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Marina Martorelli Pinho

Atypical aspects in aging: extensive neuropsychological assessment in normal aging, Mild Cognitive Impairment and Alzheimer's disease.

Tese de Doutorado

Thesis presented to the Programa de Pós-gradução em Psicologia of PUC-Rio in partial fulfillment of the requirements for the degree of Doutor em Psicologia.

Advisor: Prof (a) Helenice Charchat-Fichman

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ABSTRACT

Aging is a major healthcare challenge worldwide. With aging, the prevalence of conditions such as dementia and Mild Cognitive Impairment increase. The most frequent and studied cause of dementia is Alzheimer's dementia (AD). Traditionally, AD is characterized by early deficit in episodic memory. However, current studies show that AD presents heterogeneity in clinical manifestations, especially cognitive manifestations. Thus, some patients present a non-amnestic cognitive profile. These profiles are called by some authors as "atypical AD". The first part of this thesis was aimed at studying the neuropsychological heterogeneity in AD by means of 2 studies: a systematic review on neuropsychological heterogeneity in AD (published) and cases of study with typical and atypical AD patients (published). The systematic review was necessary, as it was the first published review about the topic. The findings of the two studies show that atypical aspects in AD need to be further explored, since AD is not a homogeneous condition. Understanding these cognitive profiles in AD will interfere in diagnostic methods and therapeutic interventions, either pharmacological or behavioral ones. The second part of this thesis explores atypical aspects in three samples: normal aging, MCI and AD. Thus, a cross-sectional study was conducted to compare measures of processing speed (PS), inhibitory control, working memory and cognitive flexibility in the three samples. The results of this study showed that PS measures may be early indicators of cognition decline in aging. MCI versus normal aging showed differences in PS measures and errors in tests of PS. However, these samples did not show differences in executive function measures (EFs) and functional measures. Nevertheless, MCI versus AD show differences in PS measures, executive functions and functionality. Thus, this study showed relevant results for the diagnosis process of MCI and new guidelines for clinical settings and research. In addition, in the second part of this thesis an article was written on diagnostic

accuracy of the PS measures used in cases of MCI and AD. The literature shows a lack of studies on differences in PS measures in aging and diagnostic parameters of PS instruments. This study showed that PS measures present discriminative abilities in AD and MCI. These data are important, as there is a lack of diagnostic tools for PS in aging, especially in the Brazilian scenario.

Keywords:

Neuropsychological heterogeneity, Alzheimer's disease, Mild Cognitive Impairment, Normal Aging, Processing Speed, Inhibitory Control, Working Memory, Cognitive Flexibility, Diagnostic Accuracy.

Martorelli, Marina; Charchat-Fichman,Helenice. Aspectos Atípicos no envelhecimento: avaliação neuropsicológica extensa no envelhecimento normal, Comprometimento Cognitivo Leve e doença de Alzheimer. Rio de Janeiro, 2019.91p. Tese de Doutorado- Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

RESUMO

O envelhecimento em todo o mundo é um dos maiores desafios da saúde. Nesse contexto, condições clínicas como demências e Comprometimento Cognitivo Leve (CCL) também aumentam suas prevalências. A causa de demência mais frequente e estudada é demência de Alzheimer (DA). Tradicionalmente, DA é caracterizada pelo déficit precoce na memória episódica. Entretanto, estudos atuais mostram que a DA apresenta heterogeneidade neuropsicológica e alguns pacientes apresentam déficits cognitivos precoces não-amnésticos. Essas apresentações são chamadas por alguns autores de DA atípica. Dessa forma, a primeira parte dessa tese dedicou-se a estudar a heterogeneidade neuropsicológica na DA através de dois estudos: uma revisão sistemática sobre heterogeneidade neuropsicológica na DA (publicado) e um estudo de casos sobre perfis típico e atípico na DA (publicado). A revisão sistemática tornou-se necessária já que foi a primeira revisão sistemática publicada sobre o tema. Os achados dos dois estudos mostraram que aspectos atípicos na DA precisam ser mais explorados, já que DA não é uma condição homogênea. Compreender esses perfis cognitivos na DA irá interferir nos métodos diagnósticos e intervenções terapêuticas, seja farmacológica ou comportamental. A segunda parte dessa tese explora esses aspectos atípicos em três amostras: envelhecimento normal, CCL e AD. Assim, um estudo transversal foi realizado para comparar medidas de velocidade de processamento (VP), controle inibitório e automonitoramento nas três amostras. Os resultados desse estudo mostram que medidas de VP podem ser indicadores precoces do declínio cognitivo envelhecimento. Ao comparar CCL com o grupo de envelhecimento saudável, os dados mostram diferença nas medidas de VP e erros cometidos nos testes de VP. Entretanto, as duas amostras não apresentaram diferenças nas medidas de funções executivas (FEs) e nas medidas de funcionalidade. CCL versus AD mostraram diferenças nas medidas de VP,

funções executivas e funcionalidade. Dessa forma, esse estudo traz resultados relevantes para o diagnóstico precoce de CCL e novas diretrizes para o cenário clínico e pesquisa. Além disso, na segunda parte desta tese foi realizado um artigo sobre acurácia diagnóstica das medidas de VP nos casos de CCL e AD. A literatura mostra falta de estudos sobre diferenças nas medidas de VP no envelhecimento e parâmetros diagnósticos dos instrumentos de VP. Esse estudo mostrou que medidas de VP apresentam habilidades discriminativas, para DA e CCL. Esses dados são necessários, já que apresentamos um cenário de escassez de instrumentos com elevados parâmetros diagnósticos para medidas de VP no envelhecimento. Esse cenário torna-se ainda mais drástico, quando falamos de Brasil.

Palavras-chave:

Heterogeneidade Neuropsicológica, Doença de Alzheimer, Comprometimento Cognitivo Leve, Envelhecimento Normal, Velocidade de Processamento, Controle Inibitório, Memória de Trabalho, Flexibilidade Cognitiva, Acurácia Diagnóstica.

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I. THEORETICAL BACKGROUND

1.1 Neuropsychological heterogeneity in Alzheimer's dementia and Mild Cognitive Impairment

Dementia is a major health challenges and worldwide projections show a prevalence of over 35 million patients (WHO, 2012). Alzheimer's dementia (AD) is the most frequent dementia (Townsend, 2011), and the early deficit of episodic memory is considered the most prominent symptom. Generally, memory deficit is followed by others, such as: language, executive control, visuospatial skills, among others (Alladi et al., 2007; Petersen, 1998). Historically, this temporal sequence of cognitive deficits formed the basis of the diagnostic criteria of the National Institute of Neurology and Communicative Diseases and Stroke and Alzheimer's disease and Related Disorders Association (NINCDS-ARDA, Mckhann et al., 1984). This profile is typical of Alzheimer's disease and is supported by hippocampal atrophy on MRI (Barber et al., 1999; Killiany et al., 2000), temporoparietal hypometabolism and hypoperfusion on functional brain imaging as biomarkers for AD (O'Brien et al., 1992, Talbot et al., 1995). In addition, at the pathological level, the typical profile has marked early changes in the medial temporal lobes (Braak and Braak, 1995). The diagnosis of AD is based mainly on the observation of cognitive decline combined with functional decline, in the absence of other causes of dementia (APA; American Psychiatric Association, 1994; McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984).

However, recent studies (Scheltents et al, 2017; Peter et al., 2014, Vardy et al., 2013) show that episodic deficit is not always the primary cognitive symptom. Thus, the reviews of the criteria for AD were formalized in publications with new diagnostic criteria for AD (Dubois et al., 2010; McKhann et al., 2011). Dubois et al. (2010) refer to these heterogeneous cognitive manifestations of "atypical DA". This atypical variation has been associated with specific genetic and demographic factors, biomarkers and neuroimaging findings distinct from amnestic patients, such as age at onset of disease, hypometabolism, cerebrospinal fluid (CSF) biomarker concentrations, pathological findings, apolipoprotein genotype E [APOE], among others (Van Der Flier et al., 2006; van der Vlies et

al., 2007, Smits et al., 2014, Ossenkoppele, Cohn-Sheehy et al., 2015, Ossenkoppele, Mattsson et al., 2015). Atypical DA is relatively rare; however, such non-amnestic profiles will become better recognized and more prevalent with advances in diagnostic methods (Snowden et al., 2007). Some patients with DA show perceptual or spatial deficits (Cogan, 1985), language (Galton et al., 2000), praxis (Green et al., 1995), or frontal lobe symptoms (Johnson et al., 1999).

Scheltens et al. (2016) identified 8 AD phenotypes, 6 of which had no memory deficit as a prominent symptom. In addition, Martorelli et al. (2018b), in an analysis of 3 case studies of AD, also showed an atypical profile, in which visuo-constructive skills and language deficits were predominant, compared to 2 amnestic AD cases. Martorelli et al. (2018a) also published the first systematic review on neuropsychological heterogeneity in AD. In this review, we identified 8 studies that identified atypical neuropsychological phenotypic patterns, corroborating the idea of distinct cognitive profiles in AD. It should be emphasized that all the studies included in this review presented reliable methodological standards that could have interfered in the diagnosis of the patients analyzed.

AD is a heterogeneous condition and it is impossible to find a single therapy for every entity. Thus, the understanding of atypical cognitive aspects in AD is relevant for several aspects, such as: early diagnosis, prognosis and management of new therapies, either pharmacological or behavioral (Vardy et al., 2013).

Within aging, the prevalence of conditions such as Mild Cognitive Impairment (MCI) also increases (Petersen et al., 2018). The prevalence of MCI varies between 3% and 42% (Ward et al., 2012), depending on clinical settings and inclusion criteria (Petersen et al., 2010). MCI seems to decline from a previous level of functioning, both subjectively and by objective evidence (Petersen et al., 2014). Initially, the criteria for MCI diagnostic, generally, specify intact everyday functioning (Petersen et al., 1999). Subsequently, an international work for MCI proposed the inclusion of preserved basic activities of daily living or some minimal impairment in complex instrumental activity in the diagnostic

process (Winblad et al., 2004). Currently, there are no standard criteria on minimal functional limitation in MCI (Gold, 2012). However, decline in the ability performance of such tasks can also predict a decline from MCI to dementia (Aretouli et al., 2011).Thus, MCI show a level of objective cognitive impairment greater than that expected for age, but which is insufficient to guarantee the diagnosis of early dementia. In addition, preferably, your complaints should be corroborated by an informant (Petersen et al., 2005).

The MCI condition is recognized to shows considerable heterogeneity in several aspects, such as: etiology, clinical presentation, and prognosis and outcome (Petersen et al., 2010). It should be noted that the MCI condition is not necessarily a pre-dementia syndrome, as many individuals with MCI do not show progression of their cognitive deficits and may revert to normal cognition in some individuals (Ganguli et al., 2011; Aretouli et al., 2011; Sachdev et al., 2013).

Currently, MCI is considered a clinically heterogeneous syndrome and presents different cognitive functioning patterns (Winblad et al., 2004). Some evidence suggests that the etiology and clinical course of cognition and everyday functioning differ within the MCI subtypes (Teng et al., 2010; Yeh et al., 2011). Although most studies focus on MCI memory deficits, the European Union (EU) report emphasizes the need to study atypical aspects of aging, such as: motor and perceptual aspects or processing speed. According to this report these aspects may be early indicators of cognitive decline (Apostolo et al.,2011).

1.2 Executive Functions and Processing Speed

Executive functions (EFs) or executive control refers to a range of top-down mental processes required in controlled tasks, i.e., tasks on which we need to concentrate or pay attention to (Burgess & Simons 2005, Espy 2004, Miller & Cohen 2001). Historically, FEs had been described by Baddeley and Hitch (1974) as a "central executive". And finally, Lezak (1983) defined FEs as the aspect of human behavior responsible for "how" behavior is expressed. Thus, four components defined EFs at the time: abilities for goal formation, planning, carrying out goal-directed plans and operative performance (Lezak, 2004). Many definitions have been proposed to conceptualize EFs, as well as many components and variables that compose them. Despite this, there is a consensus about the

complexity and importance of executive functions for human adaptive behavior. Thus, EFs include: adaptation to diverse situations, inhibition of inappropriate behaviors, creation and execution of a plan and perseverance on the task at hand until its completion (Ardila and Surloff 2004). FEs can be interpreted, in general, as cognitive processes that orchestrate goal-directed activities (Royall et al., 2002), goal planning and monitoring of goal-directed activities (Jurado & Rosselli, 2007).

