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Neuropsychological predictors of conversion to dementia and cognitive trajectory of older adults with mild cognitive impairment in a two-year follow-up study

Tese de Doutorado

Thesis presented to the Programa de Pós-Graduação em Psicologia (Psicologia Clínica) of the Departmento de Psicologia, PUC-Rio as partial fulfillment of the requirements for the degree of Doutor em Psicologia.

Advisor: Profª. Helenice Charchat Fichman

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Abstract

Faria, Camila de Assis; Charchat-Fichman, Helenice (Advisor). **Neuropsychological predictors of conversion to dementia and cognitive trajectory of older adults with mild cognitive impairment in a two-year follow-up study**. Rio de Janeiro, 2016. 94p. Thesis – Psychology Department, Pontifícia Universidade Católica do Rio de Janeiro.

This study aimed to determine the best neuropsychological predictors of dementia and analyze the cognitive trajectory of older adults with mild cognitive impairment (MCI) in a two-year follow-up study. 87 older adults with MCI were submitted to a broad neuropsychological battery and 62 were evaluated two years later. 21.8% converted to dementia. The results revealed that episodic memory and working memory are the best predictors of dementia from MCI after two years. Older adults showing decline in two or more cognitive functions showed greater deficits in functionality and higher percentages of conversion to dementia when compared to older adult with executive function decline. In addition, the results showed that depressive symptoms are specifically associated with older adults showing exclusively executive function decline.

Keywords

neuropsychological tests; executive functions; mild cognitive impairment; dementia; conversion.

Resumo

Faria, Camila de Assis; Charchat-Fichman, Helenice. **Preditores neuropsicológicos de conversão para demência e trajetória cognitiva de idosos com comprometimento cognitivo leve em dois anos de acompanhamento**. Rio de Janeiro, 2016. 94p. Tese de Doutorado – Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

O presente estudo teve como objetivos determinar os melhores preditores neuropsicológicos de demência e analisar a trajetória cognitiva de idosos com comprometimento cognitivo leve (CCL) em dois anos. Oitenta e sete idosos com CCL foram submetidos a uma bateria de testes neuropsicológicos e 62 foram reavaliados após dois anos. 21,8% converteram para demência. Os resultados revelaram que a memória episódica e a memória de trabalho foram os melhores preditores de conversão de CCL para demência após dois anos e que idosos com declínio em duas ou mais funções cognitivas apresentaram maior prejuízo na funcionalidade e maior porcentagem de conversão para demência que os idosos com declínio apenas nas funções executivas. Além disso, os resultados mostraram que os sintomas de depressão estão mais associados ao perfil de idosos que declinam somente nas funções executivas.

Palavras – chave

testes neuropsicológicos; funções executivas; comprometimento cognitivo leve; demência; conversão.

Sumary

"O seu conhecimento vai ajudar a muitos!"

Sr. Armando Martinho

Cover page

This study is presented through four manuscripts developed during the doctoral program. Each manuscript corresponds to a chapter. Before each chapter, has a brief introduction.

The first chapter is a systematic review of the most commonly used tests to evaluate executive functions in elderly patients with different levels of education, in clinical and experimental research. It was published in Dementia & Neuropsychologia in June 2015 (Faria et al., 2015). The second chapter discusses how different dimensions of executive functioning are grouped in a sample of older adults with mild cognitive impairment, from geriatric and neurology outpatient clinics of a public hospital in Rio de Janeiro. In the third chapter, the neuropsychological factors that are predictive of dementia are shown. The last chapter presents the cognitive trajectory of older adults initially diagnosed with mild cognitive impairment, two years later. At the end, the conclusions are presented.

1.

Introduction

Mild cognitive impairment (MCI) is characterized by deficits in one cognitive function. Mild deficits in other cognitive functions and relative loss in activities of daily living may occur concurrently (Petersen et al., 1999; Radanovic et al., 2015). MCI is classified as "amnestic" when memory is impaired; as "amnestic multiple domains" when there is a loss of memory and of other cognitive functions; as "non-amnestic" when there is loss of a cognitive function other than memory; as "non-amnestic multiple domains" when there is a loss of other cognitive functions other than memory (Petersen et al., 1999; Radanovic et al., 2015). Although MCI can be considered a transition stage to dementia, older adults with MCI may improve or remain stable over the years (Radanovic et al., 2015).

According to DSM-IV criteria (APA, 1994), the diagnosis of dementia consists of changes in memory (learning and recall of learned content) and aphasia or apraxia, agnosia, executive dysfunction, and impairment of social or labor activity. Older adults with MCI represent a group with a high probability of conversion to dementia, when compared to healthy older adults (Petersen et al., 2009). The percentage of conversion to dementia from MCI is 10% - 15% a year (Petersen et al., 2009). In the literature, there are few longitudinal studies regarding the trajectory of cognitive decline in older adults with MCI (Cloutier et al., 2015; Ramel et al., 2015; Albert et al., 2007). Characterizing cognitive decline in such a group over time is important to identify the cognitive profile of elderly individuals who convert to dementia.

This study is presented through four manuscripts. Each manuscript corresponds to a chapter. The first manuscript aimed to present a systematic review of the instruments most frequently used to assess executive functions in older adults with different levels of education, in clinical and experimental research. The need for effective measures for the early diagnosis of dementia, and the impact of executive dysfunction in activities of daily living, autonomy, and quality of life of older adults justify the need to identify which instruments are most used to assess executive functions in aging. The second manuscript aimed to investigate different dimensions of executive functioning, according to the performance in neuropsychological tests, in older adults diagnosed with mild cognitive impairment by medical specialists from neurology and geriatric ambulatories of a public hospital in the city of Rio de Janeiro. Studying executive functioning in older adults is important because its decline during aging may be related to mild cognitive impairment and dementia (Espinosa et al., 2009) and negatively affects the performance of activities of daily living (Cahn-Weiner et al., 2007), results in a loss of independent living, low quality of life for the older adults and their caregivers (Mograbi et al., 2014; Amieva et al., 2003). The third manuscript aimed to determine which neuropsychological tests are the best predictors of conversion to Alzheimer's disease from MCI after two years in older adults from neurology and geriatric ambulatories of a public hospital in the city of Rio de Janeiro. It is important for the identification of individuals at a high risk for the conversion to dementia. The fourth manuscript aimed to analyze quantitative and qualitative cognitive trajectory of older adults with mild cognitive impairment from neurology and geriatric ambulatories of a public hospital in the city of Rio de Janeiro over a two-year period. Understanding the cognitive functioning of elderly with mild cognitive impairment and their cognitive trajectory enables the selection of the right testing instruments, an early diagnosis of dementia, and prevents losses in activities of daily living, especially in those with executive function deficits. The manuscripts 2, 3 and 4 are original studies, which analyzed a sample of older adults with mild cognitive impairment in the city of Rio de Janeiro, Brazil.

2.

Manuscript 1: The most frequently used tests to assess executive functions in aging

Abstract

Introduction: There are numerous neuropsychological tests of executive functions in aging and they vary according to the different domains assessed. Objective: To present a systematic review of the instruments most frequently used to assess executive functions in older adults with different levels of education, in clinical and experimental research. Methods: We searched for articles published in the last five years, using the PubMed database with the following terms: "neuropsychological tests", "executive functions", and "mild cognitive impairment". There was no language restriction. Results: 25 articles fulfilled all the inclusion criteria. The seven neuropsychological tests most frequently used to evaluate executive functions in aging were: 1) Trail Making Test (TMT) Form B; 2) Verbal Fluency Test (VFT) - F, A and S; 3) VFT Animals category; 4) Clock Drawing Test (CDT); 5) Digits Forward and Backward subtests (WAIS-R or WAIS-III); 6) Stroop Test; and 7) Wisconsin Card Sorting Test (WCST) and its variations. The domains of executive functions most frequently assessed were: mental flexibility, verbal fluency, planning, working memory, and inhibitory control. Conclusions: The study identified the tests and the domains of executive functions most frequently used in the last five years by research groups worldwide to evaluate older adults. These results can direct future research and help build evaluation protocols of executive functions, taking into account different levels of education and different socio-demographic profiles for older adults in Brazil.

Keywords: review, mild cognitive impairment, dementia, older adults, executive functions, neuropsychological tests

2.1 Introduction

EF’s are complex cognitive abilities that enable the identification of goals, mental planning, behavior organization, and planning actions to achieve these goals (Diamond, 2013; Kluwe-Schiavon et al., 2012). In addition, EF’s impact affective-emotional, motivational, and social skills (Kluwe-Schiavon et al, 2012; Uehara et al, 2013). EF’s are especially important for older adults, for performing and troubleshooting routine tasks, from the most simple to the most complex. Executive functions are composed of six domains, which will be described below. Planning refers to the identification of a sequence of actions required to achieve a goal. Efficient planning includes thinking about alternatives and choosing the most effective one (Uehara et al, 2013). Working memory is defined as a system of temporary storage and manipulation of information. This system is activated during the process of learning, language comprehension, reasoning, and production of one’s conscience (Uehara et al, 2013). Mental flexibility refers to the ability of alternating between mental sets or tasks, and changing strategies within the same task (Lehto et al., 2003). Inhibitory control refers to the inhibition of an prepotent response, which facilitates the choice of an adequate response and avoids errors (Uehara et al, 2013). Verbal fluency is the ability to generate an appropriate strategy for word search (Brocki & Bohlin, 2004). Processing speed refers to the time required to process a specific information (Brocki & Bohlin, 2004). Neural substrates of these domains are mainly located in the prefrontal cortex of the brain, and they are connect to several other brain areas and the central nervous system as a whole (Kluwe-Schiavon et al, 2012).

Executive dysfunction creates important limitations in older people’s daily routines, such as the impact on functionality, i.e., in the performance of activities of daily living (ADLs), which reduces autonomy and quality of life (Mograbi et al, 2014; Amieva et al, 2003). Deficits in EF found in older patients include inflexibility of thought, reduced working memory processing, difficulty in solving problems, decreased behavioral initiation, perseveration errors, inadequate planning strategies, and disinhibition (Espinosa et al., 2009; Amieva et al, 2003). Mild cognitive impairment (MCI) is considered an intermediate state of cognitive functioning between the changes seen in healthy aging and those typically found in dementia. MCI criteria include self- or informant-reported cognitive complaint, objective cognitive impairment, preserved Independence in functional abilities and no dementia (Petersen et al, 2014; Petersen et al, 2009). Executive dysfunction in aging may appear in the MCI or it may be an early sign of dementia (Espinosa et al., 2009).

Executive dysfunction in aging can be measured objectively with neuropsychological tests (Mitchell et al., 2012). There are several executive functions tests and they vary according to the domains assessed. In general, a neuropsychological test predominantly assesses one of the EF domains. The great variability of tests, the need for effective measures for the early diagnosis of dementia, and the impact of executive dysfunction in ADL, autonomy, and quality of life of older adults justify the need to identify which instruments are most used to assess executive functions in aging. This study aims to present a systematic review of the instruments most frequently used to assess executive functions in older adults with different levels of education, in clinical and experimental research.

2.2 Methods

A systematic review was conducted on July 30th, 2014 using the PubMed database and combining the terms "neuropsychological tests", "executive functions", and "mild cognitive impairment", without any language restriction. The study included articles that fulfilled the following criteria: 1) all participants aged over 50 years; 2) healthy older adults, MCI or dementia; 3) neuropsychological tests used to assess executive functions; 4) published in the last 5 years; and 5) cross-sectional or longitudinal studies. The studies that fulfilled the following criteria were excluded: 1) review studies; 2) studies with psychiatric or neurological patients, except for dementia and MCI. To assess which executive functions tests were most commonly used, a percentage of usage above 20% was used as the counting criterion, considering only the articles that met the inclusion and exclusion criteria.

2.3
Results

Seventy-four articles published between July 2009 and July 2014 were found in Pubmed. Of these, only 25 fulfilled all the inclusion criteria and 49 articles were excluded according to the exclusion criteria.

Seven tests of executive functions were used in more than 20% of the selected articles: 1) Trail Making Test (TMT) Form B; 2) Verbal Fluency Test (VFT) - F, A and S; 3) VFT Animals category; 4) Clock Drawing Test (CDT); 5) Digits Forward and Backward subtests (WAIS-R or WAIS-III); 6) Stroop Test; and 7) Wisconsin Card Sorting Test (WCST) and its variations. The EF domains most frequently studied by the researchers were mental flexibility, verbal fluency, planning, working memory, inhibitory control, and processing speed. Table 1 describes the relationship between the most used neuropsychological tests and their cognitive domains.

Table 2 presents all the executive function tests used in the 25 articles, with their respective frequencies and percentage of usage. Table 2 also shows the number of studies by domain evaluated.

Few studies chose to use only one EF test, considering only one domain, and most studies combining two or more EF domains, as follows: 1) Only one EF domain: 4 studies; of these, three were interested in the psychometric properties or validation of a specific test and one study opted for a mental flexibility test as the single measure of executive function; 2) Combining two EF domains: five studies; of these, four chose one or more verbal fluency tests plus one inhibitory control test, planning test or mental flexibility test; only one study combined tests assessing mental flexibility and inhibitory control; 3) Combining three EF domains: nine studies; 4) Combining four EF domains: six studies; 5) Combining five EF domains: only one study; all domains were included in this study, except for inhibitory control. These results and the studies' references are shown in Table 3.

Table 1. The seven executive functions tests most frequently used in aging research

Names of the EF tests	Predominant domain	Task description
Trail Making Test (TMT) Form B	mental flexibility	Connect 13 numbers and 12 letters alternately and as quickly as possible (Tombaugh, 2004; Hamdan & Hamdan, 2009).
Verbal Fluency Test (VFT) - F, A and S	verbal fluency	The test consists in saying as many words beginning with F, A and S in 1 minute. Participants cannot use proper nouns or use a stem word with different endings (Tombaugh et al, 1999; Machado et al, 2009).
Verbal Fluency Test (VFT) - Animals category	verbal fluency	The test consists in saying as many animal names, as quickly as possible, in 1 minute, with no restrictions based on beginning letter or any other characteristic (Tombaugh et al, 1999; Charchat-Fichman et al, 2009).
Clock Drawing Test (CDT)	planning	Draw a clock with all the numbers and pointers marking a particular time (Nitrini et al., 2005; Agrell & Dehljn, 1998; Fabricio et al., 2014).
Digits Forward and Backward subtests (WAIS-R or WAIS-III)	working memory	In the Digits Forward subtest, the participant must repeat the numbers said by the examiner in the same order. In the Digits Backward subtest, the patient must repeat the same numbers in reversed order (Nitrini et al., 2005; Choi et al., 2014).
Stroop Test	inhibitory control	The test consists of three conditions: in the first condition, the subject must say, as quickly as possible, the names of the colors that are arranged in a card. In the second condition, the subject must say the names of the colors that the words "all", "today", etc. are printed in. In the third condition, the participant has to name the colors that the words "yellow", "red", etc. are printed in (Bayard et al., 2011; Klein et al., 2010).
Wisconsin Card Sorting Test (WCST) and its variations	mental flexibility	The test consists of cards that need to be classified according to color, shape or number categories. The categorization rules change every time when 10 (out of a maximum of 128) response cards have been sorted correctly. WCST variations are versions with fewer cards (Abe et al., 2004).

