Pontifícia Universidade Católica
do Rio de Janeiro

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Cognitive Cues of Pathological Aging

Measures of functionality and reaction time
as early screening variables

Dissertação de Mestrado

Dissertação apresentada como requisito parcial para obtenção do grau de Mestre pelo Programa de Pós-Graduação em Psicologia (Psicologia Clínica) do Departamento de Psicologia da PUC-Rio.

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ABSTRACT

Marques, Larissa; Charchat-Fichman, Helenice (Advisor). **Cognitive cues of pathological aging: measures of functionality and reaction time as early screening variables**. Rio de Janeiro, 2020. 73p. Dissertação de Mestrado - Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

The present dissertation aimed to investigate the role of two variables that are important to the early screening, comprehension, and intervention planning for mild cognitive impairment (MCI): reaction time and activities of daily living (ADL) performance awareness. To do so, the first study compared instrumental ADL (iADL) performance of 225 older adults divided in three neuropsychological profiles (control group, people with MCI and people with dementia). Results imply deficits in iADL begin to take place already in MCI neuropsychological profiles and are perceived both by the older adults and their caregivers, even though some cognitive impairment has already taken place. The second study investigated the diagnostic accuracy of CompCog, a computerized cognitive screening battery with different subtests, to identify MCI in a sample of 52 older adults. AUC of selected ROC curves varied from 0.804 (CI 0.674-0.933) to 0.915 (CI 0.837-0.993). The subtest with highest sensitivity and specificity – choice reaction time subtest – had 91.7% sensitivity and 89.3% specificity. The logistic regression final model correctly classified 92.3% of individuals, with 92.9% specificity and 91.7% sensitivity, and included only 4 variables of different subtests. In summary, the first study brought evidence that there is already a small impairment in functional capacity in MCI and that individuals are aware of this decline. The second study showed that reaction time assessed through CompCog is a good measure to differentiate between normal aging and MCI, more accurate than differentiation by errors. All results considered, both variables are easily assessed and can be part of clinical routine tests in order to achieve the objective to screen for MCI, understand its consequences and plan interventions.

Keywords

Mild Cognitive Impairment; Normal Aging; Pathological Aging; Reaction Time; Computerized Test; Activities of Daily Living; Diagnostic Accuracy

RESUMO

Marques, Larissa; Charchat-Fichman, Helenice. **Cognitive cues of pathological aging: measures of functionality and reaction time as early screening variables**. Rio de Janeiro, 2020. 73p. Dissertação de Mestrado - Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

A presente dissertação teve como objetivo investigar o papel de duas variáveis importantes para a triagem precoce, compreensão e planejamento de intervenção para comprometimento cognitivo leve (CCL): tempo de reação e consciência do desempenho em atividades da vida diária (AVD). Para tanto, o primeiro estudo comparou o desempenho instrumental nas AVD (AIVD) de 225 idosos divididos em três perfis neuropsicológicos (grupo controle, pessoas com CCL e pessoas com demência). Os resultados sugerem que os déficits nas AIVD já começam a ocorrer nos perfis neuropsicológicos de CCL e são percebidos tanto pelos idosos quanto por seus cuidadores, mesmo que já tenha ocorrido algum declínio cognitivo. O segundo estudo investigou a acurácia diagnóstica do CompCog, uma bateria de rastreio cognitivo computadorizada com diferentes subtestes, para detectar CCL em uma amostra de 52 idosos. As AUC das curvas ROC selecionadas variaram de 0,804 (IC 0,674-0,933) a 0,915 (IC 0,837-0,993). O subteste com maior sensibilidade e especificidade - subteste de tempo de reação de escolha - apresentou sensibilidade de 91,7% e especificidade de 89,3%. O modelo final de regressão logística classificou corretamente 92,3% dos sujeitos, com especificidade de 92,9% e sensibilidade de 91,7%, e incluiu apenas 4 variáveis de diferentes subtestes. Em resumo, o primeiro estudo trouxe evidências de que já existe um pequeno declínio na capacidade funcional no MCI e que os pacientes estão cientes desse declínio. O segundo estudo mostrou que o tempo de reação avaliado pelo CompCog é uma boa medida para diferenciar entre envelhecimento normal e CCL, sendo mais precisa que a diferenciação por erros. Considerando todos os resultados, ambas as variáveis são facilmente avaliadas e podem fazer parte de testes clínicos de rotina, a fim de atingir o objetivo de triagem, compreensão das consequências e planejamento de intervenções para MCI em idosos.