Several models (**Table 1**) have been proposed to explain EFs, however, there is no consensus on whether there is a single capacity that explains all the components of EFs (Theory of Unity) or whether they are distinct processes, but relate the various components of the EFs. A model that advocates the Theory of Unity is that of Norman & Shallice (1986). In this model, EFs are explained by the distinction between automatic and controlled processes, which are mediated by the Supervisory Attentional System (SAS). On the other hand, other theoretical models (Lehto 1996; Miyake et al., 2000; Salthouse et al., 2003) explain the EFs through multiple separable processes of a modular nature. These models are corroborated by studies that show the low intercorrelation (r = 0.4 or less) between the different tasks that evaluate EFs. In order to facilitate the research, authors (Miyake et al., 2000; Lehto et al., 2003; Diamond, 2013) who show evidence of multiple separable processes to explain EFs have developed a tripartite classification consisting basically of: 1) inhibitory control (Miyake et al., 2000; Diamond, 2013); 2) updating and monitoring (Miyake et al., 2000) and 3) cognitive flexibility (Baddeley & Hitch, 1994; Smith & Jonides, 1999; Diamond, 2013).

Author	Components of Executive Functions
Diamond, 2013	Working memory, Inhibitory Control, Cognitive flexibility and Higher-Level Efs
Piguet et al., 2002	Concept formation, Reasoning and Cognitive flexibility
Hobson and Leeds, 2001	Planning, Initiation, Preservation and Alteration of goal-directed behavior
Anderson et al., 2001	Attentional control, Cognitive flexibility and Goal setting
Baddeley and Hitch, 1974	Central executive, phonological loop and Visualspatial sketchpad
Lezak, 1983	Volition, Planning, Purpose action and Effective performance
Supervisory Attentional System	Supervisory Attentional System

Table 1. Authors and their proposed components of EFs.

Initially, EFs were associated primarily with the frontal lobe (Stuss et al., 2002). In this context, Luria (1973) associated the essential capacity to organize an intellectual activity as a whole with frontal lobes, including the programming of the intellectual act and the verification of its performance. In fact, neuropsychological advances on EFs evolved with the case studies of patients with pre-frontal damage (Stuss & Benson, 1986). Currently, EFs have been associated with the prefrontal cortex, but the integrity of their functioning also depends on frontal-subcortical systems (Cummings, 1993). In this way, frontal lesions are sufficient, but not necessary, for EFs impairment (Royall, 2000).

Cognitive functions may change across lifespan (Hedden et al.,2004; Nilsson, 2003). With aging, we may experience decline in a number of cognitive functions, such as: memory (Nilsson, 2003; Salthouse, 2003); attention (Yakhno et al.2007; Copping et al., 2006); EFs (Royall et al., 2004) and processing speed (PS; Salthouse, 1996). According Diamond (2002), PS predicts executive control and global theories of cognitive development define PS as a central mental capacity that drives changes in higher-order cognition (Hale, 1990; Kail and Salthouse, 1994).Thus, PS can be defined as the number of correct responses an individual is able to make within a finite amount of time (Salthouse, 1996). In addition, many researchers show substantial evidence that PS plays a significant role in other aspects of cognition (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Dempster, 1981; Siegel, 1994).

Currently, there is no consensus on whether processing speed is a unitary construct or is not a unitary construct and can be divided into separate “simple” and “complex” factors, with measures of each having very little shared variance (Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003). Measures of simple PS, like as reaction time, assess basic elements of attention and concentration requiring the recognition of a stimulus and a simple motor response. On the other hand, measures of complex PS in contrast require more complex processes of attention and concentration, as well as mental manipulation (Noelle et al.,2014).

II. OBJECTIVES

According to the theoretical background presented, the first part of this thesis is composed of two transversal studies with the following objectives:

-To analyze processing speed, inhibitory control, working memory and cognitive flexibility in three samples: normal aging, Mild Cognitive and Alzheimer's disease.

-To analyze the diagnostic accuracy of measures of processing speed in Mild Cognitive Impairment and Alzheimer`s disease.

The second part of this thesis is composed of two studies about heterogeneity neuropsychological with the following objectives:

-To analyze neuropsychological heterogeneity in AD through a systematic review of the literature.

-To compare three cases of Alzheimer's disease with neuropsychological profiles typical versus atypical.

II. ARTICLES SECTION

ARTICLE 1

Marina Martorelli, Felipe Kenji Sudo, and Helenice Charchat-Fichman. This Is Not Only About Memory: A Systematic Review on Neuropsychological Heterogeneity in Alzheimer's Disease. Psychology & Neuroscience. Advance online publication. http://dx.doi.org/10.1037/pne0000149 Online First Publication, September 27, 2018. http://dx.doi.org/10.1037/pne0000149

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NEUROPSYCHOLOGY OF AGING

This Is Not Only About Memory: A Systematic Review on Neuropsychological Heterogeneity in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the most prevalent cause of dementia and memory deficits are described as predominant in early AD. However, current knowledge demonstrated that the disorder may also manifest as non-amnestic phenotypes, which were referred to as "atypical". Thus, the objective of this study is to analyze the neuropsychological heterogeneity of patients with AD. This study consists of a systematic review, as Prisma guideline. In this systematic review they fulfilled the eligibility criteria. In this systematic review they met the eligibility criteria. A clustering approach resulted in several cognitive phenotypes, showing "atypical" dementia subtypes of those described predominantly in the literature. Clustering subjects with AD associated cognitive profiles with different sociodemographic, genetic, clinical and neurobiological characteristics. Furthermore, patients with APOE e4 positive genotype were more often associated with membership of memory-impaired cluster.

Keywords:

Neuropsychological heterogeneity, Alzheimer's disease, Cluster Analyses.

This Is Not Only About Memory: A Systematic Review on Neuropsychological Heterogeneity in Alzheimer's Disease

1. Introduction

Important estimates of the worldwide prevalence of dementia suggested that 44 million people may be living with the disorder, and projections indicated that this number may triple by 2050 (Carrillo et al., 2009; Prince, Guerchet & Prina, 2013). Alzheimer's disease (AD) is the most prevalent cause of dementia (Townsend, 2011), accounting for approximately 35 million cases in the world (World Health Organization, 2012). Although the knowledge about the disorder has expanded over the last decades, the need for accurate and affordable methods for timely detection of AD in primary care has been recognized as a major challenge for the geriatric practice (Moore et al., 2014).

Traditionally the diagnosis of AD has been based on the observation of cognitive and functional decline, in the absence of other causes of dementia (American Psychiatric Association, 1994; McKhann et al., 1984). In 2011, a work group of experts sponsored by the National Institute on Aging and the Alzheimer's Association suggested that biomarkers associated with disturbances on the metabolism of the β-amyloid protein and with neurodegeneration should be measured in research settings in addition to the clinical criteria, which could enhance the accuracy of the diagnosis (Jack et al., 2011). The lack of studies assessing the validity of quantifying those biomarkers has been acknowledged by the authors of this document (Jack et al., 2011). Cognitive assessment, on the other hand, remains as a recommended practice for identifying and predicting the progression of cognitive impairments associated with AD in research and clinical settings (Gomar, Bobes-Bascaran, Conejero-Goldberg, Davies, & Goldberg, 2011).

Memory deficits are described as predominant in early AD, followed by impairments in other cognitive domains, such as language and spatial abilities (Dubois et al., 2010). However, current knowledge about the pathophysiology of AD demonstrated that the disorder may also manifest as nonamnestic phenotypes, which were referred to as atypical AD by some authors (Dubois et al., 2010; McKhann et al., 2011; Galton, Patterson, Xuereb, & Hodges, 2000; Ralph,

Patterson, Graham, Dawson, & Hodges, 2003). Reports suggested that those atypical presentations, such as focal syndromes, may not be infrequent (Galton et al., 2000), and they may reflect heterogeneous patterns of brain pathology in AD (Becker, Huff, Nebes, Holland, & Boller, 1988; Celsis, Agniel, Puel, Rascol, & Marc-Vergnes, 1987; Davidson et al., 2010; Fisher, Rourke, & Bieliauskas, 1999; Foster et al., 1983; Martin, Brouwers, Cox, & Fedio, 1985, 1986; Martin, 1987; Price et al., 1993; Strite, Massman, Cooke, & Doody, 1997). Different cognitive syndromes because of AD were associated with a wide array of pathology (Kanne, Balota, Storandt, McKeel, & Morris, 1998; Pappas, Bayley, Bui, Hansen, & Thal, 2000); neuroimaging (Snowden et al., 2007; Stopford, Snowden, Thompson, & Neary, 2008); cerebral metabolic (Martin et al., 1986); and genetic, clinical, and demographic features (Fisher et al., 1996; Fisher et al., 1999; Jacobs et al., 1994; Sevush, Leve, & Brickman, 1993; Sevush, Peruyera, Bertran, & Cisneros, 2003; Snowden et al., 2007).

Identifying clusters of cognitive impairments associated with AD may improve early diagnosis, but it may potentially allow the adoption of therapeutic interventions, such as cognitive rehabilitation, formulated specifically for the type of deficits presented in each case (Alladi et al., 2007; Davidson et al., 2010; McKhann et al., 2011; Townsend, 2011). The present study aims to review and analyze data on the variability of neuropsychological profiles in AD.

2. Method

2.1 Literature Search

In June 2018 a comprehensive literature search was performed to identify studies that assessed neuropsychological heterogeneity in AD through cluster analysis. The electronic databases, Medline, Science Direct, Scielo, Psy-cINFO, PsycArticles, Lilacs, JAMA Evidence, New England Journal of Medicine, Index Psi Journals, and FreeBooks 4 doctors, were systematically searched including the descriptors, Alzheimer`s disease, heterogeneity, neuropsychological, phenotype, and cognition. No limits were placed for date of publication, language, or field. Other sources of information included personal contact with recognized researchers in the field for relevant unpublished data. The PRISMA Statement Checklist was used in the present review.

2.2 Selection of Studies and Quality Assessment

Three researchers have analyzed independently the retrieved articles. Inclusion criteria were: (a) studies that used neuropsychological testing on patients with a clinical diagnosis of AD and (b) articles that evaluated the results of cognitive tests through cluster analyses. Studies were excluded if (a) a detailed description of the procedures was not acknowledged; (b) the drop-out rate was greater than 50%; or (c) consisted on reviews, case reports, essays, or posters. Disagreements about the inclusion of articles were solved through consensus among the researchers. A flowchart with the steps for the selection of the studies was elaborated (see Figure 1).

Quality evaluation of the included studies was performed by two independent authors through the checklist (see Table 1).

2.3 Data Extraction

The following information was extracted independently by each author: year of publication, first author, neuropsychological tests, sample size, and identified neuropsychological profiles (see Table 1). For articles with incomplete data, a contact with the corresponding author was performed and the missing information was requested. In the event of contact failure, after two attempts, the articles were excluded.

3. Results

Of a total of 504 retrieved studies, eight were included in the present review. The descriptions of the selected articles are depicted below.