Table 2. Frequency of use of executive functions tests in aging research

Executive functions tests	**Frequency of test use**	**Percentage of use, considering the 25 articles (%)**	**EF Domain**	**Total of studies evaluating the domain**
Trail Making Test (TMT) Form B	9	36	mental flexibility	15
Wisconsin Card Sorting Test (WCST) and its variations	6	24		
Rule Shift Cards Test (BADS)	2	8		
Trail Making Test (TMT) Oral	1	4		
Intra-Extra Dimensional Set Shifting (IED) of the CANTAB	1	4		
VFT - F, A and S	7	28	verbal fluency	13
VFT Animals category	6	24		
VFT Fruits category	3	12		
VFT semantics without specifying the category	2	8		
VFT "S"	1	4		
VFT Vegetables category	1	4		
VFT Supermarket category	1	4		
VFT "A" of the EXIT-25	1	4		
Clock Drawing Test (CDT)	6	24	planning	13
Complex Figure of Rey Copy	3	12		
Action Program Test (BADS)	3	12		
Key Search Test (BADS)	3	12		
Zoo Map Test (BADS)	3	12		
Tower of London	2	8		
Setting Clock Test	1	4		
Verbal Clock Test	1	4		
Block Design subtest (WAIS-R)	1	4		
Raven's Colored Progressive Matrices	1	4		
Digits Forward and Backward subtests (WAIS-R or WAIS-III)	6	24	working memory	13
Codes subtest (WAIS-R or WAIS-III)	5	20		
Arithmetic subtest (WAIS-R)	1	4		
Number-Letter Sequencing subtest (WAIS-III)	1	4		
Mind Control (WMS-R)	2	8		
Clock Reading Test	1	4		
Updating Test	1	4		
SWM Strategy (CANTAB)	1	4		
Cognitive Estimation Test	1	4		
PaSMO	1	4		
Stroop test	6	24	inhibitory control	13
Rule Shift Cards Test (BADS)	2	8		
Inhibitory control subtest (FAB)	2	8		
D-KEFS Interference Inhibition Test	1	4		
Inhibitory control subtest (EXIT-25)	1	4		
Hayling test	1	4		
Codes subtest (WAIS-R ou WAIS-III)	5	20	processing speed	6
Simple reaction time (SRT) test (CANTAB)	1	4		

VFT - Verbal Fluency Test; BADS - Behavioral Assessment of the Dysexecutive Syndrome

Table 3. Frequency of studies by number of domains used in the evaluation of executive functions in aging research

Number of EF domains evaluated in the study	Domain (number of studies)	Studies' references
1	planning (3) or mental flexibility (1)	Armentano et al, 2013; Berna et al, 2012; de Paula et al, 2012; Espinosa et al, 2009
2	verbal fluency (4), mental flexibility (2), planning (2) and inhibitory control (2)	Schroeter et al, 2012; Parra et al, 2012; Bangen et al, 2010; Forti et al, 2010; Vicini-Chilovi et al, 2010
3	working memory (7), mental flexibility (6), verbal fluency (4), planning (4), inhibitory control (4) and processing speed (2)	Jacus & Gély-Nargeot, 2014; de Paula et al, Maio 2013; Bastug et al, 2013; Bombin et al, 2012; Summers & Saunders, 2012; Chang et al, 2011; Nordlund et al, 2010; Leyhe et al, 2009; Karantzoulis et al, 2009
4	working memory (5), mental flexibility (4), inhibitory control (4), verbal fluency (4), processing speed (3) and planning (3)	de Paula et al, Setembro 2013; Gaudreau et al, 2013; Rainville et al, 2012; Malek-Ahmadi et al, 2011; Yubero et al, 2011; Pereira et al, 2010
5	mental flexibility, verbal fluency, planning, working memory, processing speed	Cercy, 2012

2.4

Discussion

The systematic review presented here identified that the tests most frequently used to assess executive functions in aging research in the last five years were: 1) Trail Making Test Form B, 2) Verbal Fluency Test - F, A and S, 3) VFT Animals category, 4) Clock Drawing Test, 5) Digits subtests (WAIS-R or WAIS-III), 6) Stroop Test, and 7) Wisconsin Card Sorting Test (WCST) and its variations (Table 1). The EF domains predominantly evaluated were: 1) mental flexibility (15 studies), 2) verbal fluency (13 studies), 3) planning (13 studies), 4) working memory (13 studies), and 5) inhibitory control (13 studies), as shown in Table 2. Processing speed was evaluated in 6 of the 25 studies (Table 2). The assessment of processing speed is of uttermost importace in aging because it is one of the first processes to decline in the early stages of dementia (Thorvaldsson et al., 2011). However, processing speed was assessed in only six studies. Most of the selected articles favored the use of tests involving the most complex processes of executive functions that require greater action control.

As seen in Table 3, none of the 25 selected studies evaluated all six domains and only one study combined EF tests covering five domains (Cercy, 2012). This can be explained by the attempt to reduce the time spent on a long neuropsychological assessment. In other words, if many neuropsychological tests were used to evaluate EF domains, in addition to tests assessing other cognitive functions, data collection would take too long, resulting in high dropout rates and making it difficult to conduct research with a large sample (Bangen et al., 2010; Vicini-Chilovi et al., 2010). However, important EF data is lost when some domains are not contemplated in a neuropsychological assessment.

There is no established criterion in the literature with respect to the optimal number of tests needed to evaluate executive functions, but, according to the results of the present review, combining 3 to 4 EF domains into comprehensive batteries was the most frequent procedure adopted (Table 3). The choice of three or more combinations selected by the majority of studies in this review is because EF are multidimensional construct, ie comprise a series of interrelated skills and high-level cognitive processing and recruit several domains in parallel as mental flexibility, planning, verbal fluency, inhibitory control, processing speed, and working memory (Kluwe-Shiavon et al., 2012; Uehara et al., 2013). Researchers seem to avoid using only one or two EF measures to ensure that most of the EF domains are contemplated. Few studies (table 3) have restricted the EF assessment to two tests, usually combining a flexibility, planning or inhibitory control test with a verbal fluency test, which is quick, easy to apply, and it is sensitive to discriminate people with dementia, MCI and healthy older adults (Caramelli et al., 2007).

As seen in Table 2, the TMT Form B and WCST and its variations were the most frequently selected tests to assess mental flexibility. The TMT Form B was used in nine studies (from a total of 14 studies assessing flexibility) and the WCST or one of its variations were used in six studies. The TMT Form B is predominantly a mental flexibility measure (Oliveira-Souza et al., 2000; Tombaugh, 2004). The individual must switch the focus of attention repeatedly between two sequences (numerical and alphabetical). Mental engagement, motor dexterity, and working memory are also recruited during the test. (Oliveira-Souza et al., 2000; Tombaugh, 2004). The WCST and its variations also assess mental flexibility (Fernandes-Lopes et al., 2010). The subject must migrate from one classification rule to another during the test. Selective attention and impulsivity are also evaluated in this test (Fernandes-Lopes et al., 2010). The fact that the TMT Form B has a simpler and faster application procedure than the WCST and its variations justifies the choice of most studies.

Other tests commonly used to evaluate executive functions in aging were the VFT - F, A and S and the VFT Animals category. These tests were mainly chosen for the evaluation of verbal fluency. Seven studies that assessed this domain chose VFT - F, A and S and six chose VFT Animals category. The VFT - F, A and S evaluate verbal fluency and are carried out through an active search for specific information in memory (Machado et al., 2009). The VFT Animals category predominantly evaluates verbal fluency (Charchat-Fichman et al., 2009). During the execution of the task, there is an active search for information falling into a certain category. Language and semantic memory are also evaluated in this test (Charchat-Fichman et al., 2009).

Another frequently used task was CDT, which was chosen by six studies out of a total of 13 that evaluated planning. Planning is the main cognitive process recruited during the CDT, since the circle should be large enough to accommodate the 12 numbers of the clock, which in turn should be equally distributed and correctly positioned. In addition, the hands must mark the requested time, with the minute hand greater than the hour hand. Visual constructive skills are also evaluated in this test (Nitrini et al., 2005). CDT is simple and widely used in cognitive aging research and for cognitive impairment screening in geriatric services (Nitrini et al., 2005).

A working memory measure, the Digits subtest (WAIS-R or WAIS-III) was the most frequently used, having been chosen by six out of thirteen studies. This test encompasses two tasks, the forward and the backward tasks. A detailed description of the test can be found in Table 1. The Digits forward subtest (WAIS-R or WAIS-III) evaluates information storage by verbal working memory. A string of digits is dictated by the examiner and the participant has to repeat it immediately after. The Digits backward subtest (WAIS-R or WAIS-III) measures verbal content processing in working memory. Finally, the Stroop test was the most frequently chosen test (6 out of 11 studies) for evaluating inhibitory control. It assesses the subject's ability to inhibit an automatic behavior (reading a word) and perform a controlled behavior (saying the color the word is printed in).

Executive functions undergo changes during the normal aging process, that is, performance on EF tests is expected to deteriorate with increasing age (Tombaugh, 2004; Hamdan & Hamdan, 2009; Machado et al., 2009; Klein et al, 2010). Decline in EF during the aging process can be mild or severe. Older people with a significant decline in executive functions fall within the Mild Cognitive Impairment (MCI) and may progress to dementia. Executive dysfunction in aging is related to a reduced ability to perform activities of daily living, which creates dependency, loss of autonomy, and reduced quality of life (Mograbi et al., 2014), justifying the importance of investigating the functioning of EF in the elderly population and the main tests discussed in the present review.

In addition to the age effect, EF tests are affected by education, that is, the lower the subject’s educational level, the worse the test performance (Tombaugh, 2004; Hamdan & Hamdan, 2009; Machado et al., 2009; Abe et al, 2004). The Brazilian older population has a higher educational variability than older people in developed countries (Nitrini et al., 2007). The relationship between education and cognition is widely acknowledged in the literature. Foss and colleagues (2013) conducted a study and showed that the level of education is strongly correlated with subtests of executive functions and other cognitive functions (attention, visual constructive skills, language, memory, and global cognition score). The sample consisted of 502 Brazilian older adults without cognitive deficits. The results indicated that illiterate older adults performed significantly worse than participants with 1 year or more of formal education. Participants with 1 or 2 years of education had a significantly worse performance than participants with 3 or 4 years of education in all subtests, which, in turn, performed worse than the group with 11 or more years of formal education. Groups with 5-10 years of education did not show differences in performance.

There is evidence in the literature that the performance of executive functions in older adults is also influenced by socioeconomic status (Charchat-Fichman et al., 2013). Charchat-Fichman and colleagues (2013) mapped the neuropsychological profile of a sample of 88 elderly people without dementia at a geriatric outpatient clinic of a public hospital in the city of Rio de Janeiro. Patients with traumatic brain injury, stroke, Parkinson's disease, and other neurological or psychiatric disorders previously diagnosed by the medical team, were excluded. Charchat-Fichman and colleagues (2013) concluded that 94.3% of the sample had a significant EF impairment. The researchers hypothesized that this result was a reflection of the low socioeconomic status of the sample, noting that perhaps the level of education is not the only factor involved in the EF decline in older people. Socioeconomic variables may contribute to the low performance of elderly people on EF tests (Charchat-Fichman et al., 2013). These data raises the question of whether the tests commonly used to assess EF in aging are suitable for the Brazilian population.

This study identified the tests and the specific domains most frequently used in the last five years to assess EF in older people. To our knowledge, there are no other review studies in the literature of EF testing during aging. This study raises the issue of the adequacy of the most frequently used tests to the Brazilian older population, considering the inherent variability of educational and socio-demographic levels, which result in a heterogeneity of cognitive tests outcomes. Knowing which EF tests and domains are chosen by the main research groups can direct future research and help build appropriate EF assessment protocols to different levels of education and different socio-demographic profiles for older people in Brazil.

3.

Manuscript 2: Clustering of executive function domains in mild cognitive impairment

Abstract

Executive functions (EF) decline during aging may be related to mild cognitive impairment (MCI) or dementia. The present study aimed to investigate different dimensions of executive functioning, in older adults diagnosed with MCI by medical specialists from neurology and geriatric ambulatories of a public hospital in the city of Rio de Janeiro. The study included 89 individuals aged 56 years or older (mean age = 77.44 ± 6.55 years). To identify executive functioning dimensions, a Principal Factoring Analysis and a Hierarchical Cluster Analysis were conducted with 17 variables. From the results of the both analysis, a model of how EF domains are clustered in people with MCI was generated. It indicated that EF domains operate in a fractionary way in MCI. However, these domains are connected primarily by error monitoring, goal maintenance, and intrusion and perseveration inhibition. These results help characterize the performance of older adults with MCI in neuropsychological tests that evaluate executive functioning. The identification of cognitive impairment is crucial for the early diagnosis of dementia. These results also enable a better understanding of EF performance of older adults with MCI who already show impairment in activities of daily living.

Keywords: executive functions, cluster analysis, mild cognitive impairment, neuropsychological tests, aging

3.1
Introduction

Executive functions (EF) are cognitive abilities that enable the realization of complex actions. The concept of “executive functions” is multidimensional and covers a range of higher order cortical functions, such as the identification of goals and the organization of thought and behavior to achieve them (Diamond, 2013; Kluwe-Schiavon et al., 2012), attentional control, temporal organization, and planning (Lehto et al., 2003). In addition, EF regulate emotions, motivation, and social skills (Kluwe-Schiavon et al, 2012; Uehara et al., 2013). EF encompass the following domains: mental flexibility, planning, verbal fluency, inhibitory control, processing speed, and working memory (Kluwe-Schiavon et al, 2012; Uehara et al., 2013).

Mental flexibility refers to the ability to alternate between two or more tasks, such as in the Trail Making Test Part B (Korte et al., 2002), or change strategies (engagement with and disengagement from different aspects) within the same task (Lehto et al., 2003), such as in the Wisconsin Card Sorting test (Heaton et al., 1981). Planning refers to the planning of actions to achieve a specific goal. Efficient planning includes choosing the most effective way to do something (Uehara et al., 2013). Verbal fluency is the ability to search words in memory (Brocki & Bohlin, 2004). Inhibitory control refers to the inhibition of an automatic response, which facilitates the choice of an adequate response and avoids errors (Uehara et al., 2013). Processing speed refers to the time spent processing a specific information. Working memory is a temporary system of storage and manipulation of information (Uehara et al., 2013).

EF decline during aging may be related to mild cognitive impairment (MCI) and dementia (Espinosa et al., 2009). MCI is an intermediate state of cognitive functioning between normal aging and dementia, with objective cognitive impairment, preserved functional abilities and no dementia (Petersen et al., 2014). EF decline during aging negatively affects the performance of activities of daily living (Cahn-Weiner et al., 2007) and results in a loss of independent living, and low quality of life for the older adults and their caregivers (Mograbi et al., 2014; Amieva et al., 2003). This study aims to investigate different dimensions of executive functioning, according to the performance in neuropsychological tests, in older adults diagnosed with MCI by medical specialists from neurology and geriatric ambulatories of a public hospital in the city of Rio de Janeiro.

3.2
Materials and methods

3.2.1
Study Sample

The study included 89 individuals (70 women, 19 men) aged 56 years or older (mean age = 77.44 ± 6.55 years), seen in neurology and geriatric ambulatories in a public hospital in Rio de Janeiro. The study included older adults diagnosed with MCI by medical specialists, without a MCI subtype specification. The following diagnostic criteria was used: subjective complaints of memory decline, preferably confirmed by an informant; cognitive deficit indicated by tests (performance in the Mini-Mental State Examination (MMSE; Folstein et al, 1975), Verbal Fluency Test - Animal Category (Spreen & Strauss, 1998), Mini-Cog (Borson et al, 2000)); preserved global cognitive functioning; intact functional activities (socio-occupational); and absence of dementia (Koogan, 2011). For MCI diagnosis, imaging exams are not usually ordered by doctors. However, laboratory tests were ordered to rule out other diseases that could justify cognitive decline.

The sample included people with controlled cardiovascular disease, hypertension, or diabetes; corrected sensory deficits; symptoms of depression or having had previous depressive episodes, with current mood controlled by medication and/or psychotherapy. Subjects were excluded if they met DSM-IV criteria for dementia (APA, 1994); had current or previous neurological diseases; severe psychiatric disorders; a severe systemic disease that could lead to cognitive decline; recent history of alcoholism or drug addiction; and uncorrected visual and/or hearing deficits.

