cognitivo incipiente. No entanto, na Argentina, a disponibilidade de padrões atualizados é limitada, especialmente pela variante de fluência de ações. Assim sendo, a evidência de validade é escassa. **Objetivos:** Obter normas argentinas para três tarefas de fluência verbal e analisar sua validade convergente. **Métodos:** Usando um método de amostragem não probabilística, 303 argentinos de uma população não clínica (idade M=66,8, 50–91 anos) foram recrutados para participar deste estudo. Foram excluídos aqueles com condições médicas que pudessem comprometer o desempenho neuropsicológico. Três tarefas de fluência verbal (ou seja, fonológica, semântica e ações), o teste *Montreal Cognitive Assessment* (MoCA) e o teste Digit Span-WAIS III foram administrados. Correlações e regressão múltipla foram realizadas posteriormente. **Resultados:** A escolaridade e a idade explicaram significativamente 11,8% da variância da fluência fonológica, 15,8% da variância da fluência semântica e 20,2% da variância da fluência de ações. Assim, os dados normativos variaram de acordo com a escolaridade e a faixa etária, com limite de desempenho normal entre 9 e 14 para fluência fonológica, 11 e 18 para fluência semântica e 8 e 17 para fluência de ações. Foram obtidas correlações positivas entre todas as tarefas de fluência verbal, bem como entre estas, o teste MoCA e o *Digit Span*. **Conclusões:** Este estudo apoia a aplicabilidade de três tarefas de fluência verbal no contexto argentino, fornecendo normas corrigidas por idade e educação e evidências aceitáveis de validade convergente.

Palavras-chave: Testes Neuropsicológicos; Idioma; Fala; Argentina; Reprodutibilidade dos Testes; Fluência Verbal.

This study was conducted by the Centro de Investigación en Neurociencias de Rosario (CINR), Facultad de Psicología, Universidad Nacional de Rosario, Rosario, Argentina.

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INTRODUCTION

Neuropsychological evaluation (NPE) is the test of choice to characterize the state of higher brain functions, such as attention, memory, language, agnosias, or executive functions[1]. Regarding the use of NPE among adults, this type of procedure offers useful information to clinical neurologists to confirm or rule out the presence of amnesias, aphasias, hemineglect, agnosias, or other neuropsychological syndromes. It also constitutes a key tool in the early detection of cognitive impairment and dementia, all growing problems that are of great concern to public health systems in the Americas and the world[2-4].

Although NPE is highly variable in terms of strategies and instruments, since it depends mainly on the patient's problems[5,6], most evaluations usually contain specific language tests, covering one or several linguistic domains, such as verbal fluency (VF), comprehension, repetition, or naming. Among the most commonly used language tests, VF tasks stand out for their easy and brief application[7] and for their good sensitivity to early cognitive impairment and other neurological pathologies[8]. VF is an appropriate strategy for assessing healthy and cognitively impaired older adults with low educational level[9]. Verbal fluency is defined as the ability to produce spontaneous speech, without excessive pauses or word search failures[10] and requires verbal information retrieval strategies, with simultaneous activity of several cognitive processes, such as sustained attention, semantic memory, working memory, processing speed, flexibility, and even inhibitory mechanisms[5].

From a procedural point of view, VF tasks require the examinee to say as many words as possible in a given time, usually 1 min[5,11]. Its main variants are two, phonological fluency, in which words beginning with a specific letter must be mentioned, avoiding proper nouns, conjugations of the same verb, or words of the same family, and semantic fluency, which requests words belonging to a specific category (e.g., animals). A less conventional variant that has recently begun to be used is the action VF task[12], in which the examinee is asked to enunciate verbs in Spanish ending in ar, er, or ir.

All neuropsychological tests require norms or scales according to their correct interpretation; that is, reference values that allow the professional to contrast the scores of the person examined with the scores of the general population. In this regard, the literature on the subject warns about the influence of age and education on the performance of neuropsychological tests[1,8] and, therefore, it is advisable to take into account these demographic variables in the construction of norms. It is important to emphasize that the norms should come from the same cultural context in which the administration of the test is planned, since the performance of a test may vary significantly among subjects of different nationalities[13,14]. Furthermore, according to the recommendations of the Argentine Association for Study and Research in Psychodiagnostics[15], it is necessary to use updated norms that are less than 10 years old. Regarding VF task norms in Argentina, a recent systematic review[16] reported nine normative studies[7,8,10,17-22]. Most of these normative studies are more than 10 years old and focus only on the two classical variants of VF (i.e., phonological or semantic), with the exception of Abraham and collaborators[17] who provide norms for the action VF task.

In addition, as with any psychometric test, it is essential that neuropsychological tests are valid and reliable[23,24] and that the analysis of their metrics takes into account different cultural contexts, since a neuropsychological test may work correctly in one context, but not in another. Regarding VF tasks, in general, acceptable metric properties are reported[11,12,25], although in Argentina, as Martino et al.[16] have warned, the volume of psychometric studies is limited. In fact, there is only one study with an adult population[18] in which the validity of the semantic VF task was tested. Results showed significant correlations with the Trail-Making Test, part A (r=-0.36) and part B (r=-0.40), a test that evaluates attention and flexibility, respectively, and with the Porteus Maze test (r=0.26) that evaluates mental planning. Fernández et al.[18] proposed that prefrontal cortex activity is the common factor that would group the measures of these three instruments.

The present study has two objectives: first, to obtain updated normative data for three variants of VF tasks in Argentine adults; and second, to analyze whether these tasks present adequate convergent construct validity. The information provided in this study will enrich the process of neuropsychological assessment and diagnosis in Argentina.

METHODS

Study type

The present study falls within the field of psychometric research or instrument testing based on the classification devised by Ato et al.[26]

Sample

A total of 303 Argentines, aged 50 years or more, participated in the study. Figure 1 reports the sample selection criteria. For this study, nonprobabilistic, purposive