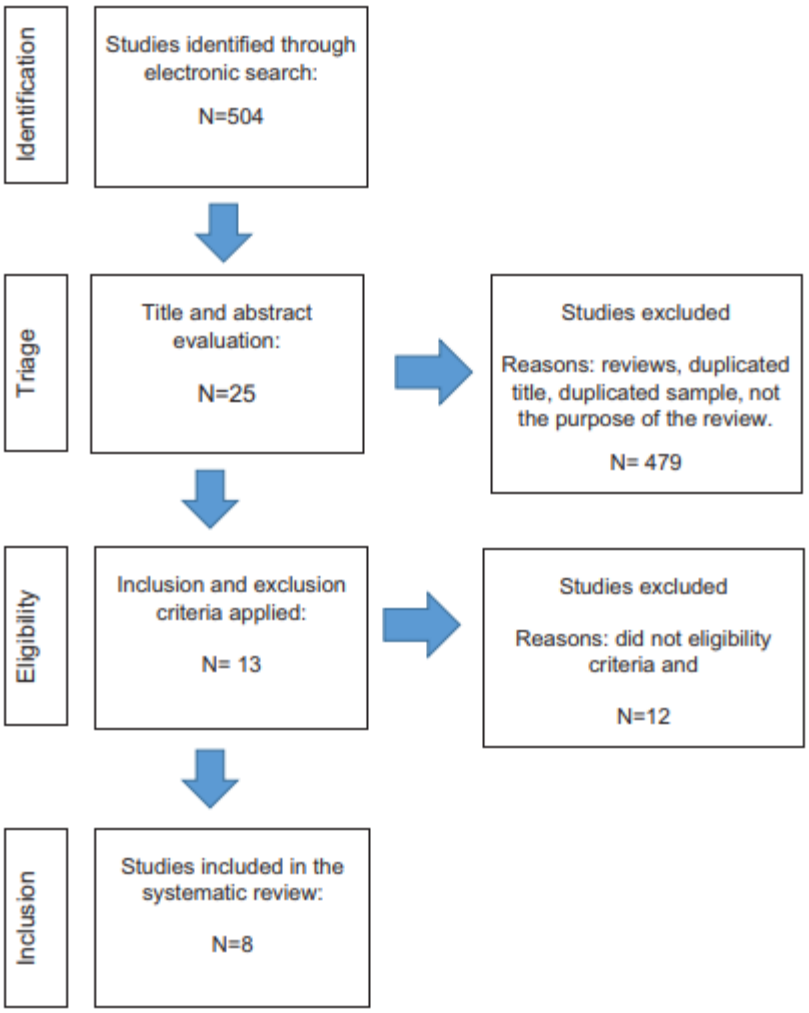

Figure 1. Studies identified through electronic search and reasons for exclusion.

3.1 Samples

The selected studies included 4,008 subjects with mean ages ranging from 63.0 (Stopford et al., 2008) to 76.9 years (Davidson et al., 2010). Samples comprised participants of large cohort studies (the Amsterdam Dementia Cohort, the Alzheimer's Disease Neuroimaging Initiative, the German Dementia Competence Network, and the University California, San Francisco, Memory and Aging Center research cohort in Scheltens et al., 2017; the Amsterdam Dementia Cohort in Scheltens et al., 2016; the Alzheimer's Disease Neuroimaging Initiative in Peter et al., 2014; Neuropsychological Service of the Centre for the Medicine of the Aging of the Catholic University of Rome in Cappa, Ciccarelli, Baldonero, Martelli, & Silveri, 2014 and University of Michigan Medical Center in Fisher et al., 1996) or were cross-sectionally assessed by the authors (Stopford et al., 2008; Davidson et al., 2010; Vardy et al., 2013).

Selection of participants followed different criteria among studies. Scheltens et al. (2017) included subjects presenting clinical diagnosis of probable AD and Mini-Mental State Examination (MMSE) scores greater than 15, which resulted in mean MMSE of the participants ranging from 22 to 24 points. MMSE above 10 points and diagnosis of probable AD was adopted as inclusion criteria by Scheltens et al. (2016). Davidson et al. (2010) applied the cutoff of 14 points in the MMSE for the selection of those with mild and moderate AD in the study. On the other hand, Vardy et al. (2013); Cappa et al. (2014), and Fisher et al. (1996) did not limit the inclusion of participants for the cognitive performance or the severity of AD.

Dropout rates were most significant in Peter et al. (2014): 29 of 127 cases (22.83%) were lost in the last point at follow-up.

Title	***Author, year***	***Population: Alzheimer`s disease-control***	***Neuropsychological instruments***	***Cluster number***
"Cognitive subtypes of probable Alzheimer's disease robustly identified in four cohorts"	Scheltents et. al, 2017.	1982-0	CERAD; California Verbal Learning Test; German Dementia Competence Network; Digit Span; Frontal Assessment Battery; Letter Digit Substitution Test; CERAD Logical Memory; RAVLT; TMT; VAT; CERAD Word List; ABCD; LDST; FAB; DCN; DS; CVLT WL; LM	Two clusters
The identification of cognitive subtypes in Alzheimer's disease dementia using latent class analysis"	Scheltens et al.,2016.	938-0	MMSE, RAVLT, VAT, VAT naming, Arizona Battery for Comunication Disorders of Dementia (ABCD naming), category fluency (animals), letter fluency (D-A-T), digit span backward, TMT-B, Frontal Assessement Battery e questões comparativas, Trail Making Test A,	Eight clusters

			Digit Span Forward, Visual Object and Space Perception Battery e "money counting test"	
"Subgroups of Alzheimer's Disease: Stability of Empirical Clusters Over Time"	Peter et al., 2014.	127-0	MMSE, TMT-A; Clock Drawing Test; RAVLT; Digit Span from the Wechsler Memory Scale; Category Fluency; reduced version of the BNT.	Five clusters
"Posterior AD-Type Pathology: Cognitive Subtypes Emerging from a Cluster Analysis"	Cappa et al., 2014	16-0	RAVLT, Babcock memory test, digit span forward; facial expression of emotion: stimuli and tests; memory face, Benton face recognition, famous face recognition, Vosp (visual object and space perception battery, X-detection, color naming, spatial span forward, double barrage, Navon letters, letter cancellation, Rey's figure copy, letter fluency (F, A, S), semantic fluency, reading, writing, object naming, sentence comprehension, Calculation (addition, subtraction, multiplication.	Four clusters.
Distinct cognitive phenotypes in Alzheimer's disease in older people"	Vardy et al.,(2013)	109-91	CAMCOG and MMSE	Three clusters
"An exploration of cognitive subgroups in Alzheimers disease"	Davidson et al., 2010	627-0	MMSE and Mattis	Four clusters
"Variability in cognitive presentation of Alzheimer's disease"	Stopford et al.,2008.	75-20	Series speech, repetition, sentence comprehension, metaphor interpretation, object naming, spelling, arithmetic, elementary perception, dot counting, drawing, gesture and action pantomime, immediate memory, visual memory for faces, verbal memory for story, category fluency, letter	Thirteen clusters

			fluency, Weigl's.	
"Neuropsychological Subgroups of Patients with Alzheimer's Disease"	Fisher et al., 1996	134-0	MMSE, Grip Strength Test, Finger Tapping Test, Blessed Dementia Rating Scale, Wechsler Memory Scale, Wechsler Adult Intelligence Scale–Revised, BNT, Controlled Oral Word Association Test, Animal Name Fluency Test,Southern California	Four clusters.

Table1. Characteristics of the Studies Included in the Review and Outcomes *Note*. CERAD Consortium to Establish a Registry for Alzheimer's Disease; RAVLT Rey Auditory Verbal Learning Test; TMT Trail Making Test; VAT Visual Association Test; MMSE Mini-Mental Statement Examination; BNT Boston Naming Test; CAMCOG Cambridge Cognitive Examination; ABCD Arizona Battery for Communication Disorders of Dementia; LDST Letter Digit Substitution; FAB Frontal Assessment Battery; DCN German Dementia Competence Network; DS Digit Span; CVLT WL California Verbal Learning Test; LM CERAD Logical Memory.

3.2 Diagnosis

The National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD were adopted by most of the studies (Cappa et al., 2014; Fisher et al., 1996; Peter et al., 2014; Scheltens et al., 2016, 2017; Stopford et al., 2008; Vardy et al., 2013). In addition, the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria for AD was also used by Davidson et al. (2010).

3.3 Neuropsychological Clustering in AD

Classification of cognitive impairments was performed by Scheltens et al. (2017) through a dual-clustering approach, which resulted in two clusters for each cohort with strong cophenetic correlation (0.90). Across all cohorts, the memory clusters included about 60% of the patients, ranging from 48% to 71%, whereas the nonmemory clusters included on average 40% of the patients, ranging from 29% to 52%. Pooled data from the cohorts were analyzed, and as a result,

patients in the non-memory cluster reported shorter disease duration, had lower MMSE scores, were less often apolipoprotein ε (APOE) 34 carriers, had less severe hippocampal atrophy, and presented more severe atrophy of the posterior cortex than subjects in the memory clusters.

In Scheltens et al. (2016), the neuropsychological data generated eight clusters, and the criterion used to categorize them was the presence of memory impairment. Thus, clusters were grouped into three categories: memory impairment, memory spared, and memory indifferent. Two clusters were characterized by the most prominent memory impairment and together they included 43% of the cohort. In addition, three clusters showed relatively spared memory and three others did not reveal either distinct memory impairment or a memory-spared profile; therefore, they were called memory indifferent. The first memory-impaired cluster, which had a mean MMSE of 24, was referred to as mild-memory group (MILD-MEM). The other memory-impaired cluster had a mean MMSE of 19; therefore, they called it moderate memory (MOD-MEM). MOD-MEM also presented relatively low scores on tests assessing executive functioning. The first memory-spared cluster showed poor performances on both language and visuospatial tasks—It was named as mild-visuospatial-language group (MILD-VILA). The second memory-spared cluster was characterized by prominent impairment in executive functioning and showed a mean MMSE of 23. This cluster was called mild executive (MILD-EXE). The last memory-spared cluster was characterized by remarkably low scores on the visuospatial tests. This cluster had a mean MMSE of 19 and they called it moderate visuospatial (MOD-VISP).

The first memory-indifferent cluster had global cognitive impairment and a mean MMSE of 21; they called this cluster mild diffuse (MILD-DIFF). The second memory-indifferent cluster presented prominent language impairment and a mean MMSE of 20. It was called moderate language (MOD-LAN). The third memory-indifferent cluster also had a diffuse profile and had a mean MMSE of 14; they called this cluster severe diffuse (SEV-DIFF). Compared with MILD-MEM, younger patients were 6 times more likely to be classified in MOD-VISP and females were twice as likely to be classified in MILD-DIFF. Patients with longer duration of symptoms were twice as likely to be included in the SEV-DIFF

group. Less educated patients showed three greater risks for inclusion on MOD-MEM and SEV-DIFF clusters. APOE4-negative patients were 2 times more likely to be members of MOD-VISP. Patients with higher amyloid total concentrations were twice as likely to be classified in MOD-LAN. Patients with higher phosphorylated at threonine-181 concentrations were half as likely to be members of MILD-EXE and MILD-DIFF. Patients with prominent hippocampal atrophy presented half the odds to be included in the MILD-EXE cluster. Prominent atrophy of the posterior cortex or global cortical atrophy were major features for membership of MOD-VISP and SEV-DIFF clusters. Finally, patients with more white matter hyperintensities were 3 times more likely to be members of the MOD-LAN group.

At baseline, cluster analyses revealed four distinct cognitive phenotypes, whereas five distinct clusters were found at 24-month follow-up by Peter et al. (2014). The sample comprised 66% of patients with atypical AD. The clusters identified by the authors at follow-up were typical AD, focal semantic impairment, preserved memory with focal visuoconstructive impairment, focal intrusions, and preserved delayed recall. Vardy et al. (2013) divided the sample into three distinct clusters. There were no significant differences between the clusters concerning the disease duration. Cluster 1 was significantly younger, presented less severe cognitive impairments, and had an earlier age of onset of AD than the other groups. Cluster 3 demonstrated poorer overall cognitive performances, especially on tasks assessing memory (orientation, learning, recall). Cluster 2 also demonstrated poor performances on memory tests but with inferior severity compared with cluster 3. This group showed more depressive symptoms than the others.