3.2.2 Ethical issues

The study was submitted to the hospital's Ethics Committee (CEP/HFSE) and was approved on May 12th, 2008 (protocol 000.320). All participants received an oral and written explanation about the purpose of the research, willingly agreed to participate, and signed an Informed Consent form prior to the beginning of the study.

3.2.3 Procedure

The subjects were submitted to the same neuropsychological assessment protocol that included: 1) a semi-structured interview to check subjective complaints of cognitive impairment; 2) scales to assess the degree of independence in instrumental activities of daily living and depression symptoms; and 3) a wide neuropsychological assessment.

For this study, the following scales were used to characterize the sample: Pfeffer Functional Activities Questionnaire (Pfeffer; Pfeffer et al., 1982) and Geriatric Depression Scale (GDS-30; Yesavage et al., 1983). Older adults with scores equal to or greater than the cut-off point of the two scales were not excluded. The following neuropsychological tests were used to identify how EF dimensions were grouped: Clock Drawing Test (Sunderland et al., 1989), Verbal Fluency Test - Animal Category (Spreen & Strauss, 1998), Verbal Fluency Test - phonemic FAS (Spreen & Strauss, 1998), Mattis Dementia Rating Scale (DRS) - Supermarket (Porto et al., 2003; Foss et al., 2013), Mattis Dementia Rating Scale (DRS) - Building (Porto et al., 2003; Foss et al., 2013), Digits Forward and Backward subtests (WMS-R; Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987), Extension (Span) of Visuospatial Digits Forward and Backward subtests (WMS-R; Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987), Rey–Osterrieth Complex Figure Test – Copy (Spreen & Strauss, 1998; Rey et al., 1999), Stroop test – Victoria version (Spreen & Strauss, 1998; Lezak, 1995), Trail Making Test -

Part B (Spreen & Strauss, 1998; Lezak, 1995), Block Design (WAIS-R; Wechsler et al., 1981), Coding Task (WAIS-R; Wechsler et al., 1981), and Mazes (Wechsler et al., 1991).

3.2.4 Measures

Geriatric Depression Scale (GDS-30): assesses the degree of depressive symptoms (mild to severe). There are thirty questions with yes or no answers to describe how the subject has felt in the last two weeks (Yesavage et al., 1983). The cut-off point of the GDS-30 is 14 (Yesavage et al., 1983). Individuals with scores of 14 or more are considered at a high probability of having symptoms of depression. However, these individuals were not excluded from the study.

Pfeffer Functional Activities Questionnaire (Pfeffer): evaluates the performance of older adults in activities of daily life through 10 questions. Each question receives a score ranging from 0 to 3. The scale goes from 0 to 30. If the individual reaches five points or more, he/she is considered as having impairment in instrumental activities of daily living (Pfeffer et al., 1982). Individuals with a score of 5 or more were not excluded.

Mattis Dementia Rating Scale (DRS) - Supermarket: consists in saying names of things that we can buy at the supermarket, as quickly as possible, in 1 minute (0-20 points) (Porto et al, 2003; Foss et al, 2013).

Mattis Dementia Rating Scale (DRS) – Building: assesses constructive skills through the copy of geometrical figures (Porto et al., 2003; Foss et al., 2013).

Digits Forward and Backward subtests (WMS-R): Digits Forward subtest: the participant must repeat the numbers said by the examiner in the same order. Digits Backward subtest: the patient must repeat the same numbers in reverse order. The scores of the two parts of this test are obtained separately and the sum of the two subtests produces the total score (Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987).

Extension (Span) of Visuospatial Digits Forward and Backward subtests (WMS-R): The Forward subtest consists of repeating a sequence of visuospatial items, in the same order. The Backward subtest consists of repeating a sequence of visuospatial items, in reverse order. The scores of the two parts of this test are obtained separately and the sum of the two subtests produces the total score (Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987).

Stroop test – Victoria version: The test consists of three cards: in the first card, the subject must say, as quickly as possible, the names of the colors that are arranged in the card. In the second card, the subject must say the names of the colors that the words "all", "today", etc. are printed in. In the third card, the participant has to name the colors that the words "yellow", "red", etc. are printed in. The time to complete the third card is divided by time to complete the first card (Spreen & Strauss, 1998, Lezak, 1995).

Trail Making - Test Part B: The test consists of alternately connecting 13 numbers and 12 letters as quickly as possible (Spreen & Strauss, 1998; Lezak, 1995). The number of errors in the Trail Making Test - Part B was recorded, including the number of omissions.

Rey-Osterrieth Complex Figure Test – Copy: The test consists of copying the Rey complex figure on a blank sheet of paper. The number of accurate elements drawn and the total execution time in seconds are recorded (Spreen & Strauss, 1998; Rey et al., 1999).

Clock Drawing Test (CDT): The test consists of drawing the face of a clock on a blank sheet. Total score varies from 1 to 10 points (Sunderland et al., 1989).

Mazes: It consists of finding a way out of mazes without removing the pencil from the paper. The number of mistakes and the total time in seconds are recorded. Four mazes were used and the number of completed mazes calculated (Wechsler et al., 1991).

Block Design (WAIS-R): It consists of constructing figures using cubes. The answer is considered correct when the figure is the same as the model and is built within the time limit (Wechsler et al., 1981).

Coding Task (WAIS-R): assesses working memory and processing speed, evaluating correlations between numbers and symbols in a 2-minutes period (Wechsler et al., 1981).

Verbal Fluency Test (VFT) - phonemic FAS: The test consists of saying as many words beginning with F, A and S in 1 minute. Participants cannot use proper nouns or a stem word with different endings (Spreen & Strauss, 1998).

Verbal Fluency Test (VFT) - Animal Category: The test consists of saying as many animal names, as quickly as possible, in 1 minute (Spreen & Strauss, 1998; Mitrushina et al., 1999).

3.2.5
Statistical procedures

All analyzes were performed using SPSS software, version 18.0 for Windows. Means, standard deviations, and range of age, education, EF test scores, and scores of the functional and depression scales were calculated to characterize the sample. Percentage scores lower than expected in each variable used were also calculated according to the standards available in the literature.

A Pearson correlation test was performed among all EF variables and 17 were chosen, respecting a 5:1 ratio (5 subjects to 1 variable; Wilkinson, 1975), that are: Clock Drawing Test (CDT); Digits Backward subtests of WMS-R (DigOral Backward); Digits Forward and Backward subtests of the WMS-R (DigOral Total); Extension (Span) of the WMS-R Visuospatial Digits Backward subtests (Visuosp Backward); Extension (Span) of the WMS-R Visuospatial Digits Forward and Backward subtests (Visuosp Total); total score of the Verbal Fluency Test - phonemic FAS (FAS total); Building Subtest of the DRS (Building); Supermarket score of the DRS (Supermark); Verbal Fluency Test - Animal Category (Animals); time to complete the third Stroop card (Stroop 3 time); time to complete the third Stroop card divided by the time to complete the first card (Stroop T3T1); Block Design of the WAIS-R (Block Design), Coding Task of the WAIS-R (Coding); number of errors in the Trail Making Test - Part B (TMT B errors); number of completed mazes (Mazes); time to complete the Rey-

Osterrieth Complex Figure Test – Copy (Rey time) and score of the Rey-Osterrieth Complex Figure Test – Copy (Rey score). Data were standardized (score Z) and missing values were replaced by the mean of that specific variable.

To identify executive functioning dimensions, a Principal Factoring Analysis (PFA) and a Hierarchical Cluster Analysis (HCA) were conducted with the chosen variables. In the Principal Factoring Analysis (PFA), Kaiser-Meyer-Olkin (KMO) was performed to measure sampling adequacy. Bartlett's sphericity test was performed to check if there was a correlation between variables and if the factor analysis was appropriate. No fixed number of factors was used in the PFA. The rotation method used was the maximum proportion. The same standard variables used in the PFA were used in the Hierarchical Cluster Analysis (HCA). The dissimilarity between variables was verified by Pearson Correlation in the HCA.

3.3
Results

3.3.1
Sample characterization

The study included 89 individuals, 70 women (78.65%) and 19 men (21.35%). The age of the selected sample ranged from 56 to 89 years and had a mean (SD) of 77.44 (6.55). The sample had a mean (SD) of 5.13 (3.84) years of formal education, ranging from 0 to 16. All participants had MCI, as diagnosed by medical experts. The MCI subtype was not specified. 84.3% of the sample presented systemic arterial hypertension, 20.5% diabetes, 16.9% depression, 14.5% osteoporosis, 13.3% arthrosis, 10.8% hypothyroidism, 10.8% heart diseases, 9.6% urinary incontinence, 9.6% dyslipidemia, 9.6% high cholesterol, 6% blood circulation problems, 6% glaucoma, and 28.9% other health problems (vagal nerve dysfunction, macular degeneration, cataracts, rhinitis, allergy, osteopenia, bronchitis, asthma, chronic obstructive pulmonary disease, stomach cancer, prostate problems, kidney failure or labyrinthitis).

Table 1 presents the means, standard deviations and performance variation of the elderly sample in the EF tests, GDS-30 and Pfeffer. In the GDS-30, 28.7% of the sample had scores equal to or greater than 14. In the Pfeffer, 45.3% of the sample was classified as "dependent" in instrumental activities of daily living. Less than 10% of the sample had scores lower than expected in Stroop T3T1 (3.4%) and Animals (6.7%). More than 20% of the sample had a score lower than expected in FAS total (22.7%), Stroop 3 time (22.7%), Block Design (24.4%), and Coding (43.5%). More than 60% of the sample had a score lower than expected in DigOral Backward (62.9%), Building (64.4%), Rey score (73.4%), CDT (75.6%), and Visuosp Backward (79.8%). There are no standardized values available in the literature for the other variables.

Table 1 – Sample size, mean, SD and range of participants' scores for the measures assessed in the presente study.

Measure	n	Mean (SD)	Range
GDS-30	87	10,83 (6.15)**	1-26
Pfeffer	86	5.43 (5.58)**	1-21
CDT	86	5.66 (2.68)***	1-10
DigOral Backward	89	3.28 (1.40)***	1-7
DigOral Total	89	8.35 (2.86)	3-17
Visuosp Backward	89	3.15 (1.76)***	0-8
VisuospTotal	89	8.08 (2.70)	2-15
FAS total	88	19.26 (9.93)**	0-60
Supermark	87	16.05 (3,82)	5-20
Animals	89	11.49 (3.57)*	3-22
Stroop 3 time	88	53.89 (29.79)**	20-238
Stroop T3T1	88	2.27 (1.11)*	0.60-7.21
Block Design	86	14.31 (7.51)**	0-36
Coding	85	15.96 (11.75)**	0-53
TMT B errors	85	10.93 (8.35)	0-25
Rey time	79	361.06 (193.73)	90-1321
Rey score	79	20.79 (8.80)***	0-36
Building	87	3.83(1.50)***	0-6
Mazes	87	2.52 (1.35)	0-4

*Less than 10% had a test score lower than expected; **more than 20% had a test score lower than expected; ***more than 60% had a test score lower than expected. Variable names are described in the Data Analysis section.

3.3.2
Cluster analysis of executive function variables - Principal Factoring Analysis (PFA)

The Kaiser-Meyer-Olkin measure verified sample adequacy for analysis [KMO = 0.79]. Bartlett's sphericity test [X2(136) = 779.29; $p < 0.001$] indicated that the correlations among items were sufficient to perform the factor analysis. PFA with standardized variables showed that four factors complied to the Kaiser criterion of eigenvalues greater than 1 (eigenvalues 6.25, 1.94, 1.52, and 1.10) and explained 63.56% of total variance. The scree plot indicated only one point was positioned before the inflection (Figure 1), however, the number of factors in the final analysis was kept at five in accordance to the Kaiser criterion. The first factor explained 36.76% of the variance. Variable loadings are given in Table 2. Rey time and Building variables showed low correlation with all factors (less than 0.60).

Figure 1. Scree Plot of the obtained eigenvalue for each factor.

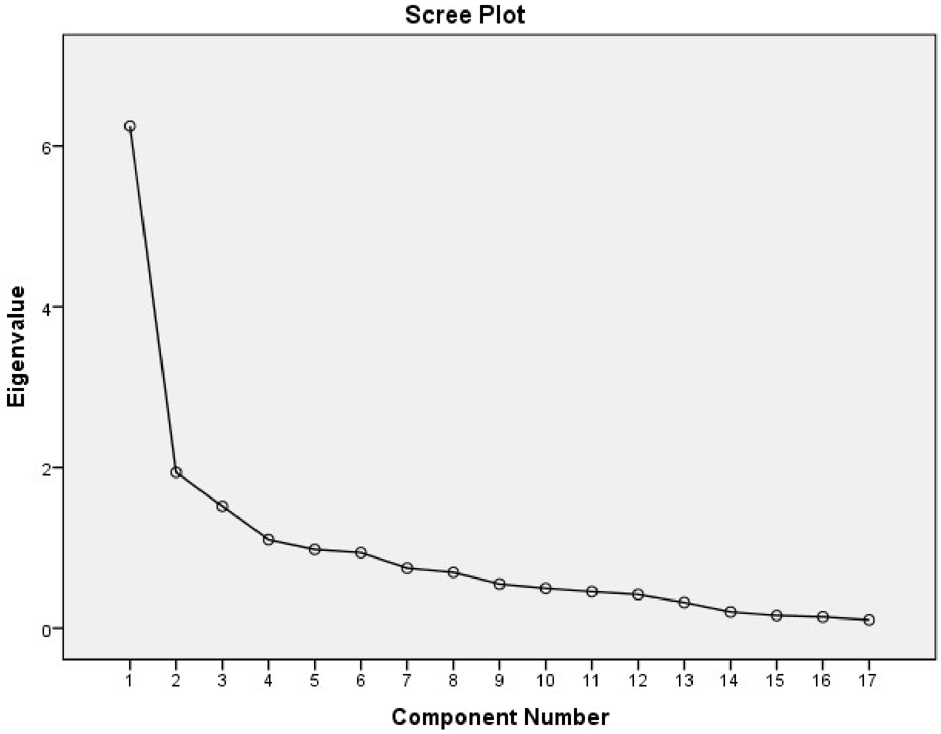


Table 2 – Factor loadings for EF measures (Z score)

	Factors				
Measure	**1.**	**2.**	**3.**	**4.**	**Communalities**
CDT	**.64**	.48	.54	-.03	.53
DigOral Backward	.45	**.90**	.24	-.06	.82
DigOral Total	.59	**.89**	.34	-.05	.81
Visuosp Backward	**.81**	.54	.15	-.06	.68
VisuospTotal	**.84**	.49	.11	-.02	.74
FAS total	.49	.56	**.60**	.03	.53
Supermark	.25	.21	**.82**	-.17	.67
Animals	.35	.48	**.72**	-.05	.58
Stroop 3 time	-.32	-.08	-.29	**.91**	.91
Stroop T3T1	.07	.01	-.07	**.94**	.92
Block Design	**.78**	.48	.14	.00	.64
Coding	**.78**	.56	.27	-.07	.62
TMT B errors	-.51	**-.66**	-.15	-.14	.48
Rey time	-.13	-.13	.48	-.12	.36
Rey score	**.76**	.30	.34	-.09	.62
Building	.59	.34	.47	-.08	.43
Mazes	**.64**	.54	.33	-.13	.47

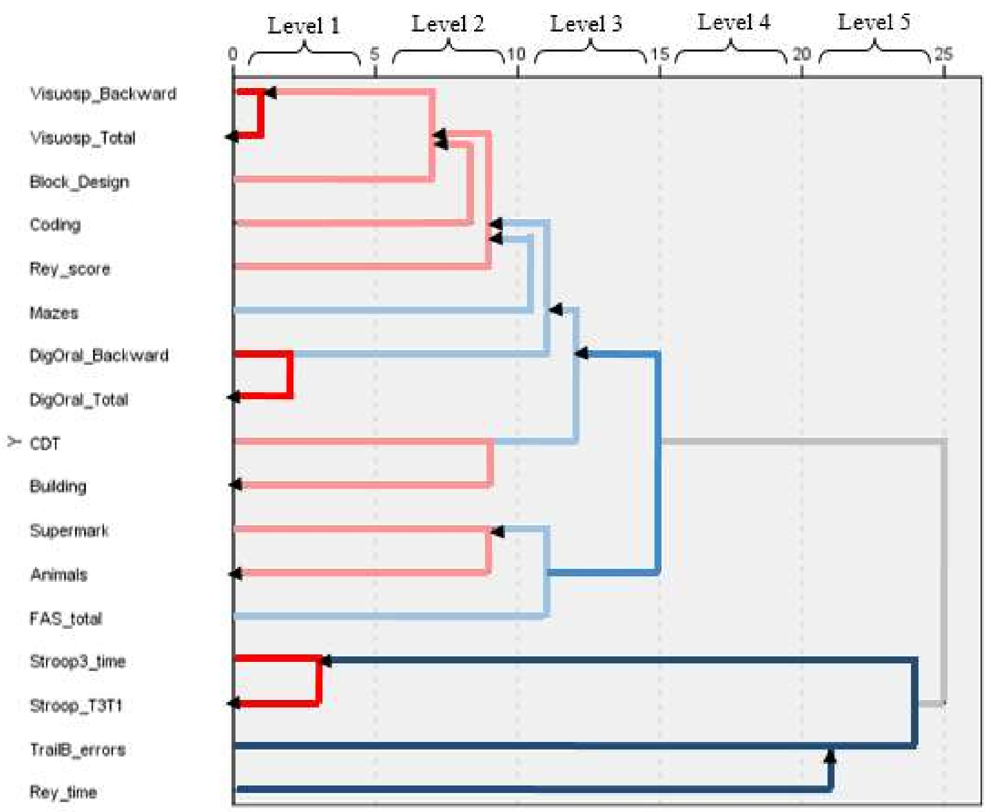
Variable names are described in the Data Analysis section.