Palavras-chave

Comprometimento Cognitivo Leve; Envelhecimento Normal; Envelhecimento Patológico; Tempo De Reação; Teste Computadorizado; Atividades Da Vida Diária; Acurácia Diagnóstica

RIASSUNTO

Marques, Larissa; Charchat-Fichman, Helenice. **Cognitive cues of pathological aging: measures of functionality and reaction time as early screening variables**. Rio de Janeiro, 2020. 73p. Dissertação de Mestrado - Departamento de Psicologia, Pontifícia Universidade Católica do Rio de Janeiro.

La presente tesi di laurea mira a indagare il ruolo di variabili promettenti per lo screening precoce, la comprensione e la pianificazione dell'intervento per il deterioramento cognitivo lieve (MCI): tempo di reazione e consapevolezza dei deficit nelle attività della vita quotidiana (ADL). Pertanto, il primo studio ha confrontato la performance nelle attività strumentali della vita quotidiana (IADL) di 225 soggetti anziani suddivisi in tre profili neuropsicologici (gruppo di controllo, persone con MCI e persone con demenza). I risultati suggeriscono che i deficit di IADL iniziano già a verificarsi nei profili neuropsicologici MCI e sono percepiti sia dagli anziani che dai loro badanti, anche se si è già verificato un declino cognitivo. Il secondo studio ha analizzato l'accuratezza diagnostica di CompCog, una batteria di screening cognitiva computerizzata con diversi subtest, per identificare MCI in un campione di 52 soggetti anziani. Le AUC delle curve ROC selezionate sono variate da 0,804 (CI 0,674-0,933) a 0,915 (CI 0,837-0,993). Il subtest con la massima sensibilità e specificità - il subtest del tempo di reazione di scelta – ha avuto una sensibilità del 91,7% e una specificità dell'89,3%. Il modello finale della regressione logistica ha correttamente classificato il 92,3% dei soggetti, con una specificità del 92,9% e una sensibilità del 91,7%, e ha incluso solo 4 variabili di diversi subtest. In sintesi, il primo studio ha dimostrato che c'è già un piccolo declino della capacità funzionale nell MCI e che i pazienti ne sono consapevoli. Il secondo studio ha dimostrato che il tempo di reazione valutato tramite CompCog è una buona misura per distinguere tra invecchiamento normale e MCI, piuttosto efficiente di quella per errori. Considerando tutti i risultati, entrambe le variabili sono facilmente valutabili e possono far parte di test clinici di routine al fine di raggiungere l'obiettivo di screening, comprendere le conseguenze e pianificare gli interventi per l'MCI negli anziani.

Parole chiave

Deterioramento Cognitivo Lieve; Invecchiamento Normale; Invecchiamento Patologico; Tempo Di Reazione; Test Computerizzato; Attività Della Vita Quotidiana; Accuratezza Diagnostica

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List of Abbreviations

ADL	Activities of daily living
aADL	Advanced activities of daily living
AD	Alzheimer disease
bADL	Basic activities of daily living
BTNC	Bateria de Testes Neuropsicológicos Computadorizados
BSCB	Brief Cognitive Screening Battery
CAMRT	Correct answers median reaction time
CG	Control group
HIC	High income countries
iADL	Instrumental activities of daily living
LAC	Latin America Countries
LMIC	Low- and middle-income countries
MRT	Median reaction time
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
PwD	People with dementia
PwMCI	People with mild cognitive impairment
RT	Reaction time

1. THEORETICAL BACKGROUND

1. Mild Cognitive Impairment

1.1 Epidemiology

The latest United Nations World Population Aging Reports (The United Nations Population Division, 2017, 2019) raised important information about aging in the world. The global population aged 60 or older more than doubled from 1980 to today. The expectation is that it will double again by 2050, reaching over two billion and surpassing the number of children and teenagers aged between 10 and 24 years. According to the 2017 report, life expectancy increased more than twenty years globally since 1950 – reaching more than 70 years old. By 2050, the report estimates that global life expectancy will exceed 80 years old in Europe, Latin America, and Oceania. In Africa and Asia, it is expected to surpass 70 years old. The numbers are growing faster in developing countries, where 80% of older adults are expected to be living in by 2050.