Cappa et al. (2014) analyzed 39 patients with a probable diagnosis of AD, 23 of whom had posterior cortical atrophy (PCA) and 16 dementia of AD with typical features (AD). The agglomeration coefficients generated by cluster analysis revealed a demarcation point between four- and five-cluster solutions, suggesting that a four-cluster solution best distinguished the cases. The resultant four-cluster solution produced relatively well-sized groups labeled according to their most distinguishing characteristics. Therefore, Cluster 1 was composed by all clinically defined PCA patients (9 of 9), and Cluster 2 had a clear majority of

AD patients (eight of 10), whereas Cluster 3 (six patients) and Cluster 4 (14 patients) had a heterogeneous composition. Cluster 1 was characterized by good memory skills and spared language and calculation, which were significantly different from weak performance in perceptual and visuospatial abilities. On the other hand, Cluster 2 was characterized by severe impairment of memory with no significant deficits in other domains. Cluster 3 was defined by significant impairment in perception and calculation com-pared with all other factors, which in turn did not differ significantly from each other. Finally, Cluster 4 was characterized by language and memory deficit. Analysis using single-photon emission computed tomography evidenced hypoperfusion in the dorsal stream in Cluster 1 subjects, which was coherent with the diagnosis of PCA.

Davidson et al. (2010) named the clusters according to the severity of the cognitive deficits and to the presence of focal impairments on specific cognitive domains, as follows: Mild (corresponding to 25% of the sample), Attention/Construction (14% of the sample), Memory (35% of the sample), and Severe (25% of the sample). The Mild group showed the lowest probability of rating below the mean scores for all cognitive tasks. The Severe category included those with consistently higher impairment across all the domains relative to the other clusters. The other two classes showed focal patterns of impairment in certain cognitive do-mains, rather than performing mildly or severely below normative values. The Attention/Construction class exhibited predominant deficits in the attention and the construction subscales of both the MMSE and the Mattis Dementia Rating Scale-2 (DRS-2) tests. Moreover, this group performed poorly in the MMSE language subscale, with magnitude comparable with the Severe class. The Memory group was associated with predominant memory difficulties on the MMSE and the DRS-2 subtests and on the MMSE orientation subscale. Attention, constructional, and language tasks were pre-served in this group.

Stopford et al. (2008) have identified 13 clusters in their study. Whereas Clusters 1–9 revealed mild dissociations in performances across cognitive domains, Clusters 10 –13 presented more localized deficits within certain cognitive domains. Clusters 2, 3, and 6 showed patients with higher relative impairment in memory, whereas those in Clusters 8 and 9 showed relatively spared memory. Clusters 1 and 3 were characterized for presenting preserved

performances on perceptuospatial tests, but Cluster 5 subjects were mainly impaired in those tasks. Cluster 6 exhibited preserved executive function. Cluster 8 individuals were greatly impaired in tests assessing praxis, whereas Cluster 9 participants were preserved in those tasks. Among all the participants, those included in Clusters 10 –13, showed the most severe absolute impairments, which were observed in tasks measuring perceptuospatial ability, executive skills, praxis, and language.

Fisher et al. (1996) analyzed neuropsychological subgroups in patients with Alzheimer's dementia. In this study, three neuropsychological subgroups were identified. Overall, Cluster 3 shows as the highest functioning of the three groups. And Cluster 3 demonstrated preserved naming abilities and Block Design performance, although some difficulty in copying simple overlapping figures was in evidence. Cluster 2 demonstrated severe anomia; however, it presented relative spared visual-perception/constructional functioning. And Cluster 1 was characterized by moderate to severe anomia, mildly to moderately impaired Block Design performance, and a virtual inability to copy a simple drawing of two overlapping figures.

Table 1 summarizes the results of the selected studies.

4. Discussion

Clustering subjects with AD according to their cognitive profiles may allow the identification of groups with discernible sociodemographic, genetic, clinical, and neurobiological characteristics. Despite sharing the same cerebral pathology, namely the presence of disturbances in the β-amyloid metabolism and neurodegeneration, those with poorer performances on memory tasks may show smaller hippocampal volumes, longer disease duration, higher prevalence of APOE 34 carriers, and better scores on the MMSE than nonamnestic AD subjects. When achieving the moderate stage, amnestic AD subjects may decline most intensively in executive function tasks. The presence of depressive symptoms may impair memory, but the magnitude of those deficits is possibly subtle.

As expected, nonamnestic AD presentations are less common than AD with marked memory deficits. These categories might suffer more global

cognitive difficulties, as shown by lower scores on the MMSE than AD subjects with memory impairment. Moreover, those individuals may present earlier onset of AD (as indicated by lower age and shorter disease duration) than subjects with amnestic AD. Domains impaired in nonamnestic AD were language, visuospatial abilities, and executive function. Global and posterior cortical atrophy, as well as cerebrovascular disease, was significantly more prevalent in AD without memory deficits than in typical AD patients.

The present results are consistent with the idea of multiple clinical phenotypes in AD, as suggested by published recommendations of an experts' committee (Dubois et al., 2014). Although the importance of detecting memory deficits for the diagnosis of AD is undeniable in most of the cases, the notion that atypical presentations of AD may course with relatively spared memory, especially in its initial stages, has been recognized. Functional and structural neuroimaging have suggested that early occipitotemporal and frontal impairments usually manifest as difficulties in visuospatial abilities or with neuropsychiatric-dysexecutive syndrome, respectively, during the disease's initial phases (Cappa et al., 2014; Dubois et al., 2014; Ossenkoppele et al., 2016). Moreover, predominant problems during reading, verbal fluency, naming, word retrieval, and repetition tasks, are expected in the variant of AD with language deficits (Cappa et al., 2014; Dubois et al., 2014). Finally, differential concentrations of cerebrospinal fluid (CSF) biomarkers may be found in typical versus atypical AD, which has been theorized as a possible mechanism underlying the phenotypical diversity in AD (Paterson et al., 2015).

The strength of the present review was to highlight the diversity of neuropsychological manifestations in patients with a diagnosis of probable AD, which might be grouped as clinical syndromes associated with specific genetic, sociodemographic, and neurobiological characteristics. Differentiating profiles of AD in its initial stages may play a decisive role when choosing the best therapeutic strategies for each group of patients, including pharmacological and behavioral interventions, such as neuropsychological rehabilitation. Some limitations of this study, however, ought to be acknowledged, such as the inclusion of studies with small sample sizes, which may affect the external validity of the results. Moreover, neuropsychological assessment varied largely

among studies; some of them used relatively simple methods of cognitive assessment compared with others with more detailed psychometric testing.

In conclusion, the authors advocate that clinicians should be attentive to cognitive variants of AD because they may show different clinical, neuroimaging, and genetic features. Those aspects might impact on the prognosis of the disorder, and they might help decisions concerning to treatment options, especially those related to cognitive rehabilitation. However, further trials are still needed to measure the effects of therapeutic interventions designed according to the AD subtype.

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ARTICLE 2

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PERFIL NEUROPSICOLÓGICO TÍPICO E ATÍPICO NA DEMÊNCIA DE ALZHEIMER: DIFICULDADES DIAGNÓSTICAS EM TRÊS ESTUDOS DE CASO

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Abstract

Introduction: Alzheimer‘s disease (AD) is typically characterized by early deficits in episodic memory, followed by deficits in other cognitive functions. However, recent studies show that early deficits in other cognitive functions may be present, configuring a non-amnestic type of AD, which is referred to as ―atypical‖. Thus, this study aims to present the neuropsychological heterogeneity describing three case studies of Alzheimer‘s disease. Method: this study consists of the analysis of three cases of AD in which extensive neuropsychological evaluations were performed. Results and Discussion: the results of these cases of study show two distinct cognitive profiles - typical and atypical. Understanding this cognitive heterogeneity in AD is necessary for early diagnosis, and consequently, more specific and individualized therapies for these patients.

Keywords:

Alzheimer‘s disease, Neuropsychology, Dementia, Diagnosis

Typical and atypical neuropsychological profiles in Alzheimer's disease: diagnostic difficulties in three case studies.

1. Introduction

Dementia is the most prevalent disease of aging (Swearer et al., 1992), posing a huge challenge for health (WHO, 2012). Alzheimer's disease (AD), the more frequent cause, leads to progressive loss of cognitive functions (Braak & Braak, 1991) and, consequently, functional decline (McKhann et al., 1984). Deficits in episodic memory are traditionally described as the earliest symptoms in AD, followed by deficits in executive functions, and later in language, visuospatial skills and attention (Alladi et al., 2007; Petersen et al., 1998).

This typical cognitive profile is associated with hippocampal atrophy (Barber et al., 1999; Killiany et al., 2000), temporoparietal hypometabolism and functional cerebral hypoperfusion as biomarkers for AD (O'Brien et al., 1992; Talbot et al., 1995). In addition, there are early pathological changes in the medial temporal lobe (Alladi et al., 2007; Hodges, 2006; Braak & Braak, 1991).

In addition to this typical cognitive profile, recent studies (Scheltens et al., 2017 & 2016; Stopford et al. 2008) show that neuropsychological heterogeneity can be observed in patients with AD. Thus, these patients may present non-amnestic primary deficits, such as: in the language (Galton et al., 2000), and praxis (Green et al., 1995). Dubois et al. (2010) refers to these non-amnestic profiles as "atypical AD". However, it should be emphasized that, in the clinical setting, patients rarely present isolated deficits in a single domain, although the presentation of these focal profiles suggests that memory deficits are not always predominant in AD (Snowden et al., 2007). In this context, there is an urgent need for studies on the etiology of this disease, as well as new strategies of diagnosis and intervention.

Understanding this clinical heterogeneity in AD may be the first step towards more effective and specific therapies, aiming for increasingly individualized interventions and more significant outcomes (Scheltens et al., 2016). Thus, the aim of the present case report is to illustrate the different

cognitive profiles and other clinical manifestations in AD, something rarely focused on in research reports.

2. Method

2.1 Study design

This study consists of an analysis of three case studies with diagnosis of probable AD.

2.2 Patients and diagnosis

This study consists of an analysis of three case with diagnosis of probable AD. The clinical diagnosis was performed by a psychiatrist of the study, according to the diagnostic criteria of NINCDS-ADRDA (National Institute of Neurological Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders; McKhann et al., 1984). These criteria establish that the diagnosis of dementia should be performed by clinical evaluation, documented by screening tests and confirmed by neuropsychological evaluation. In addition, patients should have progressive impairment in one or more cognitive functions, significantly interfering with activities of daily living (ADLs). The three participants of this study agreed to participate and signed the consent form, with the study approved by the Research Ethics Committee under authorization No. 965.264.

2.2 Cognitive assessment instruments, scales and questionnaires

The neuropsychological evaluation was performed in two sessions by a trained neuropsychologist. The first session of the evaluation was composed of cognitive screening instruments, including: the Mini-Mental State Examination (MMSE; Brucki et al., 2003); Cognitive Brief Screening Battery (CBSB; Nitrini et al., 1994), composed by the Memory of Figures Test (MFT, Araújo et al., 2018), Clock Drawing Test (CDT, Araújo et al., 2018) and Categorical Verbal Fluency Test (VF, Araújo et al., 2018). In addition, in the first meeting the following were also applied: Functional Activities Questionnaire (Pfeffer, 1982),

Scale of Instrumental Activities of Daily Living (Lawton & Brody, 1969) and Reduced Geriatric Depression Scale (GDS-15) (Almeida & Almeida, 1999).

In the second session, specific cognitive domains were investigated, such as: attention, through part A of the Trail Color Test (TCT, Rabelo et al., 2010); executive functions and processing speed, through the Phonemic Verbal Fluency Task (FAS) (Machado et al., 2009), and the part B of the Trail Color Test (TCT; Rabelo et al., 2010). The assessment of the visuoconstructive praxis ability was performed using the copy part of the Rey`s Figure Test (RFT; Oliveira & Rigoni, 2014), and finally, the evaluation of memory and related processes was performed using the Rey Auditory Verbal Learning Test (RAVLT; De Paula & Malloy-Diniz, 2018).

2.3 Data analysis.

After the application of the neuropsychological instruments, the gross score was calculated and the Z score produced for each test. The Z score was chosen because it is one of the statistical measures most used in the investigation of case studies, as it offers the possibility of evaluating the singularity of the participants in relation to the normative group. The Z score represents the number of standard deviations above or below the mean of the population in which a given observation is found (Bertola et al., 2016).