3.3.3 Hierarchical Cluster Analysis (HCA)

Figure 2 is a dendrogram that shows the hierarchical distribution of groups produced by the HCA with standardized variables. In the first level of the hierarchy (distance 0 – 5), three groups showed high internal homogeneity and were colored red: Visuosp Backward and Visuosp Total; DigOral Backward and DigOral Total; Stroop 3 time and Stroop T3T1. In the second level of the hierarchy (distance 5 – 10), colored light pink, Block Design, Coding and Rey score were clustered to Visuosp Backward and Visuosp Total. Two groups were formed: CDT and Building; Supermark and Animals. In the third level of the hierarchy (distance 10 – 15), colored light blue, Mazes, DigOral Backward and DigOral Total, and CDT and Building were clustered to Visuosp Backward and Visuosp, and Block Design, Coding and Rey score. FAS total was clustered to

Supermark and Animals. In the fourth level (distance 15 – 20), colored blue, FAS total, Supermark and Animals were clustered to variables grouped in the third level. In the fifth level (distance 20 – 25), TMT B errors and Rey time were clustered to Stroop 3 time and Stroop T3T1. Then, they were clustered with all others variables.

Figure 2. Dendrogram of the hierarchical distribution of groups produced by the HCA.



Variable names are described in the Data Analysis section.

3.4 Discussion

The current study presented dimensions of executive functioning, according to the performance of older adults diagnosed with MCI. Next, sample characterization, PFA and HCA results will be discussed, as well as the Clustering Model generated from the analysis.

3.4.1 Sample characterization

This sample was composed of older adults with MCI seen in neurology and geriatric ambulatories of a public hospital in Rio de Janeiro. The number of men (21.35%), women (78.65%), and the mean of age (SD) of 77.44 (6.55) years observed in the study are in accordance with the numbers found in other Brazilian and international studies (Barbosa et al., 2015; Charchat-Fichman et al., 2015; Charchat-Fichman et al., 2013; Fischer et al., 2007). The sample had a mean (SD) of 5.13 (3.84) years of formal education. As expected, this mean is lower than the one found in international study (Fischer et al., 2007).

All participants had MCI, as diagnosed by medical experts. The MCI subtype was not specified. Most older adults presented systemic arterial hypertension (84.3%) and less than 21% of the sample presented other kinds of health problems, such as diabetes, hypothyroidism, heart diseases, high cholesterol or dyslipidemia. In the GDS-30, 28.7% of the sample had scores equal to or greater than 14, and 16.9% were diagnosed with depression by a medical specialist. Depression symptoms are common in individuals with MCI (Petersen et al., 2014).

Previous studies analyzed the characteristics of the same sample (Barbosa et al., 2015; Charchat-Fichman et al., 2015; Charchat-Fichman et al., 2013). Charchat-Fichman and collegues (2013) analysed 88 older adults with the aim of mapping the neuropsychological profile and identifying mild cognitive impairment in this sample. They used the MMSE, Figure Memory Test, VFT - Animal Category, CDT, and Lawton and Katz Daily Living Activities Scales.

Student's t test was used to compare MCI groups. Descriptive analysis of impaired cognitive processes showed that most of the participants presented executive dysfunction and 61.36% were classified as having non-amnestic disexecutive MCI. Many of the participants (19,3%) presented some decline in instrumental activities os daily living. The present study used only EF tests from a wide neuropsychological battery. The EF tests analysis confirmed that most of the participants presented executive dysfunction; more than 60% of the older adults had a test score lower than expected in five EF tests (Table 1). The percentage of older adults with functional impairment was higher in this study: 45.3% had decreased instrumental ADLs, according to the Pfeffer. This can be explained by the different scales used; in the previous study by Charchat-Fichman and collegues (2013), the Lawton Scale was applied. Lawton Scale has items about general ADLs, as using the telephone; shopping; and preparing meals. Pfeffer questionnaire was developed to functional impairment screening in people with dementia (Pfeffer et al., 1982). It is different from Lawton Scale because there is specific items of attention and memory as heating water and shutting off the stove; keeping track of current events; watching news reports and discussing them; remembering appointments.

3.4.2
Interpretation of PFA and HCA results

The PFA clustered executive function tests into four factors (Table 2). Factors were named considering the executive function domains prevailing in each test (Table 3). Rey time and Building variables had low factor loading. Factor 1 was loaded by tasks that have in common storage and processing of visuospatial information. Factor 2 was loaded by Verbal Working Memory tasks. TMT B errors was loaded into Factor 2 and this may be explained by the need to store information in Verbal Working Memory before the Flexibility process takes place. This relationship will be better explained in the presentation of the Clustering Model (Figure 4). Factor 3 was loaded by categorical and phonemic Verbal Fluency tasks that consist of saying specific words in a given time. Factor 3 was named Verbal Organization and Initiation because these tasks require a good organization of spoken words and a continuous verbal fluency to complete the task successfully. Factor 4 was loaded by Inhibitory Control tasks. These results and the results of the HCA are combined and presented in Figure 4, which will be described later.

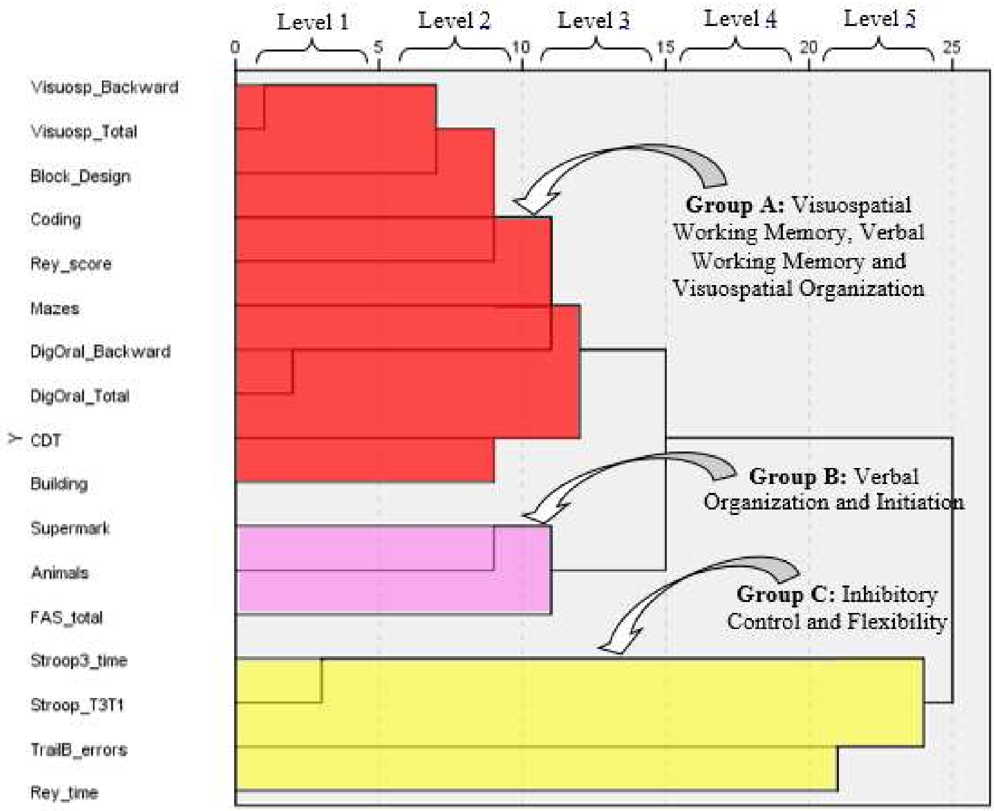
Table 3. Executive Function domains clustered in the PFA.

Factors	**1. Visuospatial Working Memory and Visuospatial Organization**	**2. Verbal Working Memory and Flexibility**	**3. Verbal Organization and Initiation**	**4. Inhibitory Control**
Variables	CDT, Visuosp Backward, Visuosp Total, Block Design, Coding, Rey score, Mazes	DigOral Backward, DigOral Total, TMT B errors	FAS total, Supermark, Animals	Stroop 3 time, Stroop T3T1

Variable names are described in the Data Analysis section.

In the HCA, three groups of executive function domains were identified and highlighted (Figure 3): Group A) Visuospatial Working Memory, Verbal Working Memory and Visuospatial Organization (red), Group B) Verbal Organization and Initiation (pink), and Group C) Inhibitory Control and Flexibility (yellow). Groups A and B are connected in the third level. Group C is connected to Groups A and B in the last level. These results and the results of the PFA are combined and presented in Figure 4.

Figure 3. Dendrogram showing executive functions domains distribution in MCI.



Variable names are described in the Data Analysis section.

3.4.3
Clustering Model of executive function domains in MCI

From the results of the PFA and HCA, a model of how EF domains are clustered in people with MCI was generated (Figure 4). It shows that, in MCI, Visuospatial Working Memory is linked to Visuospatial Organization; Verbal Working Memory is linked to Visuospatial Organization, Verbal Organization and Initiation, Flexibility and Inhibitory Control; Verbal Organization and Initiation are linked to Flexibility; Inhibitory Control is linked to all other domains. Each domain and connection is explained below.

Visuospatial Working Memory (Visuosp Backward, Visuosp Total) and Visuospatial Organization (Block Design, Coding, Rey score, Mazes, CDT, Building) formed the principal factor in the PFA, but in the HCA they clustered only in the second and third levels (Figure 3). The concept of Working Memory is a combination of storage and manipulation of information, applied across a wide range of cognitive functions (Baddeley, 2012). Visuospatial Working Memory refers to a temporary storage and processing of visuospatial content. Visuospatial Organization is the ability to solve visuospatial problems or replicate something seen through drawing or construction (Mervis et al., 1999). Visuospatial Organization consists of multi-step procedures and is linked to Visuospatial Working Memory because it supports all visuospatial tasks, from answer execution to error monitoring. For example, in the Block Design task, the given model and the scrambled pieces must be placed into Visuospatial Working Memory, where a comparison is performed. From this comparison, a solution hypothesis is generated and tested (execution). This process is repeated each time a part is moved (error monitoring), until a final solution is reached. In MCI, successful Visuospatial Organization performance requires the maintenance of visuospatial information over time in Visuospatial Working Memory.

Visuospatial Working Memory and Visuospatial Organization are important abilities for activities as going somewhere alone or walking in the mall and not getting lost. Few studies have investigated the relationship between measures of visuospatial function and daily functioning in older adults. Farley and colleagues (2011) studied this relationship with 40 community-dwelling older adults with mean (SD) age of 78.4 (7.5) years and mean (SD) education of 11.9 (2.6) years. They used JOLO, Block Design, HVOT (Hooper), WAIS-III Matrix Reasoning, WMS-III Spatial Span, and Visual Reproduction copy as traditional measures of visuospatial function; Neuropsychological Assessment Battery Map Reading subtest as an ecological test; The Revised Observed Tasks of Daily Living as a performance-based measure of IADLs (real-life stimuli to complete tasks about medication use, telephone use, and financial management) and Environmental Visuospatial Task as a measure of real-world visuospatial function (participants are required to answer 16 questions about their apartment building, including estimating distances and determining directions). The authors conducted

Regression analyses and results suggested that measures designed with ecological validity in mind make an important contribution to the prediction of daily functioning and that visuospatial function is essential for performance in daily activities in functionally independent older adults.

The relationship between Visuospatial Working Memory and Visuospatial Organization is consistent with a previous study conducted by Brown and colleagues (2012), in which both domains were also linked. The authors investigated which factors contributed to age-related changes in Visual Working Memory ability in 44 older adults (age mean = 73 years). All participants were cognitively healthy (mean MMSE score was 29.52, SD = .82). A Pearson Correlation analysis revealed that Visuospatial Backward (WMS-III) was correlated with modified Visual Patterns Test, and Block Design ($p < .01$). In the present study, Visuospatial Working Memory is also linked to Visuospatial Organization in people with MCI, as seen in the Clustering Model (Figure 4).

Verbal Organization and Initiation (FAS total, Supermark, Animals), involve the ability to rapidly search, retrieve and generate words under specific constraints within a specific time period (Weakley et al, 2013). This domain is correlated with Visuospatial Working Memory in healthy older adults (Brown & Brockmole, 2012) and is linked to Visuospatial Working Memory and Visuospatial Organization in older adults with MCI (Figure 4). One possible explanation is the action of Central Executive (CE), responsible for attentional control and information manipulation in the Working Memory (Baddeley, 2012), required in this tasks. In Visuospatial or Verbal Organization, CE helps to control the multi-step procedures and produce the final answer. Components of Verbal Working Memory (DigOral Backward, DigOral Total) are also required in the search and word production processes, because words must be kept there, while errors are monitored. Flexibility is also linked to Verbal Organization and Initiation. Here, the Flexibility domain is represented by the TMT B errors variable, which requires maintenance of response sets simultaneously and the ability to switch between two sequences (Kortte et al., 2002). The link with Verbal Organization and Initiation probably occurs because to increase word production in the given time, the individual is required to change category. For example, in VFT – Animal Category, the individual can say a list of domestic animals and then switch to a category of wild animals. In VFT – phonemic FAS, where the individual must say words that begin with "A", for example, the individual can say words that start with "AN" and then switch to "AR". This is consistent with a study conducted by Kortte and colleagues (2002), in which Verbal Fluency, Attention, Verbal learning, and Verbal Memory were related to Trail Making Test Part B performance.