Different pathological conditions are related to aging. Cognitive decline caused by neurodegenerative disorders is one of them (Brunet & Berger, 2014). Such disorders cause high amounts of disability in the long term, and there are none or few available treatments. For this reason, these disorders, grouped under the term dementia, today are a large economic and public health challenge (Brunet & Berger, 2014). Worldwide, the global costs of dementia are increasing, and went from US$ 604 billion in 2010 to US$ 818 billion in 2015 (Alzheimer's Disease International, 2015). In 2017, the mean value of care was estimated to be U$321,780 per person with dementia, more than two times the health expenses of older adults without the condition (Jutkowitz et al., 2017).

If some decades ago it was enough, regarding neurodegenerative disorders, to differentiate between normal aging and dementia, today early detection is the goal to enable early interventions (Petersen, 2016). In this context, mild cognitive impairment (MCI) rises as a relevant concept. MCI is seen as a preclinical stage of dementia (Alzheimer's Disease International, 2018). Although there are other prognostics (Kasper et al., 2020), people diagnosed with MCI have a higher rate of development of dementia when compared to those not diagnosed (Steiner, Jacinto,

Mayoral, Brucki, & Citero, 2017). Of diagnosed dementia cases, 75% are Alzheimer disease (AD) (Alzheimer's Disease International, 2018). Population studies that indicate the prevalence of MCI in the population vary greatly in their results due to the use of different diagnostic criteria, differences between prospective or retrospective analyses, and according to which MCI subtypes are being sought (Tampi, Tampi, Chandran, Ghori, & Durning, 2015). The estimate of older adults with MCI ranges from 12% to 18% globally (Petersen, 2016), although some studies reach percentages as high as 42% in specific countries (Brucki, 2013).

There is less data available in low- and middle-income countries (LMIC), although dementia increase is bigger in those places (Alzheimer's Disease International, 2018; Parra et al., 2018). In Latin America Countries (LAC), the reported prevalence of dementia varies between 2% and 13.7% (Parra et al., 2018). Usually, there are more MCI cases than dementia (Brucki, 2013), so a number higher than this should be expected. In Brazil, one study reported an incidence rate per 1000 persons-year for MCI of 13.2, whereas globally the same incidence is usually between 8.5% and 31.9% (Chaves, Camozzato, Godinho, Piazenski, & Kaye, 2009). Direct and indirect costs of dementia in Brazil are estimated to be more than U$16000 annually per patient (Ferretti, Sarti, Nitrini, Ferreira, & Brucki, 2018), so any percentage becomes a challenge not only to individuals and their families, but to the hole society.

1.2 Historic

The term MCI was used for the first time by Reisberg et al. in 1982 (Reisberg et al., 1988). It referred to the third stage in a scale of seven stages regarding AD progression. At that time, it was characterized mainly by a decline in memory capacity. The scale, named Global Deterioration Scale, goes from a normal aging profile to severe dementia, where all basic activities of daily living (ADL), verbal and psychomotor behaviors are compromised (Reisberg et al., 1988). In the same year, other authors also named *mild dementia* as the third of five stages of Alzheimer's progression (Hughes, Berg, Danziger, Coben, & Martin, 1982). This scale was named Clinical Dementia Rating (CDR). Morris (Morris, 1993) described the same condition ten years later. This scale resembles the current MCI concept, but is not identical to it (Tampi et al., 2015).

It was Petersen that, in 1999, refined the concept and started its current use (Petersen, 2016; Tampi et al., 2015). Regarding this definition, MCI was firstly described as the initial stage of AD. It was characterized predominantly by a decline in memory above the expected for a specific age, but not yet sufficient for the diagnosis of dementia (Petersen et al., 1999). In 2004, the diagnostic entity of MCI was expanded. It went from being a stage of AD marked by memory decline to (1) embracing other cognitive domains and (2) being associated to other etiologies besides AD. Some examples are cognitive impairment related to vascular disease, frontotemporal and Levy Bodies dementia, sleep and mood disorders (Petersen, 2016). Based on this new definition, MCI was divided into 4 subtypes: (1) amnestic single-domain; (2) amnestic multiple-domain - when there is a memory decline concomitantly with decline in other functions; (3) non-amnestic single-domain; and (4) non-amnestic multiple-domain - when there is not a memory decline, but there are one or more compromised functions other than memory (Petersen, 2016).