3. Results:

3.1 Description of results

This study evaluated three patients with AD in the mild phase of dementia (CDR 1, Clinical Dementia Rating; Hughes et al., 1982). The neuropsychological evaluation showed two distinct profiles: typical and atypical. Two patients presented prominent deficits in the incidental memory, short-term memory, episodic memory, learning and recognition, however, showed relative preservation of executive functions and preservation of visuoconstructive abilities and language. One patient presented an atypical profile, since he presented deficits in visuoconstructive abilities and language (naming), however, relative preservation of the other cognitive functions evaluated. It should be noted that the presentation of these focal profiles serves to characterize prominent deficits,

therefore, in this article relative preservation is considered when the patient has -1<Z>-1.5, and preservation of the cognitive function when the patient presents Z≥-1.

3.2 Demographic characteristics of patients.

Patient 1	Female gender, 90 years of age, with 16 years of education, using anticholinesterase (rivastigmine) and in the mild phase of dementia, CDR 1, according to the Clinical Dementia Rating criteria (CDR, Hughes et al., 1982).
Patient 2	Female gender, 83 years of age, with 16 years of education, using anticholinesterase (rivastigmine) and in the mild phase of dementia, CDR 1.
Patient 3	Male gender, 90 years of age, with 1 year of education, with using anticholinesterase (rivastigmine) and in the mild phase of dementia, CDR 1.

Table 1. Demographic characteristics of patients.

3.3 Results of the applied tests:

Cognitive function and instrument	*Patient 1 (Z score)*	*Patient 2(Z score)*	*Patient 3(Z score)*
MMSE (global cognition)	Z= -0.5	Z= 0.7	Z= -1.1
Naming (MFT)	Z= 0	Z= 0	Z= -2.6
Incidental Memory (MFT)	Z= -0.8	Z= -2.5	Z= -1.4
Short-term memory (MFT)	Z= -1.8	Z= -2.4	Z= -0.4
Visual Learning (MFT)	Z= -2.0	Z= -2.6	Z= -1.4
Visual episodic memory (MFT)	Z= -2.5	Z= -2.5	Z= -0.5

Visual recognition (MFT)	Z= -1.9	Z= -4.25	Z= 0.3
Visuoconstructive praxis (RFC)	Z= 0.04	Z= 0.7	Z= -1.9
Verbal Learning (RAVLT)	Z= -2.3	Z=-2,3	Z=-0,9
Episodic Auditory Memory for Recent Events (RAVLT)	Z= -3.0	Z= -4.0	Z= -0.5
Episodic Auditory Memory for Later Events (RAVLT)	Z= -3.0	Z=-3,0	Z=-1,25
Auditory recognition (RAVLT)	Z= -3.0	Z=-2,7	Z=0,4
Executive Function (VF)	Z= -0,04	Z=-1,0	Z=0,6
Executive Function (FAS)	Z= -0,2	Z=-0,6	Z=-1,15
Attention (Part A of the TCT)	Z=0,6	Z=0,4	Z=-0,8
Executive Function (Part B of the TCT)	Z=0,4	Z=0,6	Z=1,0

Table 2. Cognitive profile of patients and Z score in each test.

3.4 Comparisons of cognitive profiles

Patient 1 and 2: Amnestic profile

These two patients presented a cognitive profile typical of Alzheimer's disease, with them demonstrating indices for global cognition, preserved visuoconstruction and relative preservation of the executive functions. However,

they presented prominent deficits in incidental memory, short-term memory, episodic memory, learning and recognition. Thus, these 2 patients were denominated the “amnestic profile”.

Patient 3: Visuoconstruction-language profile

This patient presented an “atypical” Alzheimer’s disease profile, demonstrating relative preservation in the indices that evaluate global cognition, short-term memory, incidental memory, episodic memory, learning, recognition and executive functions, however, deficits in visuoconstruction skills and language. Therefore, this patient was denominated the “visuoconstruction-language profile”.

4. Discussion:

The results of these case reports show the clinical phenotypic difference in AD, contrasting two cognitive profiles: typical and atypical. Although the cases analyzed in this study were in the mild phase of the dementia, the atypical case presented a lower score in the MMSE (global cognition), fewer years of education and reported a shorter duration of the disease (Martorelli et al., 2018). Conversely, the typical profiles were related to a more severe disease progression (van der Vlies et al., 2009; Smitis et al., 2015), corroborating the results of the present study with consistent and current studies in the literature.

The literature associates the difference in neuropsychological manifestations in AD to genetic, clinical, demographic and pathological characteristics (Fisher, Rourke, Bieliauskas, Giordani, Berent, & Foster, 1996; Fisher, Rourke, & Bieliauskas, 1999; Jacobs et al., 1994; Sevush, Leve, & Brickman, 1993; Sevush, Peruyera, Bertran, Cisneros, 2003; Snowden et al., 2007). Thus, the difference in the cognitive profiles presented in this case report may be associated with years of education that distinguished the two cognitive profiles found.

The diagnosis in AD is based on clinical criteria and neuropsychological findings, thus, atypical AD profiles are often underdiagnosed and/or classified as other dementias or psychiatric disorders. In this way, understanding the cognitive

heterogeneity in AD, in spite of the typical conditions, becomes essential for early, accurate diagnoses, and consequent early interventions.

A limiting factor of this study is the fact that these are case reports; therefore possible generalizations of the study will be questionable. However, due to the hiatus in the literature on the subject, multiple case studies present relative clinical and research relevance; especially in situations where there are doubts about the details of the clinical characterization of the condition. On the other hand, a strong point of this study is the extensive neuropsychological evaluation battery compared to other relevant studies in the literature that have used cognitive screening instruments (Vardy et al., 2013). This point is of particular relevance since it is difficult to characterize important clinical details using screening instruments. In addition, few studies in the literature evaluate "visuoconstructive skills" when studying neuropsychological heterogeneity in AD, therefore this subtype is still little discussed.

Heterogeneity in AD can also be seen in different anatomopathological patterns. Janocko et al. (2012), in addition to the description of the typical pattern, demonstrated two other patterns related to the deposition of neurofibrillary tangles, with a presentation that spares the hippocampus and another with limbic predominance. There are distinct clinical features among the three types. The hippocampal predominance has the earliest onset and the limbic predominance the latest (Janocko et al., 2012; Murray et al., 2011). Magnetic resonance imaging of the skull with voxel-based morphometry is able to distinguish the three patterns, with their individual profiles of atrophy of cortical territories and the hippocampal/cortex volume relationship (Whitwell et al., 2012). In this way, in vivo imaging studies can aid in the differentiation between different AD presentations.

It can be concluded that understanding cognitive heterogeneity in AD is of paramount importance, since it will directly influence the treatment of these patients. Failures in the treatment for AD may be associated with the fact that this clinical condition is not homogeneous, with the treatment offered not being differentiated or specific for each profile. It is recommended that the scientific production on the subject progresses with more robust samples and more

extensive neuropsychological evaluations, since worldwide populational aging is increasing.

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ARTICLE 3

Martorelli, M., Marques, L.Coutinho, G., Charchat-Fichman,H. Processing speed, working memory, inhibitory control and cognitive flexibility in Alzheimer's dementia and Mild Cognitive Impairment (submitted).

ABSTRACT

Introduction: Increases in life expectancy are well documented worldwide. The aging of the population leads to an increase in the prevalence of dementia and Mild Cognitive Impairment (MCI). Alzheimer`s disease (AD) is the most common cause of dementia. Recent studies highlight the early non-amnestic deficits in AD and MCI. Furthermore, the European Union (EU) shows the importance of the need to assess the cognitive aspects that are currently being poorly evaluated in greater depth, such as motor and perceptual aspects or processing speed (PS), which could represent early indicators of cognitive decline. PS can be defined as the number of correct responses an individual is able to make within a finite amount of time. Thus, the objective of this study was to analyze PS, working memory (WM), cognitive flexibility and inhibitory control and their relationships as early indicators of cognitive decline in three samples: normal aging, MCI and AD. **Method:** A cross-sectional study was conducted in which an extensive neuropsychological assessment was performed in three samples: 26 control participants, 22 MCI cases and 21 AD. In addition, the relationship between dependent variables and the clinical group was tested with an analysis of variance (ANOVA).**Results and Discussion:** the results of this study show that deficits in PS measures are early indicators of cognitive decline in cases of MCI, even when executive functions (EFs) and functionality are preserved. However, AD versus MCI showed differences in PS, EFs and functionality. These results are important because they indicate that measures of PS may be early markers of impairment in aging.

Keywords:

Processing Speed, Working Memory, Inhibitory control, Cognitive Flexibility, Alzheimer`s disease, Mild Cognitive Impairment and normal aging.

Processing speed, working memory, inhibitory control and cognitive flexibility in Alzheimer's dementia and Mild Cognitive Impairment.

1. Introduction

Increases in life expectancy are well documented worldwide (Wimo et al., 2006). The aging of the population leads to an increase in the prevalence of dementia, which is a major healthcare challenge (Who, 2012).Alzheimer`s disease (AD) is the most common cause of dementia (Townsend, 2011). It is reported that the number of affected people is expected to double in the next 20 years (Ron et al., 2007) and that number is expected to increase to more than 131 million by 2050 (Herrera et al, 2016).In this way, there has been a great interest a clinical group with a high probability of conversion to dementia and other clinical conditions for which cognitive decline is a feature, called MCI cases (Cooper, 2013; Petersen, 2016). A review of studies projected the overall prevalence of MCI at 6%–12% (Sachdev et al.,2015),but prevalence increases with age with 25.2% in people ages 80–84 years (Petersen et al.,2018).

Recent studies (Martorelli et al., 2018a; Scheltens et al, 2017; 2016, Peter et al., 2014, Vardy et al., 2013) highlight the early non-amnestic deficits in AD. Likewise, MCI shows cognitive variability in the subtypes presented, such as: deficit in executive functions (EFs), processing speed (PS), language, in addition to memory (Bangen et al., 2010; Delano-Woods et al., 2009; Rosenberg et al., 2011). Furthermore, the European Union (EU, Apostolo et al., 2016) also shows the importance of the need to assess the non-amnestic aspects that are currently being poorly evaluated in greater depth, such as motor and perceptual aspects or processing speed, which could represent early indicators of cognitive decline.

In this context, EFs refer to a family of top-down mental processes required when you have to pay attention, when going on automatic or relying on instinct would be insufficient or impossible (Burgess & Simons 2005, Espy 2004, Miller & Cohen 2001). Thus, EFs impairment include poor attention and disinhibition, poor self-regulation, difficulties in generating and implementing strategies, inability to utilize feedback, cognitive rigidity, reduced working

memory, and disorganization (Kurowski et al., 2013). There is general agreement that EFs are composed of three core: 1) inhibitory control, including self-control and interference control; 2) working memory (WM), and 3) cognitive flexibility (Lehto et al. 2003, Miyake et al. 2000). From this model and its three core, higher-order EFs are built such as reasoning, problem solving and planning (Collins & Koechlin 2012, Lunt et al. 2012). Diamond (2013) published a literature review corroborating this model and relation of the three core with the higher-order EFs.

Lines of evidence suggest that traditional measures of processing speed (PS) overlap the measures of EFs (Nuechterlein et al., 2004). Diamond (2002) showed that PS predicts executive control. This evidence is understandable, since the PS can be conceptualized as either the amount of time it takes to process a specific quantity of information, or the quantity of information that can be processed within a finite amount of time (Kalmar & Chiaravalloti, 2008).

Literature has shown that the decline of EFs is associated with age (Royall et al., 2004; Brennan et al., 1997). EFs impairment has been associated with some conditions, such as: Alzheimer`s disease, and even normal aging (Royall, 2000). In the same way, PS involves a variability of components of executive control, which vary according to age. Individual differences in PS are a reflection of variation in neural speed (Birren & Fisher, 1995; Mendelson & Ricketts, 2001), as well as age-related changes in neural processing, including the decline of axonal myelination across the lifespan (Charlton et al., 2006, 2008).

Thus, the objective of this study is to analyze the difference in the measures of processing speed and executive functions in three independent samples, as follows: MCI cases, AD and normal aging.