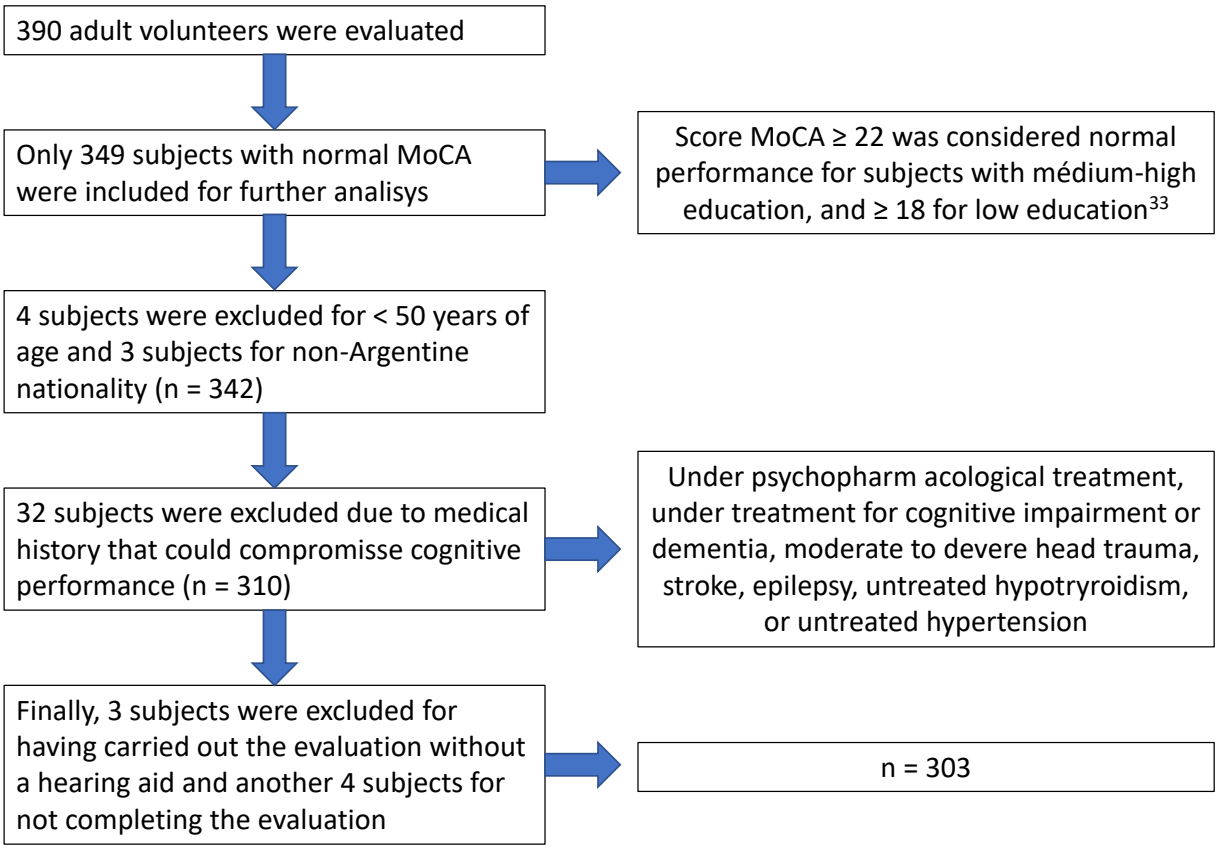

Figure 1. Participant selection criteria and process.

sampling was carried out between November 8 and 26, 2021, in the city of Rosario, Argentina, as part of a community campaign for the prevention of cognitive impairment and dementia.

The mean age of the sample was 66.8 years (SD=9.2, min.=50, max.=91) and 74.9% were female. A total of 57.4% reported >12 years of education (mean=18.1, SD=3.4), 34.7% between 8 and 12 years of education (mean=11.6, SD=1.1), and 7.9% reported ≤7 years of education (mean=6, SD=1.4).

Instruments

Verbal fluency tasks[5,11]

Phonological, semantic, and action VF tasks were administered. Regarding phonological VF, participants were asked to name words beginning with the letter "p," with the exception of proper nouns, verb conjugations, and words of the same family. The semantic VF was evaluated by asking participants to name as many animals as possible. For the action variant, infinitive verbs in any of their endings (i.e., ar, er, or ir) were requested. For each task, participants were given 60 s, and one point was awarded for each correct word. A higher score was indicative of a higher VF. Previous studies showed good psychometric properties[11,12,16,25].

Montreal Cognitive Assessment (MoCA)[27]

It is a screening test widely used for the global assessment of neuropsychological performance in adulthood. It is characterized by its easy application, between 10 and 15 min, and is composed of tasks that demand visuospatial and visuoconstructive skills, executive functions, memory, attention, calculation, language, and temporospatial orientation. The maximum score is 30 points, and a higher score is indicative of better performance. This test has been translated into Spanish by the same authors of the original version with acceptable validity and reliability indicators[28-30], including validation and norm studies in the Argentine population[31-33].

Digit Span-WAIS III test[34]

The test consists of two parts, namely, forward and backward, which evaluates attentional span and

working memory, respectively. The "forward" part requires the repetition of a list of numbers in the same direction as they were formulated by the evaluator, while the "backward" part requires repeating the numbers in the opposite order. One point is obtained for each correct attempt with a total of 16 points forward, 14 points backward, and 30 points between both parts. Higher scores indicate greater attentional span/working memory. Good psychometric properties were reported[34].

Data collection procedure

The evaluation of the participants was carried out in the context of a prevention campaign carried out in November 2021, in Rosario, Argentina. The campaign was a university extension activity organized and coordinated by the researchers themselves. Its purpose was to raise awareness of protective habits of cognitive functions and routinely assess the general cognitive status of interested adult bystanders. The activity had the support and logistics of the state university of that same town, with tents installed in public spaces and other material means. After receiving brochures on protective habits and being evaluated with the free routine cognitive test (MoCA), the bystanders were invited to participate in the research, signing their consent and subsequent resolution of the specific neuropsychological tests (Digit Span-WAIS III test and three VF tasks). The instruments were administered by researchers and professionals in collaboration with a group of advanced psychology students, who were systematically trained through theoretical and practical workshops.

Ethical and legal aspects

The research was conducted in accordance with the Declaration of Helsinki. Only subjects who agreed to participate voluntarily and gave written informed consent were included in the study. The study was approved by the Research Ethics Committee of the School of Psychology of the National University of Rosario, Argentina.

Data analysis

The SPSS v26.0© was used. Measures of central tendency and dispersion were obtained for the VF tasks, total MoCA, and the three Digit Span test scores (i.e., total, forward, and backward). Bivariate correlations were performed to analyze the association of years of education and age with VF task performance. Then, a stepwise multiple regression analysis was performed to estimate the extent to which years of education and age explain performance on VF tasks. For this purpose, years of education and age were entered as predictor variables, and phonological, semantic, and action VF scores were considered explained variables.

Regarding the normative data, normal performance limit values were established based on the SD of the mean. According to *DSM-V*[35], values below this limit are considered indicative of poor performance.

Later, to analyze the convergent construct validity, a possible correlation was tested between the three VF tasks and between each of these and the MoCA and Digit Span test scores. It is important to note that while the MoCA test provides a measure of general neuropsychological performance, the Digit Span test provides measures of attentional span and working memory, all of which are theoretically constructs related to VF. Consequently, positive correlations should be obtained between VF tasks, the MoCA test, and the Digit Span test.