But studies using different criteria lead to distinct classifications (Clark et al., 2013). Other categories have been proposed mostly because there is not one clear and specific guideline to identify MCI (Giau, Bagyinszky, & An, 2019). Criteria has been modified over time and has not yet reached a consensus (Kasper et al., 2020). Nevertheless, the American Academy of Neurology concluded from an evidence-based medical review that the construct of MCI is of great clinical utility given the higher rate of conversion of diagnosed individuals to dementia compared to undiagnosed individuals (Petersen et al., 2001). Besides that, the Diagnostic and Statistical Manual of Mental Disorders also incorporated similar concepts The fourth version of the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)" mentioned *Age-Related Cognitive Decline* in the section "Other Conditions That May Be a Focus of Clinical Attention". DSM-V, on the other hand, incorporated *Mild Neurocognitive Disorder* in the neurocognitive disorders chapter, with diagnosis criteria that are similar to MCI (Petersen, 2016).

1.3 Diagnosis

Although there are not unified guidelines to diagnose MCI, today neuropsychological assessment is seen as an useful tool to detect the condition (Kasper et al., 2020). Different options have similar diagnostic accuracy (Breton,

Casey, & Arnaoutoglou, 2019), but brief options seem to primarily identify only the amnestic subtype, whereas other types would need a more comprehensive battery (Tsoi et al., 2017). Studies using the Mini Mental State Examination (MMSE) as a gold standard show MoCA as the best tool to screen for MCI (Razak et al., 2019), but there are recommendations to not use MMSE as a measure for comparison (Breton et al., 2019). In Brazil, one study also found that MoCA is the most recommended tool to screen for dementia, but it is not so accurate when screening for cognitive decline before a dementia diagnosis or for low educational levels (Cesar, Yassuda, Porto, Brucki, & Nitrini, 2019). In these scenarios, characterized for population with a more diverse culture and education background, other options seem to have advantages, but are better for detecting dementia than MCI (Ortega, Aprahamian, Borges, Cação, & Yassuda, 2019; Razak et al., 2019). Therefore, there is still space to the development of new tools that are able to detect MCI considering its heterogeneity and considering different contexts.

At this point, it is necessary to mention and analyze use of biomarkers to reach the latter objective. Biomarkers are measurable biological indicators of a biological condition (Alzheimer's Disease International, 2018). Examples are analysis of tau and phospo-tau protein, cerebrospinal fluid, beta amyloid, fibrillar AB burden and brain imaging (Giau et al., 2019; Kasper et al., 2020). Current studies indicate that analyses of the levels of tau protein and beta amyloid in the brain can be very useful not only to detect MCI, but to define its etiology (Petersen, 2016). Biomarkers can also help define likelihood of progression from MCI to AD (Kasper et al., 2020), and even detect cognitive alterations before MCI takes place (Giau et al., 2019). Although this would make a preclinical diagnosis possible, the clinical utility and benefits of biomarkers have also been questioned (Giau et al., 2019; Parra et al., 2018). The method is accurate and valued in research settings, but the cost is high (Giau et al., 2019) and most LMIC do not have access to the equipment needed (Parra et al., 2018). High income countries (HIC) can and have been using biomarkers in research and clinical settings, but the approach seems restricted to those and some upper-middle-income countries (Parra et al., 2018).

Due to all this disadvantages and difficulties, neuropsychological assessment is still a more reasonable approach to detect MCI, especially in LMIC (Parra et al., 2018). Considering the original criteria proposed by Petersen