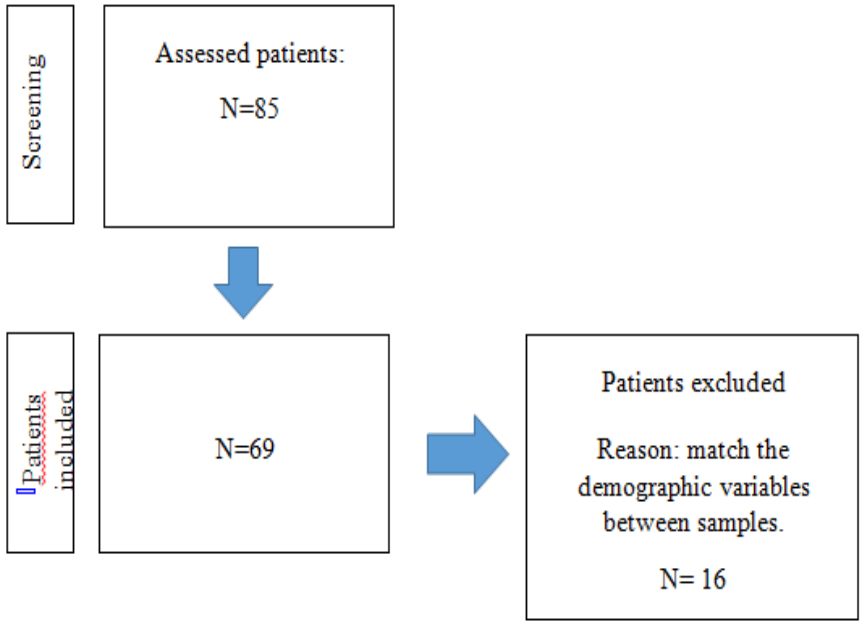
2. Material and Methods

2.1 Patients

We selected 38 control participants (CP), 26 MCI cases and 21 patients with a diagnosis of probable AD. All the patients were recruited from a social program that was offered by the government of Rio de Janeiro. The assessments were performed between 2016 and 2018 by a certified board psychiatrist (FS) and all neuropsychological evaluations were conducted by a senior neuropsychologist

in Rio de Janeiro. Only patients with probable mild to moderate AD were included. Some CP and MCI cases were excluded to match the variables years of education and age between the two groups, resulting in a study with 26 CP and 22 MCI cases **(see Figure 1).** Although the AD group presented a higher mean age, we did not exclude individuals with such diagnosis, keeping the 21 AD cases of baseline. All participants agreed to participate in the study and signed an informed consent form that was approved by the Research Ethics Committee (opinion no.965.264). Furthermore, all participants were over 60 years old and were proficient in Brazilian Portuguese.

Figure 1. Description of the sample selection criteria



2.2 Diagnosis

The diagnosis of AD was made according to the NINCDS-ADRDA criteria (McKhann et al., 1984).The clinical diagnosis of AD was made by a psychiatrist using clinical interviews with patients and caregivers, neuropsychological assessment and imaging. The evaluation of CP and MCI cases were based on clinical history, neuroimaging and initial neuropsychological protocol that included the following tests and scales: 1)Mini Mental State

Examination (MMSE, Brucki, 2003); 2)Cognitive Brief Screening Battery consisting of the following tests: Memory of Figures Test, MFT; The Categorical Verbal Fluency Test, VF; Clock Drawing Test, CDT; Geriatric Depression Scale, GDS-15; The Functional Activities Questionnaire, Pfeffer and The Lawton Instrumental Activities of Daily Living, IADLs (Nitrini et al., 1994; Araújo et al., 2018);3)Rey Auditory Verbal Learning test (RAVLT; de Paula et al., 2018); 4)Phonemic Verbal Fluency test (FAS, Machado et al., 2009) and 5)Rey`s Figure Copy (Oliveira et al., 2017). The MCI cases should have a score of 1.5 below the standard used in one of the initial protocol tests and maintenance of the activities of daily living (ADLs). Exclusion criteria were: 1) history of cerebral infection, stroke; 2) brain tumor; 3) head trauma;4) history of alcohol or substance abuse; 5) history of diagnosed major psychiatric illness and 6)brain imaging that indicated any possibility of brain lesions other than MCI or AD.

2.3 Neuropsychology assessment, scales and questionnaires

The standard neuropsychological test battery was designed to assess the major cognitive functions. Auditory memory was assessed with RAVLT (de Paula et al., 2018), whereas visual memory was evaluated by Memory of Figures test (Nitrini et al., 1994). Language was evaluated by the categorical verbal fluency test (animals; Araújo et al., 2018) and phonemic verbal fluency test (FAS, Machado et al., 2009). PS was assessed by the Wechsler Adult Intelligence Scales third Edition (WAIS-III; Coding, CD; Symbol Search, SS). Finally, the attention and executive functions were assessed with the Trail Color Test (TCT, Rabelo et al., 2010), the Victoria Stroop Test (VST, Regard, 1981; Dot condition—Card 1; Word condition—Card 2; Interference condition—Card 3) and Digit Span (DS; WAIS-III). On the other hand, the assessment of visuoconstructive praxis was performed by the Rey`s Figure Copy (Oliveira et al., 2017). Depressive symptoms were assessed by the Geriatric Depressive Symptoms (GDS-15; Almeida & Almeida, 1999), the functional activities were evaluated by the Pfeffer (Pfeffer et al, 2009) questionnaire and the IADL was evaluated by the Lawton scale (Lawton & Brody, 1969).

2.4 Data Analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS, version 21). The normality of distribution was determined by a histogram. The data did not show normal distribution, so parametric and nonparametric tests were performed. The results of the analyses differed only in TCT A (MCI cases) and VST (Card 1; MCI cases). Thus, skewness and Kurtosis were analyzed and indicated the use of parametric tests. The relationship between dependent variables and the clinical group was tested with an analysis of variance (ANOVA). If a significant ANOVA was found, post hoc tests (Bonferroni test) controlling for multiple comparisons were used to identify pairs of clinical groups that differed significantly. The clinical groups also were compared according to demographic characteristics (i.e. age, sex, and years of education).

3. Results

3.1 Demographical characteristics

Table 1 shows the mean and standard deviation (SD) of the demographic data, Lawton score (patient version) and MMSE score. In addition, **table 1** presented pairwise comparisons between samples. Repeated-measures ANOVA showed no difference between clinical group with respect years of education (*F* (2,66)=2,5, p=.083). However, there were difference with respect age (F (2,66) =5.7, p=.005), Lawton score (version for patient) (*F* (2,65)=28.1, p=.001) and MMSE score (*F* (2,66)=21.5,p=.001). Pairwise comparisons showed difference MMSE score and Lawton score between MCI cases and AD.

Demographics	CP	MCI	AD	*p value (CP versus MCI)	*p value (MCI versus AD)
Age	73,3 (4,9)	75,6 (6,2)	79,2 (6,7)	>0.05	>0.05
Education (years)	13,1 (3,0)	10,4 (5,1)	11,4 (4,5)	>0.05	>0.05
Male gender	4 (22)	1 (21)	7 (14)	ns	ns
MMSE scores	31,6 (1,8)	29,6 (2,6)	24,4 (5,9)	>0.05	<0.05
Lawton scores (patient version)	20,8 (0,4)	20,3 (0,6)	18,0 (2,2)	>0.05	<0.05

Table 1.Demographics characteristics, MMSE score and IADL score between three samples. Note: Mini Mental State Examination (MMSE); IADL was evaluated by the Lawton scale. Control Participants (CP), Mild Cognitive Impairment (MCI) and Alzheimer`s disease (AD).

3.2 Comparisons between samples

The mean and sd of neuropsychological measures and pairwise comparisons of the sample are summarized in **Table 2.** Repeated-measures ANOVA presented difference between clinical group with respect The Processing Speed Index (PSI, WAIS; *F* (2,66)=25.1, p=.000), SS score (*F* (2,66)=20.3, p=.000), CD score (*F* (2,66)=13.4, p=.000), VST-Card 1(*F* (2,57)=6.3, p=.003, VST-Card 2(*F* (2,57)=6.6, p=.002), VST-Card 3(*F* (2,57)=9,5,p=.000), TCT A(*F* (2,66)=15.5, p=.000), TCT B (*F* (2,66)=18.0, p=.000). And pairwise comparisons showed difference in SS score, CD score, PSI and SS errors between MCI versus control participants. As expected, MCI versus AD presented difference in CD score, PSI, VST-Card 2, VST-Card-3, TCT A and TCT B.

Neuropsychological Measures	CP	MCI	AD	*p value (CP versus MCI)	*p value (MCI versus AD)
VST-Card 1	14,8 (3,6)	21,7 (8,4)	32,3 (25,0)	>0.05	>0.05
VST-Card 2	21,0 (6,3)	24,7 (7,3)	53,2 (51,6)	>0.05	<0.05
VST-Card 3	33,6 (13,4)	40,2 (12,8)	87,3 (70,8)	>0.05	<0.05
TCT A	67,0 (27,0)	94,5 (27,6)	153,9 (88,3)	>0.05	<0.05
TCT B	130,9 (45,2)	179,3 (38,3)	266,2 (126,2)	>0.05	<0.05
TCT A errors	0,0 (0,1)	0,1 (0,4)	0,6 (1,2)	>0.05	>0.05
TCT B errors	0,1 (0,3)	0,6 (1,0)	1,9 (4,3)	>0.05	>0.05
SS	14,9 (2,6)	11,8 (2,3)	10,2 (2,8)	<0.01	>0.05
CD	13,1 (3,6)	11,0 (2,1)	8,7 (2,4)	<0.05	<0.05
PSI	123,0 (12,5)	107,1 (11,2)	97,1 (14,2)	<0.01	<0.05
SS errors	1,5 (1,5)	3,0 (1,7)	24 (2,2)	<0.05	>0.05

Table2. The mean and SD of neuropsychological measures and pairwise comparisons .*Note.*Victoria Stroop Test (VST); Trail Color Test (TCT), Search Symbols (SS), Code(CD),Processing Speed Index (PSI).

4. Discussion

The results of this study present that MCI cases can be early identified by the performance in PSI (WAIS-III) and the tests that assess PS, compared to the control participants. In addition, these two samples can also be differentiated by the number of errors made in one of the PS tests. However, differences in executive functions (inhibitory control, cognitive flexibility and working memory) were not enough to distinguish control participants from the MCI cases. On the other hand, when AD patients are compared to the MCI cases, there is difference

in PSI, measures of PS and EFs, which are enough to differentiate the two samples.

The early deficit in the PSI (WAIS-III), while we compare control participants and MCI cases, can be explained by the test paradigm used: finite amount of time versus correct-errors made. Thus, the data show that MCI cases present difficulties in controlling this equation. However, the same MCI cases do not show any difference in the paradigms of EFs used. This cognitive dissociation can be explained, since the tests of EFs used in this study do not present limited time of execution, although the errors are also considered. The European Union (EU, Apostolo et al.,2016)) report emphasizes the importance of assessing cognitive aspects, such as PS or perceptual and motor aspects. In this study, they showed that these parameters may be early indicators of cognitive decline, as well as the difference between modifiable risk factors and protective factors

Using EFs is effortful; it is easier to go on "automatic pilot" than to consider what to do next (Diamond, 2013) In this context, note that in the VST paradigm, only the first part of the test can be considered automatic, while the second and third parts are considered controlled processes. Likewise, in TCT, only part A of the test can be considered an automatic process. MCI cases compared show difference in PSI, measures of PS and controlled processes of EFs. However, automatic processes (VST-Card 1) do not present differences, which show that this is not a good criterion to differentiate the two samples. Of note, it should be emphasized that although TCT A is considered a automatic process, this test requires greater cognitive complexity, such as visual screening, and maintenance of the numerical sequence. Thus, the two samples showed differences in TCT A.