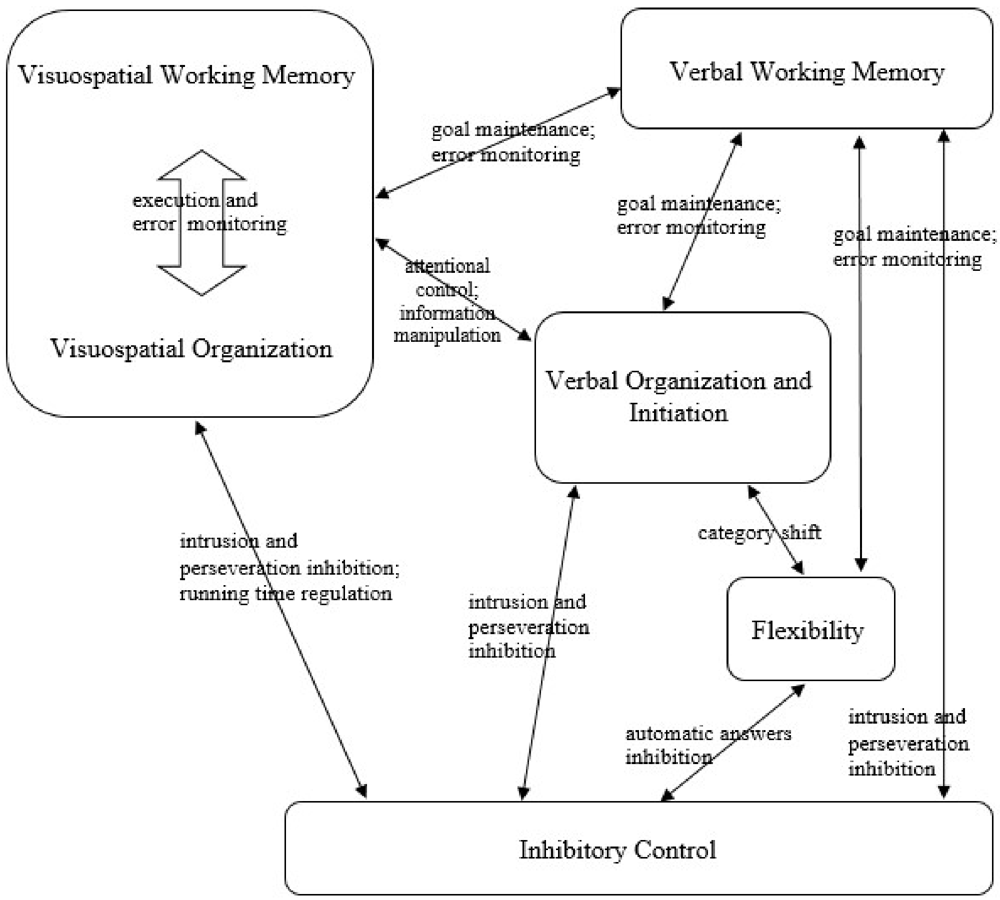
Verbal Organization and Initiation are important abilities for activities as keep conversation or explain something. Mograbi and colleagues (2014) conducted a study in Brazil, aimed to investigate the association between cognitive functions and ADLs. The sample consisted of 48 healthy older adults and 29 people with dementia. They conducted regression analysis and results indicated that the best predictors for ADLs were performance categorical fluency task (Animals) to people with dementia. These results indicate that EF tasks can predict performance in ADLs.

Inhibitory Control (Stroop 3 time, Stroop T3T1) is the ability to actively inhibit or delay an automatic answer to perform a correct answer and achieve a goal (Morasch & Bell, 2011). Inhibitory Control is linked to Verbal Organization and Initiation. This can be explained by intrusions and perseverations inhibition, once the time to perform verbal fluency tasks is limited. An individual with intrusion and perseveration errors wastes time and consequently produces few words. Inhibitory Control is also linked to Visuospatial Organization, since the inhibition of intrusions and perseverations is crucial during visuospatial tasks. Thus, the individual does not waste time (running time regulation). As seen in Figure 4, there is a link between Inhibitory Control and Flexibility. This is probably because during the Flexibility process, when the individual is required to switch between two sequences (Kortte et al., 2002), Inhibitory Control helps to inhibit automatic answers and avoid errors such as the maintenance of only one sequence.

Verbal Working Memory is linked to tasks of Visuospatial Organization, Verbal Organization and Initiation, Flexibility and Inhibitory Control because it's responsible for error monitoring and the maintenance of task goals (Baddeley, 2012). During Visuospatial Organization process, Verbal Working Memory is required to keep task goals and monitor errors. As seen in Table 3, Verbal Working Memory and Flexibility loaded Factor 2 in the PFA. It is also showed in the Clustering Model (Figure 4), which combines both analysis, PFA and HCA. This may be explained by the fact that sequences to be switched in Flexibility tasks need to be kept in the Verbal Working Memory (Baddeley, 2012). For older adults with MCI, keeping sequences in Verbal Working Memory and inhibiting the automatic answers (Inhibitory Control) is important to complete the task within the expected time. There is a link between Inhibitory Control and Verbal Working Memory. This result is explained by error monitoring and goal maintenance in Verbal Working Memory. Another explanation may be the fact that in Verbal Working Memory tasks, Inhibitory Control works by blocking intrusions and perseverations.

The results of this study shows that EF domains operates in a fractionary way in MCI. However, these domains are connected primarily by errors monitoring, goals maintenance and intrusions and perseverations inhibition process (Figure 4), creating an interdependent network. These results help to understand the performance of older adults with MCI on neuropsychological tests that evaluate EF. The evaluation through objective testing is important to identify cognitive impairment and provide early diagnosis of dementia. This results also enables a better understanding of the EF domains performance of older people with MCI who already show functional impairment. EF abilities affects the performance of activities of daily living (Cahn-Weiner et al., 2007; Mograbi et al., 2014; Farley et al., 2011), and the impairment in ADLs results in low quality of life for the older adults and their caregivers (Mograbi et al., 2014; Amieva et al., 2003).

Figure 4. Clustering Model of executive function domains in MCI.



3.5
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4. Manuscript 3: Episodic memory and working memory as predictors of conversion from mild cognitive impairment to dementia in a two-year follow-up study

Abstract

Alzheimer's disease (AD) is a syndrome characterized by progressive cognitive decline in the elderly. In the early stages of the disease there is a greater response of the older adults to therapeutic interventions. Early diagnosis is essential so that older adults can benefit from treatment and prolong their autonomy, delaying the onset and / or worsening of clinical symptoms and reducing caregiver stress. Determining which neuropsychological tests are good predictors of dementia is important for the identification of individuals at a high risk for the conversion to dementia. The aim of this study was to determine which neuropsychological tests are the best predictors of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) after two years. The study included 87 older adults from geriatrics and neurology outpatient clinics of a public hospital in Rio de Janeiro. The subjects were submitted to a broad neuropsychological battery at baseline. After a two-year follow-up, data were collected from medical records for each subject concerning the updated diagnosis made by medical experts. Baseline data were analyzed. A binary logistic regression analysis was used. During the 2-year period, 19 subjects (21.8%) with MCI at baseline converted to dementia. The logistic regression analysis revealed that the memory subtest (Mattis, $p < .001$, OR = 0.633, 95% CI: 0.505-0.792) and the total score of Oral Digits test together ($p = 0.02$, OR = 0.670, 95% CI = 0.476-0.944) were the best predictors of conversion from MCI to dementia. The results show that episodic memory and verbal content storage and processing in working memory together are good predictors of conversion from MCI to dementia after two years, even after adjusting for age, education, and functionality. It is, therefore, essential to have measures of episodic memory and working memory as part of screening batteries, for an early diagnosis of dementia.

Keywords: mild cognitive impairment, neuropsychological tests, dementia, prevention, executive functions

4.1 Introduction

In Brazil, the prevalence of dementia is approximately 5.1% to 17.5% (Boff et al., 2015). Alzheimer's disease (AD) is the most common cause of dementia (Boff et al., 2015). AD is a syndrome characterized by progressive cognitive impairment in the elderly. Generally, the person with AD show deficits in memory, attention, executive functions, spatial and temporal disorientation, and personality changes (Charchat-Fichman, 2005). In the early stages of the disease, there is a greater response to therapeutic interventions. Early diagnosis is essential so that the elderly can benefit from treatment and prolong their autonomy, delaying the onset and / or worsening of symptoms and reducing caregiver stress (Charchat-Fichman, 2005).

Mild cognitive impairment (MCI) is considered an intermediate stage between normal aging and dementia, and is characterized by moderate episodic memory impairment, mild deficits in cognitive function confirmed by neuropsychological testing, some preserved cognitive functions, or mild changes confirmed by neuropsychological testing, preserved activities of daily living or slight changes in more complex activities, but without a significant impact on functionality, and absence of dementia (Petersen et al., 2014). Determining which neuropsychological tests are good predictors of dementia is important for the identification of individuals at a high risk for the conversion to dementia. The aim of this study was to determine which neuropsychological tests are the best predictors of conversion from MCI to Alzheimer's dementia after two years.

4.2 Materials and methods

4.2.1 Baseline sample characteristics

The study included 87 individuals from geriatrics and neurology outpatient clinics of a public hospital in Rio de Janeiro. All participants were diagnosed with MCI by medical experts at baseline, with no subtype specification, according to the following diagnostic criteria: subjective complaint of memory decline, which was confirmed by an informer; cognitive deficits indicated by tests (performance on the Mini-Mental State Examination (MMSE; Folstein et al, 1975), Verbal Fluency Test – Animals Category (Spreen & Strauss, 1998), Mini-Cog (Borson et al, 2000)); preserved global cognitive functioning; intact functional activities (social-occupational); and absence of dementia (Koogan, 2011). For MCI diagnosis, imaging tests were not requested by doctors. However, laboratory tests were used to rule out other diseases that could cause cognitive decline. When dementia or vascular changes were suspected, imaging tests were performed.

Since the sample was selected in geriatrics and neurology outpatient clinics, it included individuals with cardiovascular disease, hypertension and/or controlled diabetes; corrected sensory deficits; symptoms of depression or previous depressive episodes, with current mood controlled by medication and / or psychotherapy. Patients were excluded if they met DSM-IV criteria for dementia (APA, 1994); current or previous presence of neurological diseases; severe psychiatric disorders; severe systemic disease that could lead to cognitive decline; recent history of alcoholism or drug addiction; and uncorrected visual and / or hearing deficits.

4.2.2
Sample characteristics after two years

After two years, the medical records and updated diagnosis of each participant were checked. Of the 87 subjects with MCI at baseline, 19 (21.8%) converted to Alzheimer's dementia. The other remained diagnosed with MCI. Participants were diagnosed with dementia by medical experts, according to the following DSM-IV criteria: changes in memory (learning and recall of learned content) and aphasia or apraxia, agnosia, changes in executive functions, at social or labor activity impairment (APA, 1994). Doctors used imaging and laboratory tests to confirm the diagnosis. The 19 participants who converted to dementia had a mean (standard deviation) of 80.05 (7.01) years of age, 3.95 (3.50) years of education, and 68.4% were women. The group that maintained the MCI diagnosis had a mean (standard deviation) of 76.75 (6.34) years of age, 5.81 (4.21) years of education, and 80.9% were women.

4.2.3 Ethical issues

The study was submitted to the hospital's Ethics Committee (CEP/HFSE) and was approved on May 12th, 2008 (protocol 000.320). All participants received an oral and written explanation about the purpose of the research, willingly agreed to participate, and signed an Informed Consent form prior to the beginning of the study.

4.2.4 Procedures

After the MCI diagnosis given by doctors, the elderly were referred to a neuropsychological evaluation, which was scheduled by phone and held in two sessions that lasted for one hour and thirty minutes, in the hospital.

The subjects were submitted to the same neuropsychological evaluation protocol that included: 1) scales to assess their degree of independence in instrumental activities of daily living and depressive symptoms; and 2) a comprehensive neuropsychological battery.

To assess the degree of independence in instrumental activities of daily living, we used the Pfeffer's Functional Activities Questionnaire (Pfeffer; Pfeffer et al., 1982). To assess depressive symptoms, we used the Geriatric Depression Scale (GDS-30; Yesavage et al., 1983). The scales and the neuropsychological battery are described in the instruments section.

4.2.5 Instruments

First assessment session:

Functional Activities Questionnaire (Pfeffer): evaluates the performance of older adults in activities of daily living through 10 questions. Each question receives a score ranging from 0 to 3. The scale goes from 0 to 30. If the individual reaches five points or more, he/she is considered as having an impairment in instrumental activities of daily living (Pfeffer et al., 1982). Individuals with a score of 5 or more were not excluded.

Memory for Figures: 10 simple figures are shown to the participant and the following tasks are performed: Nomination, Incidental Memory, Immediate Memory 1 and 2, Late Recall after five minutes (M5) and Late Recall with clue (Recognition).

Clock Drawing Test (CDT): The test consists of drawing the face of a clock on a blank sheet. Total score varies from 1 to 10 points (Sunderland et al., 1989).

Coding Task (WAIS-R): assesses working memory and processing speed, evaluating correlations between numbers and symbols in a 2-minute period (Wechsler et al., 1981).

Mattis Dementia Rating Scale: consists of tests that evaluate cognitive functioning. It contains the following subtests: Attention, Initiation/ Perseveration, Construction, Conceptualization, Memory, Total Score (sum of subtests) (Porto et al., 2003; Foss et al., 2013).

Verbal Fluency Test (VFT) - phonemic FAS: The test consists of saying as many words beginning with F, A and S in 1 minute. Participants cannot use proper nouns or a stem word with different endings (Spreen & Strauss, 1998).

Geriatric Depression Scale (GDS-30): assesses the degree of depressive symptoms, from mild to severe. Thirty questions (yes or no answers) assess how the subject felt in the two weeks prior to the testing day (Yesavage et al., 1983). The cut-off point is 14 (Yesavage et al., 1983). Individuals with scores of 14 or more are considered at a high probability of having symptoms of depression. However, these individuals were not excluded from the study.

Second assessment session:

Digits Forward and Backward (WMS-R): Digits Forward subtest: the participant must repeat the numbers said by the examiner in the same order. Digits Backward subtest: the participant must repeat the same numbers in reverse order. The scores of the two parts of this test are obtained separately and the sum of the two subtests yields the total score (Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987).

Extension (Span) of Visuospatial Digits Forward and Backward (WMS-R): The Forward subtest consists of repeating a sequence of visuospatial items in the same order. The Backward subtest consists of repeating a sequence of visuospatial items in reverse order. The scores of the two parts are obtained separately and the sum of the two subtests yields the total score (Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987).

Rey Auditory Verbal Learning Test (RAVLT): consists of a list of 15 words that is repeated five times. It includes the following tasks: Repeat list five times (A1 to A5), total learning, recall after 30 minutes (A7), recall with clue (recognition) (Cotta et al., 2011).

Rey-Osterrieth Complex Figure Test (ROCF) – Copy: consists of copying the Rey complex figure on a blank sheet of paper. The number of accurate elements drawn and the total execution time in seconds are recorded (Spreen & Strauss, 1998; Rey et al., 1999).

Stroop Test – Victoria version: The test consists of three cards: in the first card, the subject must say, as quickly as possible, the names of the colors that are shown in the card. In the second card, the subject must say the names of the colors that the words "all", "today", etc. are printed in. In the third card, the participant has to name the colors that the words "yellow", "red", etc. are printed in. The time to complete the third card is divided by time to complete the first card (Spreen & Strauss, 1998, Lezak, 1995).

Trail Making Test – Parts A and B: Form A consists of connecting numbers from 1 to 25, as quickly as possible. Form B consists of alternately connecting 13 numbers and 12 letters as quickly as possible (Spreen & Strauss, 1998; Lezak, 1995). The number of errors was recorded, including the number of omissions.

Block Design (WAIS-R): It consists of constructing figures using cubes. The answer is considered correct when the figure is the same as the model and is built within the time limit (Wechsler et al., 1981).