To determine the use of parametric or nonparametric methods, the normal distribution (Kolmogorov-Smirnov) was tested. In the absence of normality, correlations were performed according to Spearman's coefficient. For all analyses, a value of $p<0.05$ was considered statistically significant.

RESULTS

Descriptive statistics were obtained for phonological, semantic, and action fluency tasks and for the remaining neuropsychological assessments (Table 1).

Influence of age and education on VF tasks

As shown in Table 2, the three VF tasks correlated positively with years of education and negatively with age.

Table 1. Descriptive of three verbal fluency tasks, MoCA test, and Digit Span test (n=303).

Neuropsychological tests	Mean (SD)
VF phonological	17.39 (5.5)
VF semantic	20.85 (5.9)
VF action	19.96 (7.5)
MoCA total	24.27 (3.2)
DigTest total	14.76 (3.9)
DigTest forward	9 (2.3)
DigTest backward	5.76 (2)

VF: verbal fluency; DigTest: Digit Span test; SD: standard deviation.

Table 2. Bivariate correlations.

	VF phonological	FV semantic	FV action
VF phonological	-	0.506*	0.586*
VF semantic	-	-	0.599*
Years of education	0.262*	0.232*	0.443*
Age	-0.257*	-0.347*	-0.199*
MoCA total	0.415*	0.378*	0.439*
DigTest total	0.399*	0.368*	0.509*
DigTest forward	0.245*	0.318*	0.430*
DigTest backward	0.392*	0.344*	0.490*

VF: verbal fluency; DigTest: Digit Span test; s: Spearman. *Correlation is significant at the <0.01 level (two-tailed).

Multiple regression models

Regression models indicate that education and age significantly explained 11.8% of the variance of phonological VF (r^2 corrected=0.118, F=21.27, p<0.01), 15.3% of the variance of semantic VF (r^2 corrected=0.153, F=28.3, p<0.01), and 20.2 % of the variance of action VF (r^2 corrected=0.202, F=38.15, p<0.01). Likewise, for each new year of education, the phonological VF score increases by 0.28 units (β=0.282; t=4.5, p<0.01), 0.26 units for the semantic VF (β=0.263; t=3.96, p<0.01), and 0.65 units for the action VF (β=0.658; t=8.09, p<0.01). In contrast, the phonological VF score decreases 0.14 units for each new year of age (β=–0.145; t=4.47, p<0.01), 0.21 units for the semantic VF (β=–0.212; t=6.17, p<0.01), and 0.13 units for the action VF (β=–0.132; t=3.13, p<0.01).

Convergent validity

As shown in Table 2, VF tasks correlated positively with each other, as well as with total MoCA and all Digit Span test scores (i.e., total, forward, and backward).

DISCUSSION

The present study focused on three VF tasks with the purpose of obtaining norms adjusted to the Argentine context and analyzing convergent validity. For this purpose, 303 Argentines over 50 years of age from a nonclinical population were evaluated with three VF tasks (i.e., phonological, semantic, and action), the MoCA test, and the Digit Span test.

The finding to highlight is the influence of education and age on the performance of all VF tasks. These results are consistent with a large body of scientific literature that has reported the modulating effect of these demographic variables on the execution of VF tasks and neuropsychological tests in general[1,8]. In this regard, our regression analyses confirm that increasing education increases VF in all its variants and that, on the contrary, increasing age significantly reduces fluency. Based on the impact of education and age on the performance of VF tasks, Argentine norms adjusted for education and age range were developed (Table 3). These new norms are preceded by nine other Argentine normative studies of the adult population[7,8,10,17-22], and according to our review of the available literature, it is the second study with normative data for the VF variant of action, complementing the work of Abraham et al.[17].

Nevertheless, it is important to note the low frequency of subjects with low education. A total of 57.4% had post-secondary studies (>12 years of education), 34.7% had secondary studies (between 8 and 12 years of education), and only 7.9% reported primary education (≤7 years of education).

In turn, the current norms offer normal performance limit values according to education and age, adopting as a criterion a SD from the mean, based on the *DSM-V* criteria for neurocognitive disorders[34]. According to these criteria, scores between 1 and 2 SDs from the mean should be considered indicative of minor neurocognitive disorder (mild cognitive impairment), and more than 2 SDs from the mean, indicative of major neurocognitive disorder (dementia). Due to the low sample size for all subgroups with primary education (n<10 cases), it was considered inappropriate to report normal performance limit values for these subgroups. New studies with a larger sample size will be able to overcome this difficulty.

Despite the value of this type of measurement instrument in neuropsychology, it is important to keep in mind that the isolated administration of any neuropsychological test is insufficient to draw diagnostic conclusions. Hence, it is advisable to carry out evaluations of greater breadth and depth, using multiple neuropsychological tests and the assessment of daily functioning. Other qualitative aspects that may be present in the interview or during the general process of NPE should also be considered. Consequently, two major paradigms or approaches in Clinical Neuropsychological Evaluation are evident: the quantitative of the North American tradition and subject to psychometrics; and the qualitative approach, which advocates a more comprehensive view of the evaluation process, in accordance with the Soviet school and the figure of Alexander Luria[1,23,36].

Neuropsychological tests do not differ substantially from psychometric instruments used in the field of general psychological assessment and, therefore, require

Table 3. Normative data for three verbal fluency tasks in Argentines over 50 years old according to age and education (n=303).

	Age		Education		
			≤7 years	8–12 years	>12 years
Phonological fluency	50–59	Mean (SD)	15 (4.6)	17 (5)	19.7 (5.8)
		Normal performance limit	*	12	14
	60–69	Mean (SD)	15 (6.6)	16.2 (6)	19.7 (5.6)
		Normal performance limit	*	10	14
	70–79	Mean (SD)	12 (3.7)	16.4 (6)	17.3 (4.1)
		Normal performance limit	*	10	13
	≥80	Mean (SD)	12.6 (6.8)	12.8 (3.7)	15.7 (5.2)
		Normal performance limit	*	9	10
Semantic fluency	50–59	Mean (SD)	19.2 (6.1)	22.1 (6.5)	23.3 (5.5)
		Normal performance limit	*	16	18
	60–69	Mean (SD)	18 (3.8)	19.2 (5.6)	23.6 (5.9)
		Normal performance limit	*	14	17
	70–79	Mean (SD)	18 (4.7)	20 (5.1)	19.9 (5.1)
		Normal performance limit	*	14	14
	≥80	Mean (SD)	12 (6.2)	14.3 (2.5)	17.5 (5.3)
		Normal performance limit	*	11	12
Action fluency	50–59	Mean (SD)	12.4 (3.9)	17.4 (6.7)	23.5 (6.5)
		Normal performance limit	*	11	17
	60–69	Mean (SD)	12.3 (6.5)	17.9 (6.3)	23.8 (7.6)
		Normal performance limit	*	11	16
	70–79	Mean (SD)	13.8 (7.8)	18 (7.2)	20.7 (6.3)
		Normal performance limit	*	10	14
	≥80	Mean (SD)	11.6 (6.6)	14.2 (6.2)	19.1 (6.1)
		Normal performance limit	*	8	13