A recent meta-analysis showed that cases of MCI were associated with early deficits in PS compared to normal aging (Duke Han et al., 2017). These results support our findings and the notion that neuropsychological measures are sensitive to different stages of pre-clinical AD among cognitively intact older adults. Thus, the strength of the present study was the early diagnosis of MCI cases and the impact on the prognosis of these cases. The earlier the diagnosis was made, the greater the chances of effectiveness of the proposed therapies. Although

the sample of MCI cases did not show difference in the IALDs for patient compared to CP, the PSI and PS of measures showed good markers for the diagnosis. In addition, these findings are important for the clinical practice of the neuropsychologist who works with aging.

In conclusion, the authors warn about the importance of assessing cognitive aspects that are currently being poorly evaluated in greater depth. The assessment of processing speed might have impact on the prognosis of the disorder, and they might help decisions regarding treatment options. However, more studies need to be conducted on the subject, since there is a lack of it in the literature.

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ARTICLE 4

Martorelli,M; Marques, L; Charchat-Fichman. Diagnostic Accuracy of Speed Processing Measures in Mild Cognitive Impairment and Alzheimer's disease: sensitivity and specificity (in preparation).

ABSTRACT

Introduction: With increasing aging worldwide, the conditions such as dementia and Mild Cognitive Impairment (MCI) increase their prevalence. Studies indicate that processing speed (PS) may be one of the early indicators of cognitive decline. However, there is a lack in the literature on the diagnostic accuracy of instruments that measure PS. Thus, the objective of this study is to study the diagnostic accuracy of PS measurements in MCI and Alzheimer's disease. **Method:** A ROC curve for PS measures was performed in MCI and AD. **Results and Discussion:** the results showed to the discriminative ability of the PS measures used, especially, the measures considered simple, like as the reaction time. These results are important due to the lack of studies on aging in the subject.

Keywords:

Mild Cognitive Impairment, Diagnostic Accuracy, Processing Speed, Aging, Alzheimer`s disease.

Diagnostic Accuracy of Speed Processing Measures in Mild Cognitive Impairment, Alzheimer's disease and Normal Aging: sensitivity and specificity (in preparation).

1. Introduction

Alzheimer`s disease (AD) is the most widespread form of dementia (Alzheimer's Association, 2016) and it is a major global health priority (Ferri et al., 2005). Although the average duration of the disease varies between 4 and 8 years, some patients may survive up to 20 years with the disease (Xie et al., 2008). Similarly, the aging of the population leads to the prevalence of clinical conditions, such as Mild Cognitive Impairment (MCI; Sachdev et al., 2015; Petersen et al., 2018). The prevalence of MCI varies according to variables such as clinical setting and inclusion criteria. However, it generally ranges from 11 to 20% (Petersen et al., 2010). MCI is a clinical entity that refers to a transitional phase between normal aging and somatic and psychologic disorders (Petersen, 2012; Cooper, 2013) and with substantial heterogeneity in etiology, clinical presentation, and prognosis and outcome (Petersen et al., 2005).

The diagnosis of AD is based mainly on the observation of cognitive decline combined with functional decline; in the absence of other causes of dementia (American Psychiatric Association, 1994; McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984). Similarly, for the diagnosis of MCI, neuropsychological testing has been clearly listed as an important component of the diagnostic work-up by the National Institute on Aging and Alzheimer's Association work groups (NIA-AA; MCI; Albert et al. 2011; McKhann et al. 2011). Neuropsychological instruments are typically used for both descriptive and diagnostic purposes (Busch, Chelune, & Suchy, 2006). When the tests are used diagnostically, they provide information about the probability that an individual has— or will have at some moment in the future—a cognitive disorder or deficit, such as AD and MCI (Stern & White, 2003).

The current literature recognizes neuropsychological heterogeneity in MCI by dividing it into subtypes (Jak et al., 2016; Petersen et al., 2014; Lopez et al., 2012; Bangen et al., 2010; Petersen & Negash, 2008; Busse et al. 2006). The European Union (EU; Apostolo al. 2016) emphasizes the importance of assessing

cognitive aspects in MCI as processing speed (PS). In addition, this report shows that PS could represent early indicators of cognitive decline. In the same way, recent studies (Scheltens et al., 2017; 2016; Vardy et al., 2014) highlight the cognitive heterogeneity in AD, showing the importance of studying other cognitive aspects, in addition to episodic memory.

Normal aging and some psychiatric disorders (such as AD) were associated with decline in PS. This decline leads to cognitive deficits that emerge the limited ability to control information simultaneously. Since there are lower capacity to processing information, it can also conduct to increase errors in the cognitive processing (Salthouse,1996;2004). MCI cases are also known to have worse cognitive abilities than normal aging. Takahashi et al.(2012) compared PS measures in the following samples: AD, MCI and normal aging. In this study, patients with AD and MCI (amnestic and non-amnestic) showed lower performance in measures of PS than normal aging.

The analysis of measures of PS in aging is of paramount importance, especially in Brazilian settings and neuropsychological tests are fundamental in this process. Thus, the purpose of this study is to analyze the accuracy-sensitivity and specificity- of the measures of processing speed in DA, MCI and normal aging.

2. Method

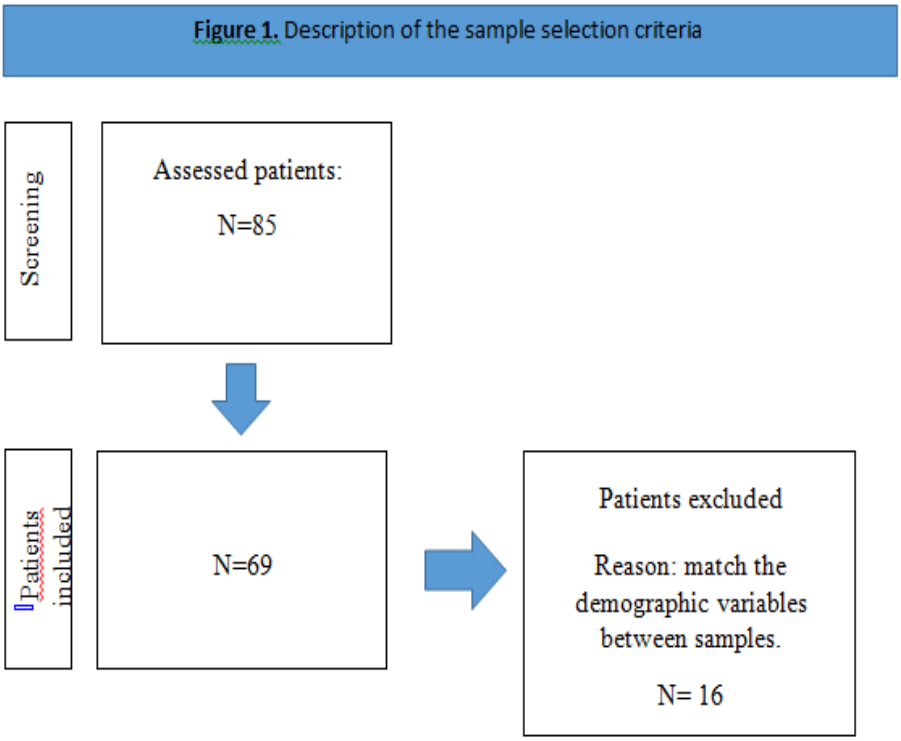
2.1. Participants

A total of 85 individuals were recruited from a social program that was offered by the government of Rio de Janeiro. Of these individuals, 36 were control participants (CP), 26 MCI cases and 21 patients with a diagnosis of probable AD. The assessments were performed between 2016 and 2018 in Rio de Janeiro. The match of the variables age and years of education was performed; thus, 12 control participants and 4 MCI cases were excluded from the sample. Although the AD group presented a higher mean age, we did not exclude individuals with such diagnosis, maintaining the 21 AD cases of baseline. After the exclusions, the sample resulted in 26 CP, 22 MCI cases and 21 AD (see flow

chart). All participants were over 60 years old and were proficient in Brazilian Portuguese, and only patients with probable mild to moderate AD were included. The participants of this study agreed to participate and signed the consent form, with the study approved by the Research Ethics Committee under authorization No. 965.264.

2.2 Diagnosis

Control participants (CP) were individuals with no changes on cognitive performance tests and without functional impairment. The assessment of control participants and MCI cases were based on clinical history, neuroimaging and initial neuropsychological protocol that included the following tests and scales: 1)Mini Mental State Examination (MMSE, Brucki, 2003); 2)Cognitive Brief Screening Battery consisting of the following tests: Mini Mental State Examination, MMSE; Memory of Figures Test, MFT; The Categorical Verbal Fluency Test, VF; Clock Drawing Test, CDT; Geriatric Depression Scale, GDS-15; The Functional Activities Questionnaire, Pfeffer and The Lawton Instrumental Activities of Daily Living, IADL (Nitrini et al., 1994; Araújo et al., 2018) ;3) Rey Auditory Verbal Learning Test (RAVLT; de Paula et al., 2018); 4) Phonemic Verbal Fluency Test (FAS, Machado et al., 2009) and 5) Rey's Figure Copy (Oliveira et al., 2017). MCI cases should have a score of 1.5 below the standard used in one of the initial protocol tests, and maintenance of activities of daily living (ADLs). Finally, the diagnosis of AD was based on the consensus criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders (NINCDS-ADRDA; McKhann et al., 1984). The clinical diagnosis of AD was made by a psychiatrist using clinical interviews with patients and caregivers, neuropsychological assessment and imaging. Exclusion criteria were: 1) history of cerebral infection, stroke; 2) brain tumor; 3) head trauma;4) history of alcohol or substance abuse; 5) history of diagnosed major psychiatric illness and 6)brain imaging that indicated any possibility of brain lesions other than MCI or AD.



2.3 Neuropsychological tests used in measures of processing speed

The assessment of the PS was performed by the tests of the Wechsler Adult Intelligence Scales Third Edition (WAIS-III): Coding (CD), Symbol Search (SS). In addition, the Processing Speed Index (PSI, WAIS-III) was performed for all participants in the sample.

2.4 Analyses

All analyses were conducted with Statistical Package for Social Sciences (SPSS, version 21). The Receiver Operating Characteristic (ROC) was performed for the following tests and Index: CD, SS and PSI. The Roc curves were plotted in order to determine the degree to which subtests discriminated between CP, MCI cases and AD. Theses analyses show the sensitivity versus one minus the specificity for each possible cutoff point. The area under curve (AUC) with 95%

confidence intervals was used as an indicator of the ability of the measures of PS in differentiating patients who were AD or MCI. All the raw scores obtained in the tests and in the index were transformed into scaled-score.

3. Results

Demographics characteristics, MMSE and Lawton scores

Table 1 presents demographic variables, MMSE and Lawton scores (version for patient) and pairwise comparisons. The data show that comparing the MCI cases to the CP does not result in differences in the following variables: age, years of education, MMSE score and IADLs score. However, AD compared to the CP showed differences in age, MMSE score and IADLs scores (patient version) and the variable years of education showed no difference in the two samples.

Demographics	CP	MCI	AD	*p value CP versus MCI	*p value CP versus AD
Age	73,3 (4,9)	75,6 (6,2)	79,2 (6,7)	>0.05	<0.05
Education (years)	13,1 (3,0)	10,4 (5,1)	11,4 (4,5)	>0.05	>0.05
Male gender	4 (22)	1 (21)	7 (14)	ns	ns
MMSE score	31,6 (1,8)	29,6 (2,6)	24,4 (5,9)	>0.05	<0.01
Lawton score (version for patient)	20,8 (0,4)	20,3 (0,6)	18,0 (2,2)	>0.05	<0.01

Table 1. Demographic variables, MMSE, Lawton score and pairwise comparisons

AD versus control participants

The first analysis examined sensitivity and specificity of the processing speed measures, such as: SS, CD and PSI. The diagnosis parameters were used to test the ability of the measures of the SP to identify cases of Alzheimer`s disease. The estimated AUC (**figure 1**) for the SS was 0.88 (95% CI: 0.79-0.98; p< 0.01); for the CD was 0.88 (95% CI: 0.77-0.98; p< 0.01). And finally, AUC for the PSI was 0.90 (CI: 0.81-0.99; p<0.01). The most appropriate cutoff point for the SS was 12, at which the sensitivity and specificity are, respectively: 85% and 80%. The most appropriate cutoff point for CD was 10, and the sensitivity and specificity are 81% and 88% respectively. And, finally, the most appropriate cut-off for the PSI was 109, at which the sensitivity and specificity are 81% and 88% respectively.