(Petersen, 2016), the diagnosis is made based on a complaint of cognitive decline verified by clinical analyses, such as neuropsychological assessment. It must be determined whether there are one or more areas of cognition affected, and the neuropsychological assessment is extremely useful to do so (Naidel et al., 2015). According to the original criteria, activities of daily living should also be analyzed. They should be preserved in MCI, what is helpful to make a differential diagnosis between this condition and dementia. Although this conventional criteria exists, there is not an unified approach to MCI diagnosis (Kasper et al., 2020) and different cutoff point are used to define when a cognitive domain is impaired (Jak et al., 2009). Besides that, these criteria cover a wide spectrum of profiles that are heterogeneous and can present itself as the initial stage of different dementias and affect different cognitive domains. Individuals with amnestic MCI single domain, for example, have an increased risk for developing AD. Attentional, concentration and visuospatial deficits, on the other hand, may indicate Levy's Body Dementia. Behavioral changes, inappropriate behavior and executive problems can indicate a dysexecutive MCI and possible frontotemporal dementia (Petersen, 2016). There is, however, also a possibility of staying stable or improving after a MCI diagnosis (Godinho, Camozzato, Onyszko, & Chaves, 2012). Moreover, data from autopsy and imaging studies reveal that mixed pathologies are common (Kasper et al., 2020).

Moreover, there still are other factors that can affect MCI categorization, and education is one of them (Giau et al., 2019). This is important when thinking about how MCI and dementia affects LMIC, where access to education is not the same as in HIC. In fact, a Brazilian study found a 12.7% higher rate of MCI among illiterates (Brucki, 2013), and another found a higher MCI rate also between older adults with low educational level when compared to standard rates (Dixe, Braúna, Camacho, Couto, & Apóstolo, 2020). An analysis of Brazilian older adults without dementia showed that education was the best predictor of MMSE total score and, therefore, cognitive function (Sposito, Neri, & Yassuda, 2016). Besides global cognitive functioning, executive functioning performance also might be linked to educational level, as a community sample of Rio de Janeiro showed (Araujo, Lima, Barbosa, Furtado, & Charchat-Fichman, 2018). Moreover, educational levels influenced the performance in the majority of analyzed tests regarding different

cognitive domains (Yassuda et al., 2009) and are also linked to functional disability and frailty (Brigola et al., 2019).

Findings show as well that predictors of successful aging may be different between developing countries, such as Brazil, and HIC. In the formers, socioeconomic status and social network structure may prevail over biological determinants (Chaves, Camozzato, Eizirik, & Kaye, 2009), although in a 16 years follow up study age and sex where the best predictors (Rinaldi, Souza, Camozzato, & Chaves, 2018). Therefore, besides not being able to use the same methods in research and clinical settings as HIC – such as use of biomarkers -, LMIC older adults may also be exposed to unique adverse conditions during life, leading to different patterns in aging. Actually, an epidemiological study in São Paulo, Brazil, and Buenos Aires, Argentina, found higher rates of dementia in slums when compared to developed countries (Alzheimer's Disease International, 2018). With all the difficulties presented in the screening for MCI, especially in LMIC, there is still one consensus: it is important to diagnose pathological aging in its early stages, when treatments will work best (Ritchie et al., 2017). To do so, as seen, there is a need of screening tools in primary care that are brief, easy to administer and with high sensitivity and specificity for different backgrounds (Razak et al., 2019). It is still necessary to investigate the topic and search for ways to screen for MCI as a routine procedure during aging, especially in LMIC.

Ideally, this screening would be able to detect MCI in all its heterogeneity. Therefore, the present dissertation aimed to investigate the role of two variables that are important to the early screening, comprehension and intervention planning for cognitive impairment. The first one is a cognitive variable: reaction time. Evidence suggests that reaction time and processing speed are compromised in many of the various neurodegenerative conditions (Haworth et al., 2016), therefore it could be affected in the beginning of cognitive impairment and be a homogenous variable in this heterogenous condition. The second one is related to the other criterion for MCI diagnosis: functionality. There is some controversy if ADL are intact or already impaired at the beginning of cognitive decline. A meta-analysis suggested the possibility of a continuum in the development of functional impairment, which would already begin to occur at MCI (Lindbergh, Dishman, & Miller, 2016).

But besides the discussion if there already are functional in MCI, it is also important to address if individuals are aware of eventual impairments. If not, this would not be a complaint, so could not be screened by self-report scales or be a variable for intervention planning. One example of functional deficit detection utility is an estimation that predicted a 10% reduction in life cost of individuals with dementia with an early intervention addressing functionality difficulties during one year (Jutkowitz et al., 2017). Assessing functionality when screening for MCI can, thus, not only be part of the diagnosis, but also part of early intervention planning. If these two variables can help detecting cognitive deficits at early stages, their assessment will be a method that is fast, cheap, and amenable to a large-scale application – something even more important in LMIC. After that, more complex and expensive exams could be requested to differentiate between etiologies and indicate further treatments.