The absolute frequency of the number of participants according to age range and educational level is reported: 50–59 years old with ≤7 education, n=7; 8–12 education, n=25; >12 education, n=37; 60–69 years old with ≤7 education, n=6; 8–12 education, n=39; >12 education, n=74; 70–79 years old with ≤7 education, n=8; 8–12 education, n=29; >12 education, n=48; ≥80 years old with ≤7 education, n=3; 8–12 education, n=12; >12 education, n=15; *n smaller than 10 cases, so no normal performance limit value is reported.

evidence of validity and reliability as well as cultural context adjustment. This study analyzed the convergent validity of three VF tasks, assuming potential associations with other tests assessing close neuropsychological constructs. More precisely, the MoCA test assesses general neuropsychological performance, and the Digit Span test explores attentional and executive processes. Positive correlations were indeed found between the VF tasks themselves and between the MoCA test and the Digit Span test (Table 2). The results of the present study will help to increase the evidence of the construct validity of VF tasks in the Argentine context and to strengthen the volume of local scientific production in neuropsychological assessment.

This study is not without limitations. First, it relied on nonprobabilistic sampling, which compromises the generalizability of the data. Second, the evaluations took place within the framework of a prevention campaign, in tents set up in public spaces. Therefore, the existence of extraneous variables such as disturbing

noises or fluctuations in luminosity cannot be ruled out. The researchers are aware that this compromises the internal validity of the study. However, a more ecological setting, such as the one provided by the study, on the contrary, considerably strengthens the external validity of a neuropsychological investigation. Third, the administration of the instruments was carried out by researchers with specific training in neuropsychology and collaborators who were advanced psychology students. The presence of different evaluators could interfere as an extraneous variable depending on the subjectivity of each evaluator. However, it is worth clarifying that all the evaluators participated in workshops and periodic meetings in order to agree on a set of guiding criteria and mitigate potential differences in the administration of the instruments. Future studies should use inter-rater reliability to minimize these differences. Finally, the medical information with which the inclusion-exclusion criteria were defined was based on self-reports provided by the participants, and, thus, omissions or overestimates of disease events could not be ruled out.

This study provides new normative data and acceptable validity evidence for three VF tasks in the Argentine population over 50 years of age. It is recommended to Argentine neuropsychologists to incorporate these tasks into the assessment protocols for adults and older adults.

Authors' contributions. PM: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, writing – review & editing. MC: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, writing – review & editing. NP: writing – original draft, writing – review & editing. MG: conceptualization, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, writing – original draft, writing – review & editing. DP: conceptualization, resources, writing – original draft, writing – review & editing. MAB: writing – original draft, writing – review & editing. JV: writing – original draft, writing – review & editing.

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Physical inactivity and dementia in Brazil: a call to action

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ABSTRACT. Low- and middle-income countries will house two-thirds of cases of dementia in the world by 2050, while the incidence is decreasing in some high-income countries. In Brazil, one in four cases of dementia can be attributable to physical inactivity. Considering the projected prevalence of dementia by 2050 in Brazil, well-coordinated task forces are needed to improve awareness of non-pharmacological approaches in order to reduce the current and projected burden of dementia in the country. In this study, we discussed the current scenario and perspectives of physical inactivity and dementia in Brazil.

Keywords: Dementia; Exercise; Brazil.

INATIVIDADE FÍSICA E DEMÊNCIA NO BRASIL: UMA CHAMADA PARA A AÇÃO

RESUMO. Os países de baixa e média renda abrigarão dois terços dos casos de demência no mundo até 2050, enquanto em alguns países de alta renda a incidência está diminuindo. No Brasil, um em cada quatro casos de demência pode ser atribuído à inatividade física. Considerando-se a prevalência projetada de demência até 2050 no Brasil, estratégias bem coordenadas são necessárias para melhorar a conscientização sobre abordagens não farmacológicas, a fim de reduzir a carga atual e projetada de demência no País. Aqui, discutimos o cenário atual e as perspectivas sobre a inatividade física e a demência no Brasil.

Palavras-chave: Demência; Exercício Físico; Brasil.

It is estimated that 55 million people are living with dementia in the world, with 10 million new cases every year, or a new case every 3 s[1]. The elevated burden of the disease for patients, family, caregivers, and society made the World Health Organization (WHO) declare dementia as a global public health priority in 2012[2]. In the United States, the number of deaths due to dementia between 2000 and 2019 increased (145%), while the number of deaths decreased for heart disease (-7.3%) and stroke (-10.5%)[3]. In the United States, one in three elderlies still died with dementia, a value higher than the observed with breast and prostate cancer combined. This chaotic scenario is even crueler in low- and middle-income countries (LMIC), where roughly two in three cases of dementia in the world are housed. In Brazil, the hospitalization rate due to dementia increased by 75% from 2010 to 2019[4]. No other chronic disease had a superior change in the same period[4]. As can be seen in Figure 1, the proportion of people aged 60 years or older will rise by 99% from 2020 to 2050 while the cases of dementia per 100,000 individuals will increase by 210%. The number of people living with dementia in Brazil is expected to reach 5.7 million in 2050[5]. This value is 206% higher than the observed in 2019 (1.9 million)[5]. In other words, from the expected 3.8 million new cases of dementia in Brazil from 2020 to 2050, 53% is not explained by population aging.

In high-income countries such as the United States and the United Kingdom,

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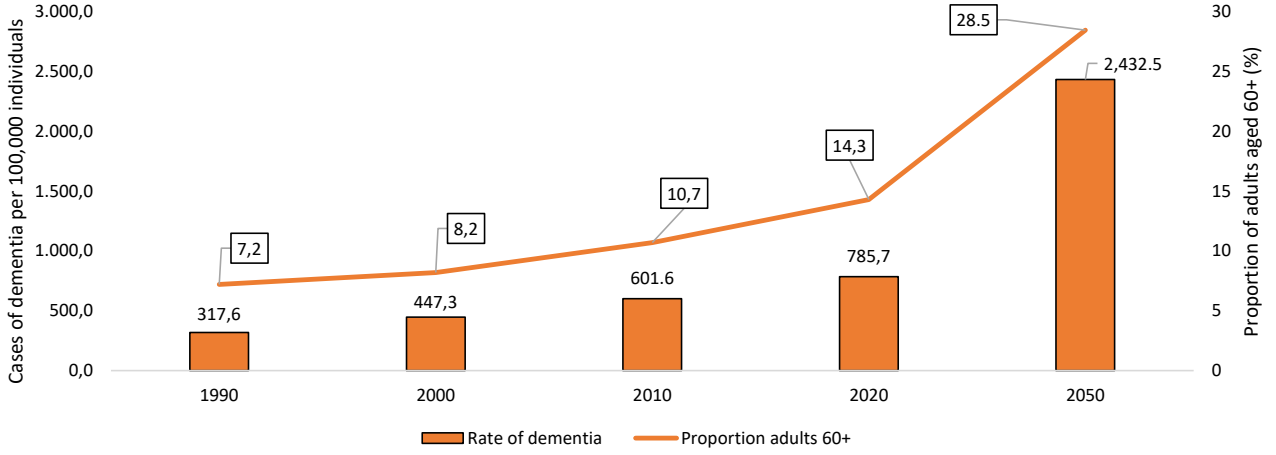