MCI versus control participants

The first analysis examined sensitivity and specificity of the processing speed measures, such as: SS, CD and PSI. These diagnostic parameters were used to test the ability of these measures of the SP in identifying cases of MCI (**figure 2**). The ROC curves for the CD, SS and PSI are shown in Fig. 1. The estimated AUC for the SS was 0.82 (95% CI: 0.70-0.94; p<0.01) and for the CD was 0.74 (95% CI: 0.60-0.88; p<0.05). In addition, the estimated AUC for the PSI was 0.83 (95% CI: 0.71-0.94; p<0.01). The most appropriate cutoff point for the SS was 13, at which the sensitivity and specificity are 86% and 76% respectively. The most appropriate cut-off point for CD was 12, and sensitivity and specificity are 77% and 62% respectively. In conclusion, the most appropriate cut-off for the PSI was 112, at which the sensitivity and specificity are 72% and 80% respectively.

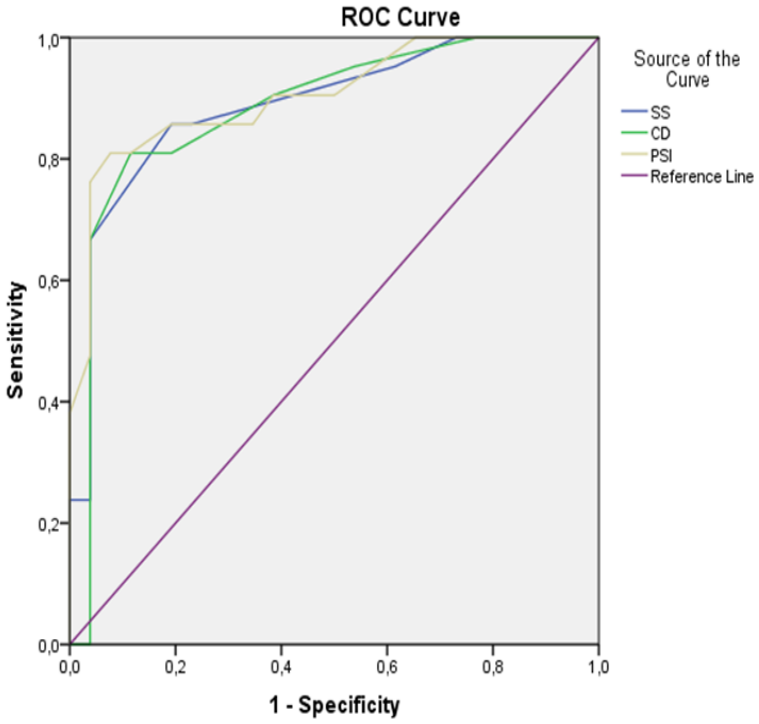


Figure 2. Roc analyses, sensitivity and specificity for AD versus CP.

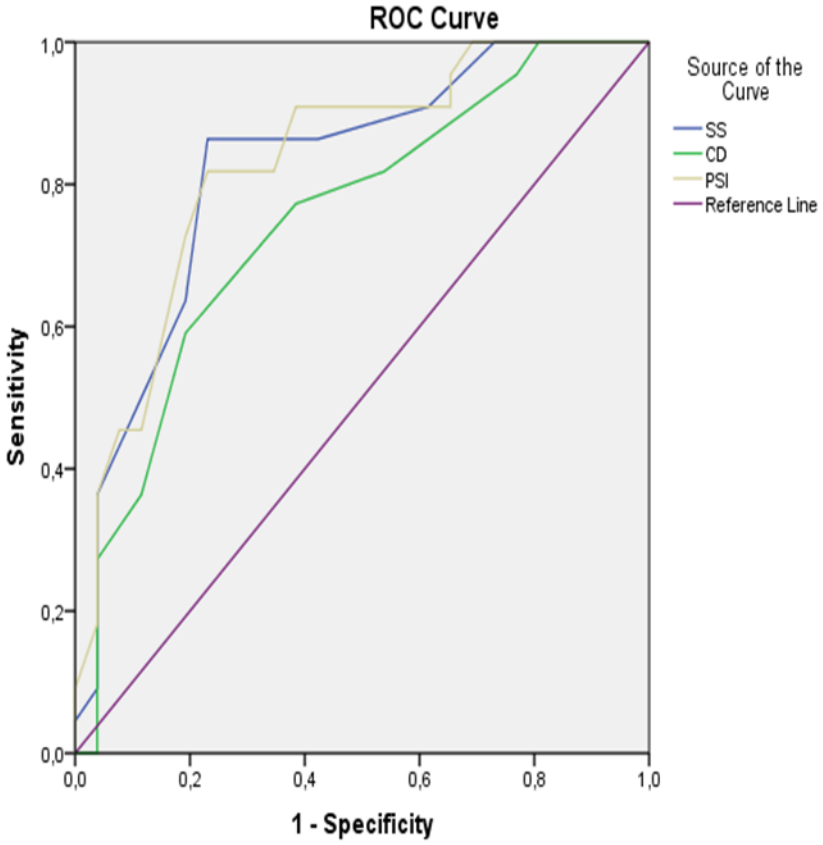


Figure 3. Roc analyses, sensitivity and specificity for MCI versus CP.

4. Discussion

In this study, we analyzed diagnostic parameters of PS measures in MCI cases, AD and normal aging. The ROC analyses showed that measures of PS had discriminative capacities and the PSI also had the highest diagnostic accuracy for the MCI cases and AD. Especially, the CD test presented the lowest sensitivity value to discriminate MCI cases. In this context, we prioritize sensitivity instead of specificity, due to the prevalence rates of MCI cases. The sensitivity of the CD test can be explained, because the measurement of this test can be considered a complex measure of PS, which requires process of attention and mental manipulation (Noelle et al., 2014).

Cognitive domains decrease, as we get older (Christensen, 2001; Singh-Manoux et al., 2012). A decline in cognitive function affects more than 50% of people over 60 years of age (Skaper et al., 2014) .Particularly, memory and PS appear to be more sensitive to age than other cognitive domains (Salthouse, 1996; Christensen, 2001). A recent study compared performance on PS tests in normal

aging versus MCI cases and AD. In this study, decline in PS measures were associated with MCI cases and AD diagnosis (Mackin et al.,2018). In addition, Park et al.(2018) analyzed the diagnostic accuracy of measures of PS and showed that measures could distinguish AD from MCI and CP. These data corroborate our findings and emphasize the importance of the diagnostic accuracy of neuropsychological measures.

According to the NIA-AA (Albert et al., 2011; McKhann et al. 2011), neuropsychological assessment is necessary and an important component for the diagnosis of MCI and AD. Furthermore, neuropsychological testing is an equally valuable and arguably more affordable, less invasive cognitive biomarker of AD (Jack et al. 2016). In this context, the strength of this study was to test precisely the diagnostic accuracy of PS measures in Brazilian samples. In addition, it provides scaled-scores for SS, CD and PSI in MCI and AD. However, it is necessary to highlight the limitations of the PS measures used in this study. The Brazilian norms of WAIS-III have limitations and need to be revised. Therefore, proposed cutoff points proposed as diagnostic parameters for MCI and AD are considered typical of normal aging, according to WAIS-III.

In conclusion, the authors emphasize the importance of early indicators of cognitive decline in aging and the diagnostic parameters in the neuropsychological instruments, in the Brazilian settings. Those aspects might impact on the prognosis of the disorder, and they might help decisions concerning to treatment options, especially those related to cognitive rehabilitation. However, further studies on the subject are still needed.

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IV. GENERAL DISCUSSION

The general purpose of this thesis was to explore the atypical (nos-amnestic) aspects in aging. In this context, we analyzed the neuropsychological heterogeneity in AD, and compared measures of processing speed (PS), inhibitory control, working memory and cognitive flexibility in three samples: normal aging, MCI and AD. In addition, we analyzed diagnostic accuracy in measures of PS in cases of MCI and AD.

The first part of this work focused on understanding the neuropsychological heterogeneity in AD. Typically, memory dysfunctions are the earliest symptoms in AD (Dubois et al., 2010). In addition, episodic memory deficits are more often studied. However, current literature (Martorelli et al., 2018a; Martorelli et al., 2018b; Scheltens et al, 2017; 2016) shows that some patients with AD present early non-amnestic deficits. This difference in the cognitive profiles in AD is due to several aspects, such as: genetic, clinical, demographic and pathological characteristics (Fisher, Rourke, Bieliauskas, Giordani, Berent, & Foster, 1996; Fisher, Rourke, & Bieliauskas, 1999; Jacobs et al., 1994; Sevush, Leve, & Brickman, 1993; Sevush, Peruyera, Bertran, Cisneros, 2003; Snowden et al., 2007). Thus, many AD patients are often underdiagnosed with other dementia or psychiatric disorders. These diagnostic errors directly interfere with the treatment and prognosis of these patients. Regarding (pharmacological or behavioral) treatment, a key factor in the failure to find effective therapy may be the fact that AD is not a homogeneous condition, and a single effective therapy for the entire AD entity can never be established (WHO, 2012; Townsend et al.,2011). Moreover, the identification of significant profiles in AD may be a necessary first step towards personalized medicine (Scheltens et al., 2016).

In this first part of the work, we published 2 articles on the topic: a systematic review (Martorelli et al., 2018a) and case study (Martorelli et al., 2018b). This part was focused on emphasizing an unexplored topic that is so important to the clinical settings and research. Martorelli et al. (2018a) published

the first systematic review on the topic. In clinical settings, these findings will have great impact, since they will guide new diagnostic methods and treatment. The limitation of the first part of this thesis was the publication of an article with only three cases. However, due to lack of studies in the literature on the topic, case studies show relevance, both in clinical and research settings. Case studies are even more relevant when considering the Brazilian settings, since data on heterogeneity with instruments validated for Brazil is not available yet.

In this context, the second part of this work focused on exploring the least studied cognitive functions in aging. The prevalence of aging is increasing worldwide. In addition, conditions such as dementia and MCI are major healthcare challenges when we refer to aging (WHO, 2012). Alzheimer's disease (AD) is the most common cause of degenerative dementia (Martin et al.,1986; Neary et al., 1986; Huff et al., 1987; Fisher et al., 1999). DA and MCI (Scheltens et al., 2017, 2016; Petersen et al.,2014; Klekociuk et al., 2014) are not homogenous conditions when the subject is cognition. Thus, understanding cognitive functions that are poorly explored and which could represent early indicators of cognitive decline are relevant (Apostolo et al., 2016).

Thus, the second part of this work was divided into two studies. The first study explored the comparison in measures of processing speed, inhibitory control and self-monitoring in three samples: normal aging, MCI and AD. In addition, we analyzed the influence of these measures on IADLs and the early diagnosis of cognitive decline. The results of this first study indicate that PS measures are more sensitive than the executive functions (EFs) in the identification of MCI. Comparing MCI cases versus CP, MCI showed no difference in IADLs and EFs, but cases of MCI showed a difference in PS and made more mistakes in PS tests. These findings are extremely relevant to the clinical setting, since the earlier the diagnosis, the better the prognosis. In addition, there is a lack of literature on these measures in aging.

The other study of this second part explored the diagnostic accuracy of PS measures in MCI and AD. The literature (Charernboon, 2017) shows some studies on diagnostic accuracy in measures frequently studied, such as: memory and language. However, studies on the diagnostic accuracy of PS measures in aging show a gap in the literature. The results of this study showed that measures of PS have discriminative capacities for cases of AD and MCI. Specially for MCI

cases, the PS measures did not present a high specificity value. However, this can be explained because the measure of the Code test is considered to be a complex measure of PS (Noelle et al.,2014).

In conclusion, this thesis shows the importance of studying cognitive heterogeneity in aging and exploring these cognitive aspects that are not much studied. These findings may change the diagnostic methods, both in the clinical setting and in research.

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