1.3.1 Reaction time

The first criterion for diagnosing MCI is cognitive. Through the history of the condition, memory impairment was the first cognitive deficit reported in individuals with MCI (Petersen et al., 1999). Even today, amnestic MCI is the most studied subtype, mainly because the diagnosis is consistent with prodromal AD (Clark et al., 2013), and AD is the most prevalent dementia (Alzheimer's Disease International, 2018). But individuals with cognitive impairment can exhibit a wide range of deficits , so that the term MCI became an umbrella term for, actually, several conditions not always consistently classified (Clark et al., 2013; Jak et al., 2009; Kasper et al., 2020). In between these deficits, processing speed has been one of the cognitive variables studied (Andriuta, Diouf, Roussel, & Godefroy, 2019; Hong, Alvarado, Jog, Greve, & Salat, 2020). It might be affected more homogenously through MCI heterogeneity because it is affected in various pathological conditions (Haworth et al., 2016), and because processing speed has been seen for long as a fundamental piece of cognition, and also a key aspect of healthy aging (Salthouse, 1996). It is also related to executive functioning, since it is associated to speed of information processing and decision-making (Andriuta et al., 2019).

Processing speed can be assessed through different variables (Salthouse, 2000). Response speed or reaction time is the most used, and can be understood as the time an individual takes to issue a response after a stimulus (Booth et al., 2019). It can be measured by a mean or median of several trials, or also considering intraindividual variability (Booth et al., 2019). Although findings are not consistent, variability and reaction time are not necessarily impaired or affected at the same time or with the same severity (Booth et al., 2019). Nevertheless, concerning MCI, both measures are of interest, as studies show they can both be impaired (Hong et al., 2020; Phillips, Rogers, Haworth, Bayer, & Tales, 2013). However, reaction time is not commonly measured clinically if considered the precision required to detect changes in the begging of pathological aging process (Fernaeus, Östberg, & Wahlund, 2013; Haworth et al., 2016) and the predominance of paper and pencil neuropsychological assessment (J. Miller & Barr, 2017).

1.3.1.1 Reaction time and computerized tests

Pencil and paper neuropsychological tests hardly have precise reaction time measurements. But this is an advantage that stands out among computerized tests: specific and complex variables, such as reaction time, can be measured even in milliseconds (Charchat, Nitrini, Caramelli, & Sameshima, 2001). However, there is a little use of computerized tests in the context of neuropsychology: this clinical practice still relies primarily on pencil-and-paper tests and the use of technologies is quite rare despite the various advantages they can bring (Marcopulos & Łojek, 2019; Rabin et al., 2014; Schmand, 2019).

Among the advantages of computerized tests, Miller and Barr (J. Miller & Barr, 2017) mention the more precise control over the administration and scoring of tests; the dynamic and colorful interfaces which add a new form of interaction; the possibility of more accurately measuring response times throughout the evaluation process; the superior control of time and order of presentation of stimuli; the possibility of developing several forms of the same test; the reduction of financial costs, with the reduction of the use of papers and the time of administration and training of professionals when compared to traditional tests; and the reduction of possible bias in the examiner's application and the possibility of errors on the part of the examiner thanks to automatic correction.

In order to measure reaction time and cognitive impairment, one of the studies presented on this dissertation used a battery of computerized tests for neuropsychological assessment that take advantage of all these benefits: CompCog. CompCog uses an iPad interface, and all responses are registered using a touchscreen. During each test, the type of response and reaction time in milliseconds are recorded. As mentioned earlier, subtle cognitive changes in MCI include variations in processing speed (Haworth et al., 2016), which are expected to be detected by this test (Charchat et al., 2001).