Figure 1. Rate of dementia per 100,000 individuals and proportion of older adults aged 60 years or older in Brazil from 1990 to 2050.

the incidence of dementia and mild cognitive impairment stabilized or even declined over the past years[6-9]. Some factors were suggested to explain this change in the incidence curve, including improved cardiovascular and metabolic health and education access. For example, a study with data from England and Wales reported a declined incidence of dementia from 2002 to 2013[8]. The authors stressed that the increase in physical activity accounted for the largest proportion of the reduction in the incidence of dementia over the period. On the other hand, change in the prevalence of other modifiable such as diabetes, smoking, and depression over time had negative to no confounding effects.

From Barnes and Yaffe's paper published in *The Lancet* in 2011[10] to the latest report from The Lancet Commission on dementia prevention, intervention, and care[11], myriad literature has emerged showing the protective effects on physical activity and the harmful impact of physical inactivity on dementia burden and prevalence. A meta-analysis with 42 cohort studies and 89,205 individuals revealed that high level of physical activity reduced the risk of cognitive decline (hazard ratio [HR]: 0.65; 95% confidence interval [CI] 0.55–0.76) and dementia (HR: 0.86; 95%CI 0.76–0.97) compared to low levels[12]. Noteworthily, the protective association remained after accounting for studies' quality, the number of covariates, and longer follow-up (≥10 years). Particularly in LMIC, the proportion of dementia cases that could be attributable to physical inactivity reached 23.3% in China, 17.0% in Latin America, and 8.4% in India, higher than the global estimative (6.5%)[13]. In Brazil, one in four cases of dementia can be attributable to physical inactivity[14]. On the other hand, four in five adolescents and half of adults in Brazil do not meet the guideline for physical activity. Among older adults, the prevalence of physical inactivity reached 72% and 82% in males and females, respectively[15]. Physical activity is likely to reduce throughout the life course, leading to an increased risk for other cardiovascular risk factors including hypertension and diabetes and, ultimately, increasing the risk of Alzheimer's disease and other dementias. Therefore, promoting physical activity from school-going children and adolescents to older adults must be prioritized in any public health plan to control the burden and incidence of dementia.

However, studies in LMIC investigating the effect of physical activity as an effective alternative to reduce the burden of dementia are scanty. For example, a PubMed, no time- or language-limited search performed in January 2022 using the combination of the terms related to dementia (cognitive impairment, dementia, Alzheimer's disease, vascular dementia), physical activity or exercise, and Brazil, returned only 12 original, non-systematic review articles investigating the effect of either physical activity or exercise in older adults with cognitive impairment or dementia. Regarding cohort studies, there are at least six population-based cohort studies investigating the factors associated with aging in Brazil: the EpiFloripa Idosos, SIGa-Bagé, Estudo Saúde, Bem-Estar e Envelhecimento (SABE), Estudo Longitudinal da Saúde dos Idosos Brasileiros (ELSI-Brasil), Bambuí study, and the COMO VAI? study. Most studies corroborate each other regarding the high proportion of physical inactivity among older adults. The SABE and COMO VAI? studies showed a prevalence of physical inactivity of 85.4%[16] and 82%[17], respectively, values higher than the observed in EpiFloripa Idosos (56.3%)[18], SIGa-Bagé (41.4%)[19], Bambuí (47.7%)[20], and the ELSI-Brasil (33%)[21]. In addition to the territorial, social, and cultural differences among the cities, the instruments to

measure physical activity were also diverse. For example, in the COMO VAI?,[17] SIGa-Bagé[22], EpiFloripa Idoso[18], and in ELSI-Brasil[21], the International Physical Activity Questionnaire (IPAQ) was used. The energy expenditure of physical activity performed in the past 90 days was assessed in the Bambuí study[20]. In SABE[16] and COMO VAI? studies[23], physical activity was also objectively measured using accelerometers. Physical inactivity has multiple consequences for the health of the elderly, and its high prevalence represents an alert for public health. Integrating care policies for the elderly with the practice of physical activity is not only a way to reduce the risk of death and chronic diseases but also an opportunity to improve the quality of life of this important and growing proportion of the Brazilian population.

Despite the relevance of the findings described, some outcomes lack investigation in Brazil, such as cognitive function and the incidence of dementia. For example, the Bambuí (Mini-Mental State Examination [MMSE]), ELSI-Brasil (memory and executive function tests), EpiFloripa (MMSE), and SABE (MMSE) cohorts included measures of cognitive function as an outcome. However, only the ELSI-Brasil included different instruments for memory (10-word Memory Test) and executive function (Verbal Fluency Test), capable of identifying the behavior of different domains of cognitive function over time. Furthermore, only ELSI-Brasil[24] and EpiFloripa[25] examined the prevalence of dementia and associated factors in their populations of interest. Considering the high social and economic burden of cognitive impairment and dementia, incorporating these outcomes in the next stages of the cohorts mentioned here could provide relevant information about its impacts on the health of the elderly population and identify factors that may contribute to attenuating such effects.

This finding is particularly curious, given that Brazil had one of the largest age-standardized prevalence of dementia in the world in 2019[5]. Recently, the Brazilian Federal Senate approved the law project of the National Policy of Integral Care of People with Alzheimer's disease and other Dementias[26]. In the approved document, controlling of dementia burden must include a care system to help patients to live as active as possible. The document also mentioned the need for robust economic investment in the development of pharmacological and non-pharmacological therapeutics for dementia. Nevertheless, the Federal budget for science and technology in Brazil was reduced by 94% in 2021[27]. Most research projects funded by the National Council for Scientific and Technological Development (CNPq, in Portuguese) were suspended due to a lack of funding. In other words, at the moment in which the world population is putting all its hope on vaccine treatment development for the COVID-19, Brazilian science was left aside.