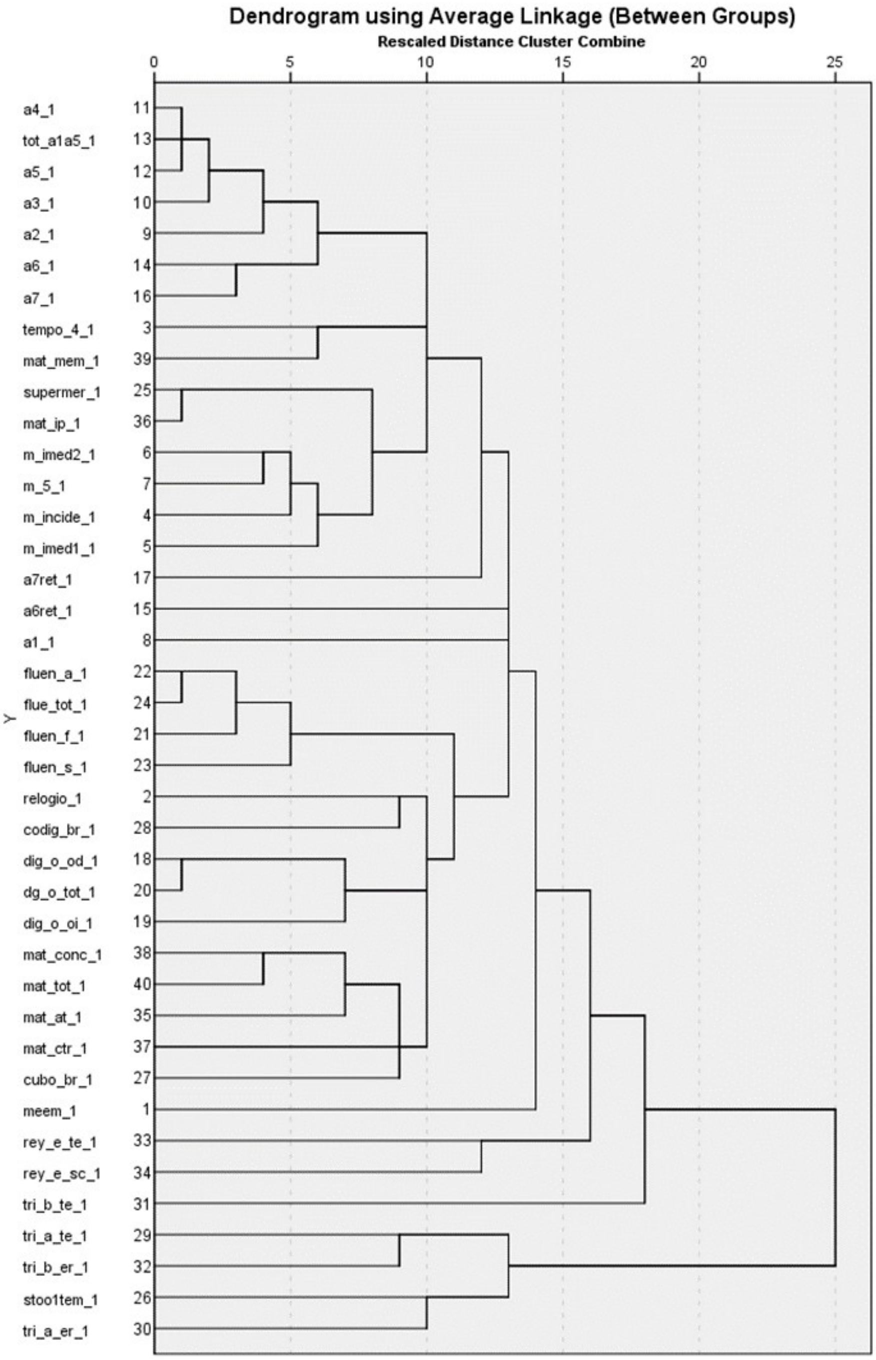
Mazes: It consists of finding a way out of mazes without lifting the pencil from the paper. The number of mistakes and the total time in seconds are recorded. Four mazes were used and the number of completed mazes calculated (Wechsler et al., 1991).

4.2.6
Statistical Analyses

All analyses were performed using the SPSS software (version 18.0) for Windows. Descriptive analyses were performed for sociodemographic characteristics and neuropsychological tests.

The Mann-Whitney U test was used to compare mean age, education, functionality, and scores in the neuropsychological tests for the group that converted to dementia after two years and the group that maintained the MCI diagnosis. The Mann-Whitney test, which is a non-parametric test, was employed due to the small number of individuals in the conversion group (19 subjects). Subsequently, a hierarchical cluster analysis was performed with only the variables that had statistical significance in the Mann-Whitney test, to asess which ones were highly correlated. From each group with a strong correlation, only one variable was chosen to cover all cognitive domains (Figure 1): global cognitive functioning, verbal episodic memory, visual episodic memory, learning, storage and processing of verbal content in working memory, storage and processing of visual content in working memory, organization and verbal fluency, visuospatial planning, selective attention, and flexibility

Figure 1. Dendrogram with variables that showed statistical significance in the Mann-Whitney test.



For the Binary Logistic Regression, 15 variables were selected, respecting the 5:1 ratio (5 subjects to 1 variable; Wilkinson, 1975). The variables were: age; education; Pfeffer; Mattis Total (sum of all subtests, global cognitive function); Mattis Memory (verbal episodic memory); Recall (M5) from Memory for Figures (visual episodic memory); Learning Total (A1A5) from the RAVLT (learning); Oral Digits Total (storage and verbal content processing in working memory); Coding (storage and visual content processing in working memory); FAS Total (phonemic fluency) - Verbal Fluency test; Supermarket (categorical verbal fluency) Mattis subtest score; Clock Drawing test (visuospatial planning); Mattis Construction (visuospatial planning); Stroop execution time card 1 (selective attention) and number of errors in the Trail Making test Form B (flexibility). The Binary Logistic Regression was performed to identify which neuropsychological tests were predictive of conversion to dementia after two years.

4.3 Results

4.3.1 Sociodemographic characteristics

During the two-year period, 19 participants (21.8%) converted to dementia and 68 (77.4%) kept the MCI diagnosis. The Mann-Whitney U test (Z) indicated that the mean age of the group that converted to dementia was higher than the group that did not convert ($Z = -2.08$, $p \leq .05$). The conversion group also had a higher dependence level in activities of daily living, according to the Pfeffer scale ($Z = -3.18$, $p \leq .001$). There was no significant difference between groups with respect to depressive symptoms (GDS) and no significant gender differences were observed (chi square test). Baseline sociodemographic data of the elderly who converted and who did not convert are shown in Table 1.

Table 1. Baseline sociodemographic data of both groups.

	Not converted		Converted		U de Mann-Whitney test (Z)
	n	Mean (SD)	n	Mean (SD)	
Age	68	76.75 (6.34)	19	80.05 (7.01)	-2.08*
Education	68	5.81 (4.21)	19	3.95 (3.50)	-1.82
Pfeffer	65	4.25 (4.86)	19	9.11 (6.36)	-3.18**
GDS	66	11.06 (6.04)	19	9.37 (6.18)	-1.16
	n	**Percentage**	**n**	**Percentage**	**Chi square test (X^2)**
Gender (female)	55	80.9%	13	68.4%	1.35

*p ≤ .05; **p ≤ .001

4.3.2 Difference between groups in the baseline means of the neuropsychological tests

The Mann-Whitney (Z) test indicated that the group that converted to dementia had smaller means than the one that did not convert in time orientation and in the cognitive functioning test (Mattis Total). Table 2 illustrates these results.

Table 2. Global cognitive functioning, time and space orientation scores of both groups.

	Not converted		Converted		U de Mann-Whitney test (Z)
	n	Mean (SD)	n	Mean (SD)	
Mattis Total	66	118.30 (11.28)	19	101.79 (14.34)	-4.28**
Time Orientation	65	3.48 (0.79)	17	2.59 (1.18)	-3.24**
Space Orientation	65	1.98 (0.12)	17	1.94 (0.24)	-1.03

*p ≤ .05; **p ≤ .001

The group that converted had worse scores than the group that did not convert in the following memory subtests: 1) memory for figures: incidental memory, immediate memory 1 and 2, M5; 2) RAVLT A1, A2, A3, A4, A5, Total A1A5, A6, A6 retention, A7 and A7 retention; 3) ROCF: recall execution time, recall execution score; 4) Mattis - Memory; 5) Oral Digits - forward. Table 3 shows the performance of the elderly in both groups, across all memory subtests.

Table 3. Performance in both groups across all memory subtests.

	Not converted		Converted		U de Mann-Whitney test (Z)
	n	Mean (SD)	n	Mean (SD)	
Memory for Figures					
Nomination	68	9.88 (0.47)	19	9.79 (0.42)	-1.64
Incidental M	68	5.53 (1.42)	19	4.00 (1.45)	-3.76**
Imed 1 M	68	7.10 (1.56)	19	5.89 (1.56)	-2.93*
Imed 2 M	68	7.97 (1.62)	19	6.37 (1.89)	-3.31**
M 5	68	7.01 (2.08)	19	4.11 (2.85)	-3.85**
Reconition	68	9.25 (1.60)	19	8.16 (3.08)	-1.60
RAVLT					
A1	68	3.93 (1.43)	19	2.79 (1.40)	-2.86*
A2	68	6.13 (1.89)	19	4.32 (1.95)	-3.45**
A3	68	6.99 (1.87)	19	4.68 (2.14)	-4.02**
A4	68	8.00 (2,29)	19	5.16 (2.24)	-4.27**
A5	68	8.43 (2.23)	19	5.42 (2.27)	-4.43**
Total A1A5	68	33.51 (7.95)	19	22.37 (8.86)	-4.45**
B1	68	3.63 (1.71)	19	2.84 (1.68)	-1.91
A6	68	5.26 (2.55)	19	2.53 (2.70)	-3.66**
Ret A6	68	0.63 (0.29)	19	0.41 (0.42)	-2.03*
A7	67	4.64 (2.72)	19	1.37 (2.29)	-4.62**
Ret A7	67	0.89 (0.49)	19	0.24 (0.35)	-4.82**
Rec A	66	8.24 (4.27)	19	6.11 (4.62)	-1.84
Rec B	66	4.29 (3.19)	19	3.79 (3.33)	-0.67
ROCF					
Rey recall execution time	47	148.77 (72.30)	7	80.29 (31.75)	-2.60*
Rey recall score	61	5.79 (5.99)	16	1.59 (2.71)	-2.91*
Rey recall classification	40	2.80 (1.45)	6	2.50 (2.26)	-0.81
DRS – Memory	66	20.17 (3.57)	19	14.26 (3.05)	-5.15**
Digits Forward	68	5.38 (1.88)	19	3.95 (1.78)	-2.80*
Span vis Forward	68	5.03 (1.49)	19	4.84 (1.12)	-0.52

$*p \leq .05$; $**p \leq .001$

Table 4 shows the performance of the elderly who converted and did not convert to dementia in the other subtests. The group who converted had worse scores than the group that did not convert in the following executive functions subtests: 1) Clock Drawing test; 2) Coding; 3) Block Design; 4) Mattis - Construction; 5) Digits backward and total; 6) F, A, S and FAS Total; 7) Supermarket; 8) Mattis - Initiation and Perseveration; 9) Trail Making Test Form B, time and errors. The group who converted had worse scores than the group that did not convert in the following attention subtests: 1) Stroop 1 time; 2) Trail Making Test Form A, time and errors; 3) Mattis - Attention. There was a significant difference between groups in the language subtest Mattis - Conceptualization, where the group who converted had a worse score than the other group.

Table 4. Sample performance in executive functions, attention and language tests.

	Not converted		**Converted**		**U de Mann-Whitney test (Z)**
	n	**Média (DP)**	**n**	**Média (DP)**	
Executive functions:					
Clock Drawing Test	67	6.03 (2.67)	17	4.24 (2.41)	-2.42*
Coding	66	18.18 (11.90)	17	8.06 (7.26)	-3.36**
Block Design	65	15.54 (7.80)	19	10.47 (5.19)	-3.02*
Mattis – Construction	66	4.12 (1.43)	19	2.95 (1.43)	-2.91*
ROCF					
Rey copy time	61	379.15 (207.51)	16	289.75 (98.31)	-1.59
Rey copy score	61	21.82 (8.69)	16	17.16 (9.01)	-1.81
Rey copy classification	52	2.88 (1.35)	13	2.85 (1.21)	-0.09
Digits					
Oral Digits backward	68	3.49 (1.45)	19	2.53 (0.96)	-2.55*
Total Oral Digits	68	8.87 (2.83)	19	6.47 (2.17)	-3.20**
Visuospacial Span backward	68	3.34 (1.84)	19	2.53 (1.39)	-1.77
Total Visuospacial Span	68	8.37 (2.74)	19	7.37 (2.17)	-1.44
FAS test					
F	67	8.40 (4.15)	19	5.37 (3.40)	-2.79*
A	67	6.46 (3.79)	19	4.00 (2.85)	-2.58*
S	67	6.33 (3.06)	19	3.74 (3.26)	-3.01*
Total FAS	67	21.19 (9.54)	19	13.11 (8.99)	-2.99*
Supermarket	66	16.57 (3.56)	18	14.33 (4.39)	-2.06*
Mattis – Iniciation/Perseve	66	30.53 (4.82)	19	26.68 (7.18)	-2.18*

ration					
Animals	68	11.90 (3.65)	19	10.26 (2.98)	-1.35
Stroop Test					
Stroop 2 time	68	32.68 (13.10)	18	44.00 (24.11)	-1.87
Stroop 2 erros	68	0.56 (1.29)	18	0.83 (1.43)	-0.67
Stroop 3 time	68	53.10 (31.21)	18	55.06 (24.40)	-0.55
Stroop 3 erros	68	3.72 (4.67)	18	6.61 (7.11)	-1.47
Stroop T3T1	68	2.35 (1.18)	18	1.91 (0.79)	-1.35
Trail Making test					
TMT B time	65	319.31 (204.40)	16	206.63 (83.84)	-2.40*
TMT B completed	66	0.58 (.498)	19	0.37 (0.50)	-1.59
TMT B erros	65	9.31 (7.685)	18	17.78 (7.26)	-3.72**
Attention:					
Stroop Test					
Stroop 1 time	68	23.88 (8.54)	18	31.17 (12.92)	-2.41*
Stroop 1 erros	68	0.62 (2.47)	18	0.11 (0.32)	-0.33
Trail Making test					
TMT A time	66	110.77 (42.92)	19	169.37 (77.99)	-2.98*
TMT A erros	66	0.65 (1.22)	19	2.26 (2.99)	-2.40*
Mattis – Attention	66	33.11 (2.55)	19	31.05 (2.57)	-3.16*
Lenguage:					
Mattis – Conceptualization	66	30.39 (4.58)	19	26.84 (5.99)	-2.29*

$^*p \leq .05$; $^{**}p \leq .001$

4.3.3
Predictors of conversion from MCI to dementia

Among the variables that were significantly different between groups at baseline, 15 were chosen to compose the binary logistic regression analysis, respecting the ratio of 5 subjects for each variable (Wilkinson, 1975). The sociodemographic variables that were significant in the Mann-Whitney test were included in the logistic regression analysis, namely, age and Pfeffer. The difference in education level was not significant between the two groups according to the Mann-Whitney test, however, a specific trend was observed: the group that converted to demential had a marginally lower education level (Z = -1.82, p = .07). Therefore, this variable was included in the binary logistic regression analysis. According to the Cluster Hierarchical analysis, the following neuropsychological variables were selected for the binary logistic regression analysis: Mattis Total; Mattis Memory; M5; RAVLT A1A5; Oral Digits Total;

Coding; FAS Verbal Fluency Test Total; Supermarket Verbal Fluency Test; Clock Drawing Test; Mattis Construction; Stroop 1 time; Trail Making Test Form B errors.