1.3.1.1.1 CompCog

CompCog was initially called Bateria de Testes Neuropsicológicos Computadorizados (BTNC; Brazilian Portuguese version; Charchat, 1999). It was created using the MEL Professional version 2.0 (Schneider, 1995) to evaluate anterograde episodic memory, attention, visual perception, processing time information and short-term memory. The first study concerning it investigated clinical markers of early AD. Forty individuals with mild AD and 73 controls, paired for age and education, were studied. The battery had six tests, and the application lasted 40 minutes on average. It was run on an IBM-PC compatible microcomputer using a 14-inch SVGA color monitor. A keypad with five buttons, labeled from 1 to 5, was used as a response input device. The AD group showed a significantly lower percentage of correct response on episodic memory and short-term memory and higher latency response on all other tests when compared to controls. The ROC analysis showed that episodic memory, short-term memory and choice reaction time tests were sensitive and specific to discriminate the groups, and therefore were clinical markers of early AD (Charchat et al., 2001)

After that study, a screening version of the instrument was created. It took only 15 minutes to be administrated and was named Computerized Cognitive Screening test – CompCogs. CompCogs had the same material as BTNC, was developed with MEL Professional, was run on an IBM-PC and had the same keypad with five buttons as a response input device. The CompCogs was applied in 47 individuals with probable mild AD and 97 controls. The idea was to investigate its validity for the early diagnosis of AD. CompCogs presented 91.8% sensitivity and 93.6% specificity for the diagnosis of AD using ROC analysis of AD diagnosis

probability derived by logistic regression. It showed high validity for AD early diagnosis and, therefore, may be a useful alternative screening instrument (Fichman, Nitrini, Caramelli, & Sameshima, 2008).

In 2011, CompCog was developed for mobile devices that operate on iOS operating system maintaining the original ideas of evaluation, but now with a new way of interaction – the touchscreen, more dynamic interface, and with the possibility to be carried out in the iPad. This new version is broad and flexible. Although there is a suggested order of application, the examiner can select the tests and their order. It is composed of eight tests that evaluate different cognitive domains such as speed of information processing and reaction time, implicit, episodic, and working memory, attention and inhibitory control. Battery administration lasts about 40 minutes in healthy individuals.

The test is available in Portuguese, Spanish and English. Demographical data is collected at the beginning, including full name, age, education, sex, and handiness. Results of each test are presented at the end of each application and at the end of the whole battery. All data is stored in the cloud and are available in an Excel spreadsheet accessible through the test's website. All answers are issued using touch screen and recorded and all tests generate reaction time measures that are registered in milliseconds for each touch, total time and as a median, to eliminate eventual discrepant data through each test. Furthermore, correct responses percentage, errors, and differences in reaction time between errors and correct answers are also registered. All stimuli tests are visuospatial, except for one test - Stroop Test, which contains written words in order to maintain the original paradigm.

This research used the test' standard tasks' order in Portuguese during all the data collection phase. They are explained below:

1. Simple reaction time assesses speed of information processing total time and median reaction time. The instructions are "Press the rectangle as soon as the white square appears. Be as fast as you can". There is a white rectangle at the bottom of the screen. As soon as a white square appears in the middle of the screen, the person should touch the rectangle.

2. Choice reaction time assesses speed of information processing through reaction time and percentage of correct responses. The instructions are: “Press the rectangle with the same color of the square. Be as fast as you can. Use only the forefinger to touch the screen”. There are two rectangles, a white and an orange one, at the bottom of the screen. As a white or orange square appears in the middle of the screen, the person should touch the rectangle of the same color.

3. Implicit learning test is a measure of implicit memory. The instructions are: “Touch the white square when it appears. Be as fast as you can. Use only the forefinger to touch the screen”. There are 10 gray squares distributed on the screen. One square becomes white at a time and, as the person touches it, another one lights up. There is a fixed sequence of 25 squares that is repeated 4 times and one last random sequence of also 25 squares. The difference between reactions of subsequent sequences are used as an implicit learning measure.

4. Visual and spatial short-term memory assesses working memory through reaction time and digit SPAN. The instructions are: “Touch the squares in the same order as they appear. Use only the forefinger to touch the screen”. There are, as there were in the last test, 10 gray squares distributed on the screen. One will become white at a time, making a sequence that must be reproduced. The sequence increases in number if the person gets two of four attempts right. The test starts with a message stating the type of sequence – first forward and then reverse - and the number of squares that will appear in sequence - from 2 to 8. When the forward sequences end, the reverse sequences starts. Results are measured by the span reached.