Experiences from other countries have shown that the promotion of healthy habits such as physical activity, increased scientific investment for dementia-related researches, and increased awareness of dementia is an effective triplet to reduce the burden of dementia. We hope that policies including the National Policy of Integral Care of People with Alzheimer's disease and other Dementias will be encouraged and supported by all government levels. Up to 2 million cases of dementia in Brazil can be potentially prevented through a healthy lifestyle, controlling cardiovascular risk factors, and access to education. The future will prove to us whether these lives, their families, and the society were considered priorities of the present and future Brazilian governments.

Authors' contributions. NF: conceptualization, data analysis, methodology, writing – original draft, writing – review & editing. JSL: conceptualization, data analysis, methodology, writing – original draft, writing – review & editing.

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Case Report

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Avoiding surgery in patients with dementia: is it the correct management?

Tomonari Koto[1], Yoji Kurihara[2], Miwako Shoji[1], Kenichi Meguro[1,3,4]

ABSTRACT. Although hospitalization for dementia is increasing, Japanese doctors often refrain from surgeries considering dementia. A woman in her 80s diagnosed with Alzheimer's disease was admitted to hospital for cholelithiasis. Due to the avoidance of surgery, the inflammation was prolonged and therefore she was unable to eat. Later, she was discharged with central venous nutrition. The care burden on family resulted in her readmission to another hospital. Eventually, the inflammation was alleviated, and she was able to eat. However, it took a long time. In this study, we not only emphasize the risks but also focus on the benefits to postoperative rehabilitation. We also discuss about the benefits of invasive procedures in patients with dementia.

Keywords: General Surgery; Choledocholithiasis; Alzheimer Disease; Dementia.

EVITAR CIRURGIA EM PACIENTES COM DEMÊNCIA: É O MANEJO CORRETO?

RESUMO. Apesar do aumento de hospitalizações por demência, os médicos japoneses geralmente se abstêm de cirurgias ao considerar a demência. Uma mulher de 80 anos diagnosticada com doença de Alzheimer foi internada no hospital por colelitíase. O adiamento da cirurgia prolongou a inflamação e a deixou incapaz de comer. Ela foi forçada a receber alta com nutrição venosa central. A sobrecarga de cuidados para a família resultou em sua readmissão em outro hospital. Eventualmente, a inflamação foi aliviada e ela conseguiu comer. No entanto, levou muito tempo. Não devemos apenas enfatizar os riscos, mas também focar nos benefícios da reabilitação pós-operatória. Gostaríamos aqui de discutir e fornecer argumentos a favor de procedimentos invasivos em pacientes com demência.

Palavras-chave: Cirurgia Geral; Coledocolitíase; Doença de Alzheimer; Demência.

INTRODUCTION

The number of dementia cases is increasing rapidly in the aging society, and such patients are hospitalized in general wards for physical illness. We previously reported that 66% of patients admitted for surgery of proximal femoral fracture suffered from dementia in Japan[1]. Although hospitalizations for people with dementia are increasing, Japanese doctors often refrain from performing invasive surgeries, in consideration of dementia. Their opinions are as follows:

- Since postoperative rest is difficult, physical restraints are needed which may cause disuse syndrome,
- Dementia progresses and delirium can occur due to hospitalization and surgery, and
- Consent cannot be obtained from people with dementia. These were not evidence-based, but are examples of arguments.

In general, these views say, "We don't recommend surgery because we see the

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person, not the illness." While these perspectives are certainly not wrong, there is a concern that the risks and benefits are being assessed appropriately for each case. The acute care wards are structurally not intended for dementia patients. Therefore, we cannot deny a bias to avoid surgeries for dementia patients, considering the postoperative nursing problems (e.g., self-removal of IV drip, falls, difficulty in understanding medical instructions, and delirium).

Moreover, it is not obvious that people with dementia cannot consent to surgery. Their language dysfunction and judgment disabilities are highly variable. Some patients have difficulty in remembering but can understand the doctors' explanation and need for surgery. Now, the process of "listening to the person himself" is often ignored in the case of people with dementia in Japan. Previous discussion about the ability of dementia patients to consent is only related to informed consent on paper in most cases.

There are quite a few patients with dementia who are returned to their houses without surgery, even though their diseases indicate the need for surgery. These patients are followed up through home-visit medical care, but less is known about their subsequent process. If doctors in acute care hospitals knew what happens after discharge, they would likely make different choices in their treatment. In this article, we present a case who took a lot of time to recover from swallowing dysfunction because cholelithiasis cholangitis surgery was withheld, which prolonged the inflammation, increased the family burden, and led to the collapse of home care.

Patient information

Patient demographics: A woman in her 80s.

Diagnosis: Cholelithiasis cholangitis, Alzheimer's disease (AD).

Chief complaint: "I want to eat a normal meal."

Medical history: Artificial anus for ischemic enteritis (X–1 year).

Family composition: Husband, son, and daughter-in-law (same household). Daughter (separate household).

Cognitive function: Functional Assessment Staging of Alzheimer's Disease (FAST) -6.

Daily life independence level of the elderly with dementia: IIIa (in the Japanese scale): She has symptoms and behaviors that interfere with her daily life and difficulty communicating and requires nursing care, especially during the daytime.

Daily life independence level of the elderly with disabilities: C1 (in the Japanese Long-Term Care Insurance scale): She spends all day in bed and requires assistance with toileting, eating, and dressing, but turns over on her own.

The patient and her family provided written informed consent for the case details to be published. The Ethical Committee of the Kurihara Hospital approved the case details to be published.

Timeline

History of present illness

In September X, she was admitted to Hospital A for cholangitis and was treated conservatively with therapeutic suspension of feeding and antibiotics. After 10 days, hepatobiliary enzymes became normalized. However, she developed fever every time she resumed oral intake, and the inflammation may have been prolonged. Her doctor judged that there was no indication for choledocholithotomy and cholecystectomy. He permitted only a small amount of rice gruel in 3°. Therefore, her main nutrition was central venous hyperalimentation. She wanted to eat more, but aggressive treatment was not provided for her.

In October X, she left the hospital and made a home visit from Home Support Clinic B. She continued to develop fever at home but was willing to eat more. The daughter-in-law, who prepared all of the meals, could not decide what to serve and only provide a very small amount due to the fear of progression of the cholangitis. The daughter also had different views on food shape and volume, which was stressful for the daughter-in-law. Due to continued central venous nutrition, she was refused to use welfare services of day care and short stay admission. Since her son worked outside all day and her husband also required care, the daughter-in-law burned out providing care for the two. Under these stressful conditions, the daughter-in law showed depressive symptoms.

Clinical findings

In November X, the patient was admitted to Clinic C because the family could not care for her anymore.