The binary logistic regression analysis was performed to determine which variables were predictive of dementia after two years. The result of the analysis indicated that Mattis Memory ($p < .001$, OR = .633, 95% CI: 0.505–0.792) and Oral Digits Total ($p = .02$, OR = .670, 95% CI= 0.476–0.944) were the best conversion predictors after two years (Table 5). The percentage classification was 83.9%.

Table 5. Binary logistic regression analysis.

Included variables	**B Coefficient**	**B (SE)**	**df**	**p**	**O.R.**	**95% C.I. for O.R.**
Mattis Memory	- .458	0.114	1	.000**	.633	0.505-0.792
Oral Digits Total	- .400	0.174	1	.022*	.670	0.476-0.944

$^{*}p \leq .05$; $^{**}p \leq .001$

4.4 Discussion

This study showed which neuropsychological tests, at baseline, best predict the conversion from MCI to dementia after 2 years. Even after adjusting for age, education and functionality, the Mattis Memory and Oral Digits Total neuropsychological tests proved to be the best conversion predictors.

The Mattis Memory subtest evaluates episodic memory and has time and space orientation items, free recall of sentences after a distractor, and verbal and visuospatial recall with clues. Other studies with the same goal as the present study also found episodic memory to be a strong predictor of dementia (García-Herranz et al., 2015; Egli et al., 2014). García-Herranz and collegues (2015) evaluated 105 elderly patients with MCI who were reassessed after a three year period. The study had the following objectives: 1) analyze the predictive value for conversion of neuropsychological tests for Alzheimer's disease; 2) determine the cutoff point for each predictor test; 3) analyze the influence of sociodemographic variables, such as: sex, age and education, and emotional state. Baseline data were analyzed. Logistic regression analysis showed that the recall subtest with clue TAVEC and Rey Figure execution time were the best predictors of conversion to dementia after a MCI diagnosis. With respect to sociodemographic variables, only gender had predictive power. Egli and collegues (2014) investigated which cognitive variables were better predictors of conversion to dementia from MCI and which variables continued as predictor with a higher power of conversion. Seventy-five elderly adults were assessed in learning, memory, language and executive functions measures. Multiple Cox regression models were used and the authors concluded that the serial position effect (when the individual recalls a list of words exceeding their working memory span capability) and the free recall word list were the best predictors of conversion to dementia. The serial position effect remained as a predictor even after a longer conversion time.

The other cognitive measure that entered the logistic regression model was the Oral Digits Total. This measure refers to the combination of storage and processing scores of verbal content in working memory. Many studies with the same objective did not include the Digits test in the neuropsychological evaluation (García-Herranz et al., 2015; Egli et al., 2014). Therefore, it is not clear whether the Digits test would have been a good predictor of the studied samples. Amieva and collegues (2004) included this measure in their analysis to identify which neuropsychological factors were predictors of conversion to dementia and found that the Digits test did not appear as an independent predictor (Amieva et al., 2004). Albert and collegues (2007) also included the Digits test in their analysis. They assessed neuropsychological change over a period of 4 years in normal and 197 MCI elderly aldults. Neuropsychological tests were divided into factors. The following factors were significantly lower in the group that converted at baseline, compared to the groups that remained normal or with MCI: episodic memory; executive functions and general knowledge (Albert et al., 2007). These results are in agreement with the results of the present study, where an episodic memory free recall test and recall with clues were important predictors of dementia. On the other hand, tests grouped in the executive functions factor (Albert et al., 2007), feature, in addition to the verbal content processing in working memory, other executive functions domains (flexibility, inhibitory control and visuospatial planning). Thus, it is not clear whether verbal content processing in working memory had an independent predictor role in the conversion to dementia.

In the literature, there is no consensus regarding which cognitive domains other than memory, contribute as predictors of dementia convertion. Albert and collegues (2007) believe this is because few studies have examined a wide variety of cognitive domains, which limits the kinds of associations that might be found. The present study used neuropsychological tests that comprise several processes involved, predominantly, in memory and executive functions, as they are the main cognitive functions involved in the conversion to dementia (García-Herranz et al., 2015; Egli et al., 2014; Albert et al., 2007; Amieva et al. 2004). The elderly group that converted to dementia had significantly lower scores than the group that did not convert in a majority of the tests (Tables 2, 3 and 4). Not all subtests were able to enter the binary logistic regression, due to the number of subjects. Respecting the rate of 5 subjects for each variable (Wilkinson, 1975), the binary logistic regression was performed with 15 variables. In the process of choosing the 15 variables, we sought to contemplate the broadest range of cognitive domains possible, as well as age, education and functionality. The following cognitive domains were included: global cognitive functioning, verbal episodic memory, visual episodic memory, learning, storage and processing of verbal content in working memory, storage and processing of visual content in working memory, organization and verbal fluency, visuospatial planning, selective attention and flexibility. The inhibitory control tasks did not reach statistical significance in the Mann-Whitney test; therefore, they did not enter the binary logistic regression. Storage and processing of verbal content in working memory stood out as the best predictor of conversion to dementia after two years in older adults with MCI.

The results of this study reveal that along with episodic memory, storage and processing of verbal content in working memory is a good predictor of conversion to dementia after two years, even after adjusting for age, education and functionality. This means that measures of both domains aid an early diagnosis of dementia. Future studies are needed, with different samples but also including various executive function domains in the analyses, so that a consensus on what cognitive domains, other than memory, contribute as predictors of dementia can be reached. In addition, it is recommended that episodic memory and storage and processing of verbal content in working memory tests be included in screening test batteries.

5.

Manuscript 4: Cognitive deficits in older adults with mild cognitive impairment in a two-year follow-up study

Abstract

Mild cognitive impairment (MCI) is characterized by deficits in one or more cognitive functions and a related loss in the ability to perform activities of daily living. Older adults with MCI represent a group with a high probability of conversion to dementia, compared to healthy elderly adults. However, older adults with MCI may improve or remain stable over the years. In the literature, there are few longitudinal studies about the trajectory of cognitive decline in older adults with MCI. Characterizing cognitive decline in older adults with MCI over time is important to identify the cognitive profile of who converts to dementia. This study aimed to analyze quantitative and qualitative cognitive decline in older adults with MCI over a two-year period. Sixty-two older adults with MCI treated at geriatrics and neurology outpatient clinics of a public hospital in Rio de Janeiro were submitted to a broad neuropsychological battery. After two years, they were re-evaluated, data were collected from the medical records of each subject, and the given diagnosis was updated by medical experts. The difference between the standardized z scores for each neuropsychological test in the first evaluation and re-evaluation after two years was calculated. Differences of 1 standard deviation were considered as indicative of decline. Descriptive analyses were conducted for the different profiles of cognitive decline observed. The Mann-Whitney U test was employed to assess differences between groups with respect to gender, age, education, functionality, the geriatric depression scale and diagnosis after two years. Of the 62 elderly adults in the sample, 24.2% converted to dementia after two years. Four older adults (6.5%) showed no decline in any neuropsychological test; 9 (14.5%) only showed decline in episodic memory or storage in working memory. Ten individuals (16.1%) showed decline specifically in executive functions and 39 (62.9%) showed decline in two or more cognitive functions. The

group with declines in two or more cognitive functions showed a higher percentage of conversion to dementia than the group with decline only in executive functions (Z = -2.11, p = .04). The group showing declines only in executive functions had higher GDS scores than groups showing only memory decline (Z = -1.99, p = .05) and decline in two or more functions (Z = -2.23, p = .03). There were no differences in gender, age, education and functionality between groups.

Keywords: mild cognitive impairment, neuropsychological tests, dementia, decline, conversion, cognitive trajectory.

5.1 Introduction

Mild cognitive impairment (MCI) is characterized by deficits in cognitive function and a related loss in the ability to perform advanced activities of daily living, such as working (Petersen et al., 1999; Radanovic et al., 2015). MCI can be classified as amnestic (when there is memory impairment), amnestic multiple domains (when there is memory loss and loss in other cognitive functions), non-amnestic (when there is loss of a cognitive function other than memory), non-amnestic multiple domains (when there is loss of other cognitive functions other than memory) (Petersen et al., 1999; Radanovic et al., 2015). MCI can be a transition stage to dementia, such as Alzheimer's disease or vascular dementia; however, elderly adults with MCI may improve or remain stable over the years (Radanovic et al., 2015).

According to the DSM-IV (APA, 1994), the diagnostic criteria for dementia include memory changes (learning and learned content recall) and aphasia or apraxia, agnosia, changes in executive functions interfering with social or work activity. Petersen and collegues (2009) reported that in memory research centers and clinical treatments, the percentage of MCI conversion to dementia is approximately 10% to 15% a year. Farias and collegues (2009) analyzed 111 elderly adults with MCI in California (46% from a clinical population and 54%

from the community) and observed an annual conversion rate of 13% in older adults who were assisted in memory clinics and 3% community-dwelling older adults. Epidemiological studies have reported lower annual conversion rates, from 6% to 10%, probably due to the cognitive heterogeneity found in baseline of these studies (Petersen et al., 2009).

Individuals with MCI make up a group with a high probability of conversion to dementia, when compared to healthy older adults (Petersen et al., 2009). Cloutier and collegues (2015) evaluated the decline trajectory of cognitive functions and compared individuals who converted to dementia and older adults who did not convert. The delayed recall of episodic memory, working memory and spatial memory had a stable profile with a sharp decline before conversion to dementia. Immediate recall, executive functions and visuoconstructive skills had a profile of gradual decline before conversion to dementia, and language had a stable profile (Cloutier et al., 2015). There are few longitudinal studies regarding the trajectory of cognitive decline in older adults with MCI. (Cloutier et al., 2015; Ramel et al., 2015; Albert et al., 2007). Studying cognitive decline in elderly adults with MCI over time is important to identify the cognitive profile those who convert to dementia. The present study aimed to analyze quantitative and qualitative cognitive decline in older adults with MCI over a two-year period.

5.2
Material e methods

5.2.1
Baseline sample characteristics

Sixty-two elderly adults with MCI treated at geriatrics and neurology outpatient clinics of a public hospital in Rio de Janeiro, were submitted to a broad neuropsychological battery. All participants were diagnosed with MCI by medical experts at baseline, with no subtype specification, according to the following diagnostic criteria: subjective complaint of memory decline, which was confirmed by an informer; cognitive deficits indicated by tests (performance on the Mini-

Mental State Examination (MMSE; Folstein et al, 1975), Verbal Fluency Test – Animals Category (Spreen & Strauss, 1998), Mini-Cog (Borson et al, 2000)); preserved global cognitive functioning; intact functional activities (social-occupational); and absence of dementia (Koogan, 2011). For MCI diagnosis, imaging tests were not requested by doctors. However, laboratory tests were used to rule out other diseases that could cause cognitive decline. When dementia or vascular changes were suspected, imaging tests were performed.

Since the sample was selected in geriatrics and neurology outpatient clinics, it included individuals with cardiovascular disease, hypertension and/or controlled diabetes; corrected sensory deficits; symptoms of depression or previous depressive episodes, with current mood controlled by medication and / or psychotherapy. Patients were excluded if they met DSM-IV criteria for dementia (APA, 1994); current or previous presence of neurological diseases; severe psychiatric disorders; severe systemic disease that could lead to cognitive decline; recent history of alcoholism or drug addiction; and uncorrected visual and / or hearing deficits.

5.2.2
Follow-up procedures

After two years, older adults were contacted by telephone and re-assessed. Data were collected from the medical records of each individual and the updated diagnosis made by medical experts was checked. Participants were diagnosed as having dementia according to DSM-IV criteria (APA, 1994); imaging and laboratory results confirmed the diagnosis.

5.2.3
Ethical issues

The study was submitted to the hospital's Ethics Committee (CEP/HFSE) and was approved on May 12th, 2008 (protocol 000.320). All participants received an oral and written explanation about the purpose of the research, willingly agreed to participate, and signed an Informed Consent form prior to the beginning of the study.

5.2.4 Instruments

The instruments described below were employed at baseline and at follow-up (two years later):

Functional Activities Questionnaire (Pfeffer): evaluates the performance of older adults in activities of daily living through 10 questions. Each question receives a score ranging from 0 to 3. The scale goes from 0 to 30. If the individual reaches five points or more, he/she is considered as having an impairment in instrumental activities of daily living (Pfeffer et al., 1982). Individuals with a score of 5 or more were not excluded.

Memory for Figures: 10 simple figures are shown to the participant and the following tasks are performed: Nomination, Incidental Memory, Immediate Memory 1 and 2, Late Recall after five minutes (M5) and Late Recall with clue (Recognition).

Clock Drawing Test (CDT): The test consists of drawing the face of a clock on a blank sheet. Total score varies from 1 to 10 points (Sunderland et al., 1989).

Coding Task (WAIS-R): assesses working memory and processing speed, evaluating correlations between numbers and symbols in a 2-minute period (Wechsler et al., 1981).

Mattis Dementia Rating Scale: consists of tests that evaluate cognitive functioning. It contains the following subtests: Attention, Initiation/ Perseveration, Construction, Conceptualization, Memory, Total Score (sum of subtests) (Porto et al., 2003; Foss et al., 2013).

Verbal Fluency Test (VFT) - phonemic FAS: The test consists of saying as many words beginning with F, A and S in 1 minute. Participants cannot use proper nouns or a stem word with different endings (Spreen & Strauss, 1998).

Geriatric Depression Scale (GDS-30): assesses the degree of depressive symptoms, from mild to severe. Thirty questions (yes or no answers) assess how the subject felt in the two weeks prior to the testing day (Yesavage et al., 1983). The cut-off point is 14 (Yesavage et al., 1983). Individuals with scores of 14 or more are considered at a high probability of having symptoms of depression. However, these individuals were not excluded from the study.

Digits Forward and Backward (WMS-R): Digits Forward subtest: the participant must repeat the numbers said by the examiner in the same order. Digits Backward subtest: the participant must repeat the same numbers in reverse order. The scores of the two parts of this test are obtained separately and the sum of the two subtests yields the total score (Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987).

Extension (Span) of Visuospatial Digits Forward and Backward (WMS-R): The Forward subtest consists of repeating a sequence of visuospatial items in the same order. The Backward subtest consists of repeating a sequence of visuospatial items in reverse order. The scores of the two parts are obtained separately and the sum of the two subtests yields the total score (Spreen & Strauss, 1998; Lezak, 1995; Wechsler, 1987).

Rey Auditory Verbal Learning Test (RAVLT): consists of a list of 15 words that is repeated five times. It includes the following tasks: Repeat list five times (A1 to A5), total learning, recall after 30 minutes (A7), recall with clue (recognition) (Cotta et al., 2011).

5.2.5 Statistical analysis

All analyses were performed using the SPSS software (version 18.0) for Windows. The difference between the standardized z scores for each neuropsychological test at baseline and follow-up (re-evaluation) was calculated. Differences of 1 standard deviation were considered as indicative of decline. Descriptive analyses were conducted for the different profiles of cognitive decline observed. The Wilcoxon test was used to identify changes in functionality, in the GDS and neuropsychological testing after two years. The Mann-Whitney U test was used to identify differences between groups with respect to gender, age, education, functionality, GDS and diagnosis after two years.

5.3 Results

5.3.1 Diferences between baseline and two-year follow-up in neuropshychological tests, functionality and depression symptoms, for participants who converted and who did not convert to dementia.

Of the 62 elderly adults in the sample, 15 (24.2%) converted to dementia after two years according to the medical specialists. Older adults who did not convert to dementia had lower scores in time and space orientation, in simple figures nomination and categorical verbal fluency (clothes category). They showed improvement in recall when given clues in the visual episodic memory measure. Older adults who converted to dementia had lower scores in recall with clues in visual episodic memory and categorical verbal fluency (supermarket category). There were no differences in functionality and depression symptoms. The Wilcoxon test results, baseline and follow-up means are shown in Table 1.

Table 1. Wilcoxon test results: baseline and two-year follow-up mean scores of participants who converted and did not convert to dementia.

	Z (p)	**Mean (SD)** **Baseline**	**2-year follow-up**
No converted (N=47)			
Time Orientation	2.17 (0.03*)	3.57 (0.75)	3.49 (0.88)
Space Orientation	6.56 (0.00**)	1.98 (0.15)	1.94 (0.32)
Nomination	5.54 (0.00**)	9.91 (0.45)	9.89 (0.47)
Recall with clue visual episodic memory	3.26 (0.00**)	9.17 (0.76)	9.36 (1.71)
Clothes	3.35 (0.00**)	7.80 (0.66)	7.77 (0.69)
Converted (N= 15)			
Recall with clue visual memory	1.94 (0.05*)	8.33 (2.58)	7.20 (2.88)
Supermarket	2.35 (0.02*)	15.00 (4.72)	10.93 (4.51)

*p≤ .05; **p≤ .001

5.3.2
Neuropsychological decline characterization after two years

The difference between the standardized scores (z) at baseline and after two years, in each neuropsychological test, was calculated for the entire sample. As described in the methods section, a decrease in 1 SD in the neuropsychological tests was considered a decline. Four different decline profiles were identified: 4 participants (6.5%) showed no decline in any neuropsychological test (No Decline Group); 9 participants (14.5%) showed decline only in episodic memory or working memory storage (Episodic Memory Decline / WM Storage Group). Ten participants (16.1%) showed decline exclusively in executive functions (Executive Functions Decline Group). Most participants, 39 (62.9%) showed decline in two or more cognitive functions (Multiple Functions Decline Group). Table 2 illustrates the characteristics of each decline profile group.

Table 2. Cognitive functions that showed a decline in each profile group. N=62.

	Recall no clue	Learn	Recall without clue	WM Storage	Space Orientation	Time Orientation	WM Processing	Verbal Fluence	Visuospacial Planning	Attention	Language	Global cognitive functioning
No Decline Group												
1												
2												
3												
4												
Episodic Memory Decline / WM Storage Group												
5	x											
6	x											
7			x									
8		x		x								
9*				x								
10*			x	x	x	x						
11				x								
12				x								
13	x		x									
Executive Functions Decline Group												
14							x					
15							x					
16								x				
17								x				
18							x		X			
19							x	x				
20							x	x	X			
21								x				
22								x				
23								x	x			
Multiple Functions Decline Group												
24	x			x			x	x		x		x
25*		x	x	x			x	x	x		x	x
26*		x	x	x		x	x	x	x	x	x	x
27*	x			x	x	x	x		x		x	x
28	x		x	x				x				
29*	x		x	x			x	x	x			
30*	x						x		x			
31	x	x		x			x	x	x	x		
32	x			x							x	
33	x	x		x		x		x				
34	x			x					x			
35*				x		x					x	
36				x				x				
37			x	x				x				
38*		x					x					
39				x					x			
40		x	x				x					
41*		x		x					x			
42			x	x				x				
43			x	x				x				
44			x	x				x				
45				x			x	x				
46		x		x				x			x	
47			x	x					x	x		
48				x				x	x			
49*		x		x	x		x	x				
50*		x						x			x	
51*			x	x				x	x			
52		x		x					x		x	
53			x	x				x	x			
54		x					x	x				
55*		x	x	x			x	x	x			
56		x	x	x			x	x	x			
57				x			x	x	x		x	
58				x			x	x	x	x		
59							x				x	
60							x	x	x		x	
61				x							x	
62*							x	x		x		

* individuals who converted to dementia

5.3.3
Functionality and depression symptoms across the four cognitive decline profiles at follow-up.

The Wilcoxon test revealed that Group 3 ($Z = 2.00$, $p = 0.05$) had significantly lower functional scores after two years. The other results did not reach statistical significance. The means, standard deviations and medians of functionality and depression symptoms at baseline and follow-up for the four cognitive decline profiles are presented in Table 3.

5.3.4
Description of the four cognitive decline profiles.

5.3.4.1
No Decline Group

This group did not show any decline in the neuropsychological tests. At baseline, 50% of the subjects in this group showed a deficit ($SD \leq 1$ on standardized scores) in episodic memory and other cognitive functions, 25% had only a deficit in episodic memory and 25% showed no deficits. None of the subjects showed, at baseline, deficits in functionality or depression symptoms. After two years, 25% showed a worsening of depressive symptoms and none converted to dementia.

5.3.4.2
Episodic Memory Decline / WM Storage Group

This group showed a decline only in episodic memory or working memory storage. At baseline, 44.4% of subjects had deficits in episodic memory and other cognitive functions, 33.3% had deficits in executive functions and other cognitive functions (except memory), and 22.2% showed no deficits. At baseline, 11.1% had depressive symptoms. After two years, 11.1% showed a worsening of functionality and the rate of conversion to dementia was 22.2%. The subjects who converted to dementia presented, at baseline, deficits in episodic memory and other cognitive functions (global cognitive functioning, working memory storage, executive functions, language, and attention).

5.3.4.3
Executive Functions Decline Group

Older adults in this group showed a decline only in executive functions. At baseline, 50% of subjects had deficits in episodic memory and other cognitive functions (especially executive functions), 20% had deficits in executive functions and other cognitive functions (except memory), and 30% showed no deficits. After two years, 20% showed a worsening in functionality and 10% in depression symptoms. None converted to dementia.

5.3.4.4
Multiple Functions Decline Group

This group showed a decline in two or more cognitive functions. At baseline, 51.3% of subjects had deficits in episodic memory and other cognitive functions, 5.1% a deficit only in episodic memory, 23.1% had deficits in executive functions and other cognitive functions (except memory), 7.7% had a deficit in other different cognitive functions of memory and executive functions, and 12.8% did not show deficits. At baseline, 25.6% had depressive symptoms. After two years, 2.6% showed a worsening of functionality and 5.1% of depression symptoms. The rate of conversion to dementia was 33.3%. Of the 13 subjects in this group who converted to dementia, 84.6% had, at baseline, deficits in episodic memory and other cognitive functions (global cognitive functioning, working memory storage, executive functions, language, attention), 7.7% had deficits in executive functions and other cognitive functions (except memory), and 7.7% had a deficit in time and space orientation.

5.3.5
Differences between the four cognitive decline profiles: socio-demographic, functionality and depression symptoms.

The Mann-Whitney test revealed that the group with multiple decline functions showed a higher conversion rate to dementia than the group with only executive function decline (U=130.0, p=0.04). For the median in the GDS, the group showing a decline only in executive functions had a higher score than the group with only memory decline (U=18.0, p=0.05; data after 2 years) and the group with decline in two functions or more (U=71.0, p=0.03; data after 2 years). There were no gender, age, education, and functionality differences across the four cognitive decline profiles. The mean, standard deviation and median values for age, educational level, functionality, and depressive symptoms of the four groups are shown in Table 3.

Table 3. Rate of conversion to dementia and sociodemographic, functionality and depression symptom characteristics of the four cognitive decline groups.

	No Decline Group	**Memory Decline Group**	**Executive Functions Decline Group**	**Two or more Functions Decline Group**
	(%)			
Converted to dementia	0.0	22.2	0.0	33.3*
Female gender	100.0	66.7	70.0	71.8
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age	78.00 (6.27)	76.44 (8.81)	77.20 (5.67)	76.74 (6.81)
Schooling	8.50 (6.75)	5.33 (5.24)	6.10 (2.60)	5.31 (4.04)
ADLs Baseline	3.25 (2.75)	4.13 (2.99)	5.67 (5.70)	5.23 (5.53)
ADLs after 2 years	3.75 (3.30)	4.00 (3.27)	4.13 (2.94)	6.73 (6.69)
ADLs difference	0.01 (0.16)	-0.09 (0.63)	-0.48 (1.11)	0.15 (0.79)
GDS Baseline	14.00 (4.83)	8.38 (6.11)	12.80 (5.80)	10.08 (6.03)
GDS after 2 years	11.00 (8.36)	8.56 (6.36)	14.89 (6.07)*	9.48 (5.68)
GDS difference	-0.46 (1.25)	0.01 (0.26)	0.42 (0.85)	0.01 (0.75)

* significant difference between the groups (data in text); ADLs. Activities of daily living; GDS, geriatric depression scale.

5.4 Discussion

This study examined a two-year cognitive trajectory of elderly adults diagnosed with MCI, from geriatrics and neurology outpatient clinics of a public hospital in Rio de Janeiro. During the follow-up period, 24.2% had converted to Alzheimer's disease. This is consistent with findings in clinical populations (Petersen et al., 2009; Farias et al., 2009).

Initially, we analyzed the difference between baseline and follow-up (two years later) in neuropsychological measures, functionality, and depression symptoms in elderly adults who converted and who did not convert to dementia, according to the diagnosis of medical specialists. After two years, both groups showed significant worsening of executive functions (verbal fluency), according to the Wilcoxon test. Those who converted showed a decline in episodic memory (recall with clues), while those who did not convert to dementia showed improvement in the same cognitive domain, according to the Wilcoxon test (Table 1). Memory decline is a characteristic of the early stages of dementia. Such results are also reported by Albert and collegues (2007), who examined, in a longitudinal study, neuropsychological changes of 197 subjects with MCI and healthy participants at baseline. After four years, the participants who converted to dementia showed greater decline in episodic memory when compared to the control group and the elderly groups that were stable or showed cognitive decline over time.

The data were also treated qualitatively. Considering 1 SD declines presented by the sample in the neuropsychological tests, the subjects were divided into the following groups: No Decline, Episodic Memory / WM Storage Decline, Executive Functions Decline, and Multiple Functions Decline. Most of the elderly who converted to dementia were part of the Multiple Functions Decline group (Table 3). This group showed significant impairment in functionality. Most of the participants who converted to dementia presented, at baseline, deficits in episodic memory and other cognitive functions, including global cognitive functioning, working memory storage, executive functions, language, and attention. That is, the elderly who converted to dementia had, at baseline, a cognitive profile similar to older adults with amnestic and multiple domains MCI. The amnestic and multiple domains MCI profiles show episodic memory impairment and changes in other cognitive functions, preserving the activities of daily living, and having no dementia (Radanovic et al., 2015). These profiles have a greater risk of converting to Alzheimer's disease or vascular dementia (Radanovic et al., 2015).

By comparing the decline groups through the Mann-Whitney test, the Executive Functions Decline group stood out with significantly higher scores of depression symptoms after two years (Table 3) than the Episodic Memory / WM Storage Decline and Multiple Functions Decline Groups. The relationship between depression and cognitive functions is thoroughly described in the literature (Wong et al., 2015; Panza et al., 2010; Kiosses et al., 2001; Taconnat et al., 2010). Depression is associated with cognitive deficits in aging and is considered a risk factor for Alzheimer's disease and vascular dementia (Wong et al., 2015; Panza et al., 2010). Wong and collegues (2015) examined the cognitive performance of 52 depressed patients. At baseline, 53.8% showed cognitive impairment in a screening tool for dementia (MoCA). After 6 months of treatment with medical experts, 61.5% improved the depression symptoms and 44.2% of the sample continued with cognitive impairment. In a study by De-Paula and collegues (2016), 274 healthy elderly adults with MCI and dementia were evaluated to investigate the association between depression and cognitive and functional performance in each group. In the group of non-demented older adults, depressed participants performed worse than non-depressed participants in the cognitive tests, with a greater effect being observed in executive function tests. There was a decrease in the association between cognition and depression in the MCI and dementia groups. An association between depression and executive functions was also observed in this study, confirming other reports in the literature (Wong et al., 2015; Panza et al., 2010; Kiosses et al., 2001; Taconnat et al., 2010; Kthryn et al., 2002).

Most longitudinal studies of elderly adults with MCI have prioritized the neuropsychological predictors of dementia and the rate of MCI conversion to dementia. Few recent studies have tried to identify the trajectory of cognitive decline in older adults with MCI, using different methodologies (Cloutier et al., 2015; Ramel et al., 2015; Albert et al., 2007). The present study showed that there are different cognitive decline profiles in elderly adults with MCI and that there are differences between them regarding depressive symptoms and rate of conversion to dementia.

6.
Conclusion

The present study investigated several cognitive functioning aspects of older adults with mild cognitive impairment. The first article showed the neuropsychological tests that are most commonly used to evaluate executive functions. Moreover, it showed that many studies on cognitive function during aging do not include all aspects of executive functioning in their neuropsychological assessment protocols (Bangen et al., 2010; Vicini-Chilovi et al., 2010). According to the second article, the executive function domains behave fractionally in elderly patients with mild cognitive impairment and bind through processes such as error monitoring, goal maintenance, intrusions and perseveration inhibition. The fact that the different domains of executive functions group fractioned and not as a single group, indicates that it is important to consider all aspects of executive functioning in neuropsychological evaluations. Identifying the different aspects of executive function deficits in elderly patients with mild cognitive impairment is important for preventing injuries in activities of daily living and for an early diagnosis of dementia (Cahn-Weiner et al., 2007; Mograbi et al., 2014; Farley et al., 2011).

The third article identified that working memory, along with episodic memory, are the best dementia predictors in the sample. Episodic memory and working memory stood out among different cognitive functions and different areas of memory and executive functions that were entered in the statistical analysis. The fourth article identified, after two years, a group of elderly adults with mild cognitive impairment that did not show a decline in any cognitive function, a group that showed a decline only in episodic memory or working memory storage, another group that showed a decline only in executive functions and another group with a decline in two or more cognitive functions. The group with only executive functions decline had more depression symptoms than the other groups. The group with a decline in two or more cognitive functions showed a higher dementia conversion rate. Understanding the cognitive trajectory of elderly patients with mild cognitive impairment is critical to identify cognitive profiles most likely to convert to dementia.

The results of the present study may foster the development of neuropsychological assessment protocols specifically targeted at elderly adults with mild cognitive impairment, which should include different executive function domains and dementia predictors. Furthermore, this study may provide a better understanding of the cognitive functioning and decline trajectory of elderly patients with mild cognitive impairment. Such understanding is fundamental to assist mild cognitive impairment diagnosis, for early dementia diagnosis, and for the prevention of injury in activities of daily living in this population.

This work contributed to the neuropsychology of aging research since identified the most frequently used executive function tests by experts and found that most surveys do not assess all dimensions of executive functions (first manuscript). It is recommended that all dimensions are contemplated in the neuropsychological batteries because, as seen in the second manuscript, executive functions domains behave in a fragmented way in mild cognitive impairment. This is also useful for clinical practice of neuropsychologists, who can now know the importance to evaluate executive functions in more detail to investigate cognition in older adults.

Another contribution of this work to the neuropsychology of aging research was to present which were the best predictors of conversion to dementia after two years, even after adjusting for age, education and functionality (third manuscript). Several domains of memory and executive functions were included in the statistical analysis and Mattis Memory and Oral Digits Total were the best predictors of conversion to dementia in this study. It was important to analyze a Brazilian sample and found similar results to the international literature. This result was also important for clinical practice because it is essential that experts use in geriatrics and neurology clinics, good predictors of conversion to dementia in the screening battery. According to the study results, Mathis Memory and Oral Digits Total should be included in the screening test batteries applied in the elderly.

The fourth manuscript had great contribution because there are few studies about the cognitive trajectory of older adults. In the neuropsychology clinical practice, know the cognitive trajectory of older adults contributes to the development of cognitive rehabilitation programs according to the different profiles of cognitive decline. Finally, the results of this study contributed to the advancement of knowledge about cognition and cognitive decline in Brazilian older adults.

7.

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