Post-hospital course: The chief doctor continued to recommend a small amount orally because the patient exhibited an appetite. Initially, she continued to develop fever, which gradually became stable and stopped in mid-November X. However, she had not had any oral intake for almost 2 months. She exhibited a decrease in swallowing function due to disuse. Therefore, she needed dysphagia rehabilitation to allow her to ingest a solid diet again. After that, she stopped central venous nutrition in mid-December X and switched to a regular diet in January X + 1. Along with the increase in oral food, her strength and awakening improved, making it possible to ride on a wheelchair. In February X + 1, she

was transferred to the Long-Term Care Health Facility D for further rehabilitation (Figure 1).

Patient perspective

She herself really wanted to recover as taking food orally and receive surgical operation.

DISCUSSION

The prevalence of choledocholithiasis in the elderly is increasing in Japan due to westernization of eating habits and extension of the life span[2]. When acute cholangitis is complicated, the mortality is high. Therefore, the guidelines recommend that choledocholithotomy be performed after inflammation has improved[3].

According to the Japanese guidelines for cholelithiasis, this case corresponded to mild-to-moderate disease. After treatment with antibiotics, cholangiolithotomy and cholecystectomy were considered. But her doctor did not adopt surgical treatment. Consequently, the inflammation was prolonged and her feeding function was reduced by disuse syndrome, requiring long-term swallowing rehabilitation. Hospital A did not perform surgery because of the presence of dementia, in addition to being bedridden with an artificial anus. The risks of surgical treatment for people with dementia include:

- Disuse syndrome due to physical restraint and
- Postoperative cognitive dysfunction and delirium. In addition, the physicians find (three) difficulties in obtaining informed consent from dementia patients.

We can refute these opinions as follows:

- First, physical restraints are not always necessary for dementia patients. The consideration is based not only on patient factors but also on nursing circumstances such as the number of nurses and the night shift system. Surprisingly, 14.6% of the approximately 71,000 elderly inpatients in general wards received medical restraints in Japan. About 23,500 of these were dementia or suspected and received restraints at a rate of 44.5%[4]. It is unlikely that every restraint was valid or fully considered. Approaches for promoting restraint-free care in acute settings are currently being attempted in Japan. We should not only state that physical restraints worsen the activities of daily living (ADL) but also provide a good opportunity to think about "nursing without binding." The need for treatment itself should be considered separately.
- Second, cognitive decline due to surgery is well known as postoperative cognitive dysfunction (POCD)[5]. Notably, 10–15% of elderly people aged 60 years and over develop POCD, which

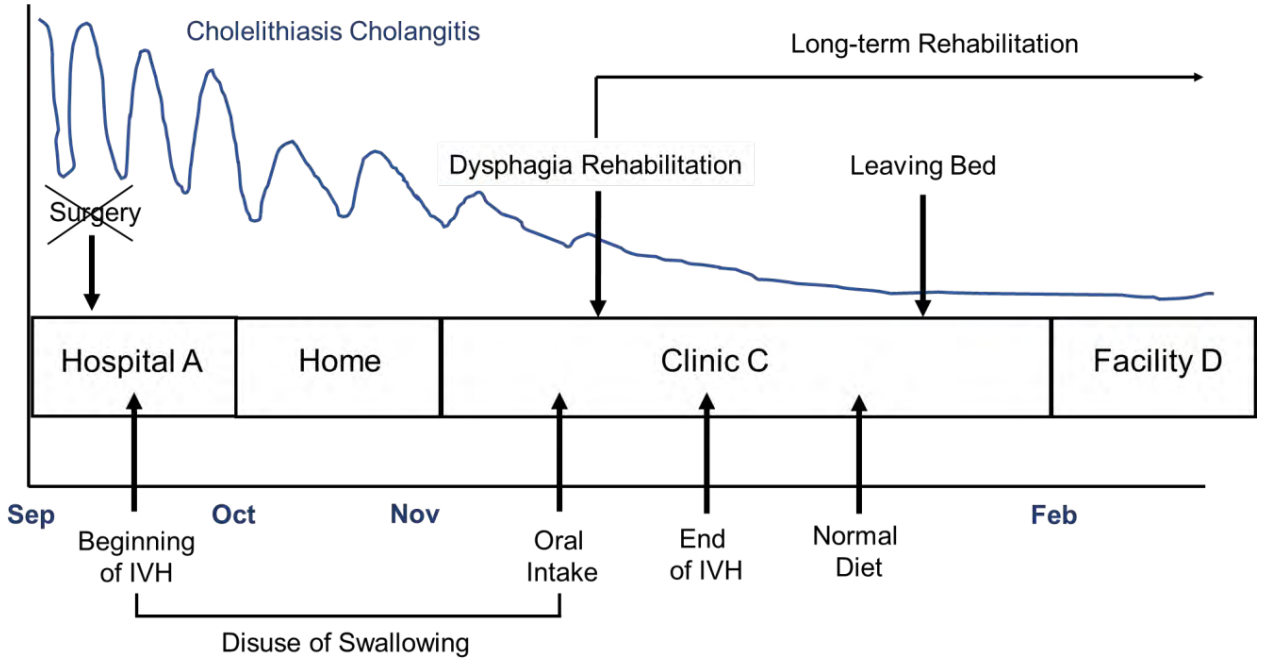

Figure 1. Clinical course and rehabilitation process. The avoidance of surgery resulted in prolonged cholangitis, very slow progress in oral intake, and long-term dysphagia rehabilitation.

lasts for 3 months or longer after major surgery, and it is associated with a long-term decrease in quality of life and an increase in mortality[5]. In addition, many studies indicate that old age and cognitive impairment are risk factors for postoperative delirium. The onset of POCD and delirium is influenced by multiple factors. Analysis and preventive intervention of these factors are indispensable in perioperative management. Since these complications can affect the postoperative course, they require coping and secondary prevention.

The common point of these two points is the fact that necessary and possible treatments are withheld from the patients due to the fact that perioperative management is difficult in the medical institutions. The deception lies in the fact that the withholding is explained as being "for the patient's sake"; the other way around. Is not this contrary to the Hippocratic Oath, which states, "I will take what I think will benefit the patient to the best of my ability and judgment, and I will never take what I know to be bad and harmful"? This statement assumes that the doctor will be prepared to administer all possible means of treatment. Meguro describes the role of the doctor in medicine as "two roles for one person." The first role of the doctor is that of a "soldier" who tries everything to save the patient. In contrast, he also plays the role of "chairman" who collects the opinions of the patient, family, and other caregivers to decide how far the treatment should be taken in reality[6].

Moreover, in such circumstances, the decision of a treatment plan based on the patient's will may be neglected, especially for people with dementia. In this case, the patient did not absolutely refuse surgical treatment. To achieve the goal of "becoming able to eat," the surgical explanation might have been accepted. Since she had sufficient appetite, she was receptive to postoperative rehabilitation. Even if the patient has severe dementia, it is desirable to listen to the will and reflect it in treatment policy. Even if the dementia patient's comprehension is flawed, there is an important therapeutic significance in directly listening to the patient's self-awareness and judgment of the situation. The patient's wishes can be reflected in the direction of treatment, as in the process at Clinic C. The patient's attitude toward life is valuable information that can be used to predict prognosis, postoperative care, and rehabilitation.

Importantly, withdrawing aggressive treatments may lead to secondary social problems for people with dementia. In areas that lack medical resources, patients who are not undergoing active treatment are not allowed to occupy hospital beds. For this reason, early discharge is unavoidable when patients are "physically" able to do so with medical visits. However, if they return home without adequate treatment, welfare services can be limited, as in this case. Outpatient services without a nurse are not available, especially if medical procedures are ongoing, such as central venous nutrition. Thus, the burdens are focused on the family caregivers, whose social, financial, and psychological losses are enormous. The withholding of invasive procedures could also lead to problems such as chronic pain and malnutrition, which, in turn, can also lead to delirium, higher caregiver burden, and immobility.

Although this case was not a palliative case and voluntarily did mention his hope that he would receive surgical operation although the surgeon hesitated for possible risks, we should also consider an importance of the palliative care approach, especially the well-established Physician Orders for Life-Sustaining Treatment (POLST)[7] decision to take or not surgical procedures should ideally be made in early stages of cognitive decline, but it may also be decided with a family reunion – but never by the doctor alone.

Although the surgeon did not consider cognitive recovery after anesthesia or surgery for the case, but the topic is important for surgery for older people. A recent review[8] summarizes the state of the relevant clinical science, including risk factors, identification and diagnosis, prognosis, disparities, outcomes, and treatment of perioperative neurocognitive disorders.

In this patient, the inflammation followed a protracted course without surgical treatment. During that time, the care burden was concentrated on the family, resulting in the collapse of long-term home care. Moreover, it took a lot of time and medical resources to recover the feeding function, including dysphagia rehabilitation. Due to "therapeutic nihilism" and medical economics, aggressive treatment for people with dementia tends to be restrained, although there is scientific evidence that prognosis in patients with dementia who underwent invasive procedures is worse[9]. However, we should not only emphasize the risks associated with the treatment but also focus on the benefits and positive factors that lead to postoperative rehabilitation, as well as the social resources available after discharge. We are required to make decisions based on more reasonable comparisons.

Authors' contributions. TK: conceptualization. YK: conceptualization. MS: methodology. KM: writing – original draft, writing – review & editing.

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Letter

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Performance on the matrix reasoning by Parkinson's disease patients: strategy is in the eye of the beholder

Desempenho de pacientes com doença de Parkinson no raciocínio matricial: a estratégia está nos olhos de quem vê

Yassar Alamri[1,2]

Dear Editor,

Matrix reasoning (MR) task is made up of a series of visual pattern completion and analogy problems. When compared with healthy controls, patients with Parkinson's disease (PD) performed significantly worse on the MR task[1]. The objective of the current study was to provide insight into possible strategies used by PD participants (by tracking eye movements during the MR task) compared with healthy controls.

We recruited 45 participants: 15 PD with normal cognition (PD-N), 14 PD with mild cognitive impairment (PD-MCI; according to MDS Task Force criteria[2]), and 16 healthy controls. The majority of participants were male: 81%, 81%, and 88%, respectively. The median age of participants was as follows: PD-N 66.1 years (range, 49.3–80.6 years), PD-MCI 71.8 years (range, 45.7–77.8 years), and controls 72.9 years (range, 56.4–81.4 years). Participants with PD had similar clinical staging according to the modified Hoehn and Yahr scar: PD-N 2.2±0.6, and PD-MCI 2.0±0.6 (p=0.58).

Details on the eye-tracking system and study setup have been published elsewhere[3]. MR items were chosen from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV). Participants were presented with one practice trial, followed by 10 test items (in an ascending order of difficulty).

All participants correctly identified the missing pattern in the practice trial. Scores in the test trials did not differ significantly among the three groups: PD-N 78% correct (±19), PD-MCI 67% correct (±17%), and controls 77% correct (±14). The number of incorrect responses increased as the test trials became more difficult (R^2=0.86, p<0.001).

A general trend of fixation density, across the MR test trials, was observed regardless of the group or the response given. The proportion of time spent fixating on the Scanning Area was longer than that on the Working Area. Within the Scanning Area, participants fixated longer on the visual pattern horizontally next to the missing one compared with the two visual patterns above or below it. Fixation behaviour on the Working Area differed according to the response given. The correct group fixated on the correct choice the longest, and not much else. Fixation durations

This study was approved by the Upper South B Regional Ethics Committee, New Zealand (reference URB/11/06/010).

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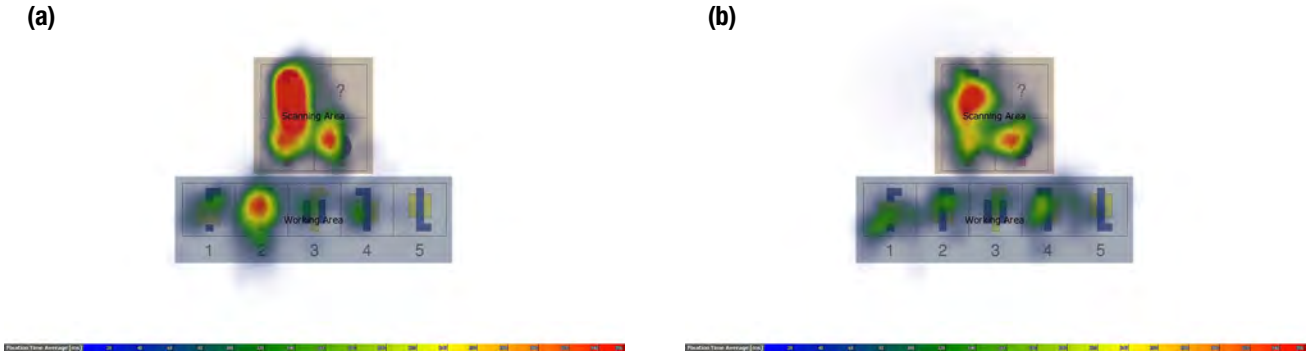

Figure 1. Heat maps of the fixations by the correct (a) and incorrect (b) participants.

of the incorrect group, in contrast, were divided almost equally between two or three choices (Figure 1).

Differences in the proportions of correct responses among the three study groups did not reach statistical significance. Our findings are contrary to the published literature, in which PD patients obtained significantly lower scores on the MR task[4]. However, our findings from eye-tracking provide novel insights into the strategy, by which participants navigate visual and analogy problems. Whilst deficits in visual search tasks have been reported in PD patients[5,6], the nature of these tasks (often highlight one or two salient features of a shape) differs from that of the MR task (i.e., complex visual pattern completion).

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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.