5. Face recognition and memory is a measure of immediate and delayed visual memory with clues assessed through the percentage of correct answers and of learning through reaction time. At first, 10 drawings of unknown faces are presented for 30 seconds on the screen with the instruction “Memorize the faces”. After that, another instruction appears: “Touch the face you memorized”. The participant should choose between 10 pairs of faces which one was among those initially shown for memorization. The task is repeated three times in a row and again after 20 minutes.

6. Inhibitory control test assesses inhibitory control and attention through reaction time and the percentage of correct responses and errors. The instructions are: “Touch all squares but don’t touch the white square. Use only the forefinger to touch the screen”. Squares of different colors will appear in the middle of the screen for one second each, white ones should be avoided.

7. Stroop test is a measure of selective attention and inhibitory control through time and errors. This test includes three tasks, like the original Stroop paradigm(Stroop, 1935). All tasks have 4 rectangles (green, red, blue and yellow) located at the bottom of the screen. The person should touch the one matching the stimuli that appears in the middle of the screen considering its color. While task one doesn’t have any distracters, with the stimuli being just a colored square, in task 2 the stimuli are fruit names written in different colors than the actual color of the fruit, and in task 3, color names that are written in another color. The instructions of each task are: “Press the button with the same color of the square color on screen center” for task one and “Press the button corresponding to the color in which the text is written” for tasks two and three.

8. Survey test assesses attention as the ability to search for a stimulus. This test consists of three tasks with a crescent number of target stimulus. The instructions are: “Tap only the white square” for the first task, “Tap the white or blue square” for the second and “Tap the white or blue or yellow square” for the last one. Squares of different colors will appear in the middle of the screen for one second each. Results are measured by reaction time and the percentage of errors and correct answers.

1.3.2 Activities of daily living

Besides having cognitive criteria, the original concept of MCI also required preserved functionality or ADL (Petersen, 2016). ADL refer to tasks that are performed daily in order to maintain an independent life and a preserved functional capacity. It is usually divided in basic, instrumental and advanced activities (Cornelis, Gorus, Van Schelvergem, & De Vriendt, 2019; Njegovan, Man-Son-Hing, Mitchell, & Molnar, 2001). Advanced ADL (aADL) are related to the most complex activities, such as maintaining hobbies or a social life. Instrumental ADL (iADL) also have some complexity, for example preparing meals and dealing with

money, but refer to more day-to-day functional activities. Finally, basic ADL (bADL) have to do with to self-care activities, such as bathing or eating. Impairment in any level can cause disability and, without the development of compensatory strategies to offset these difficulties, lead to dependence and decreases in the quality of life of people with dementia and their caregivers (Alzheimer's Association, 2018).

At first, having deficits in ADL were the distinguishing criterion between MCI and dementia (Petersen, 2016). But later evidence suggests that subtle changes already begin to occur in MCI, especially regarding complex activities (Cornelis et al., 2019; De Vriendt et al., 2012; Giovannetti, Bettcher, Brennan, Libon, Burke, et al., 2008; Lee, Jang, & Chang, 2019; Lindbergh et al., 2016). Other study (Winblad et al., 2004), proposed the inclusion of "preserved basic activities of daily living (ADL)/some minimal impairment in complex instrumental function" in the diagnostic process. Since then, the literature questioning the presence or not of difficulties in everyday abilities in MCI groups has grown (Pereira et al., 2010; Schmitter-Edgecombe & Parsey, 2014b, 2014a). Today, there are still not unified guidelines to diagnose MCI (Kasper et al., 2020). It is known, however, that there is a progressive loss of functional capacity in the course of dementia (Cornelis et al., 2019; Mograbi et al., 2017; Slachevsky et al., 2019). But previous studies provide conflicting results in relation to the extent to which functional capacity is affected at each moment of the condition (Giebel, Sutcliffe, & Challis, 2017; Mlinac & Feng, 2016; Okonkwo, Wadley, Griffith, Ball, & Marson, 2006; Schmitter-Edgecombe & Parsey, 2014a). When cognitive decline reaches the threshold for the diagnosis of dementia, functionality is undoubtfully already compromised (Schmitter-Edgecombe & Parsey, 2014a).

1.3.2.1 Activities of daily living assessment

There are many ways to measure functionality, and usually an instrument is focused in one level. Although scales are the most used tool, there are also performance-based tests and even in-home monitoring sensor technologies (Lussier et al., 2019). With regard to scales, there are many options available to measure the different levels. Some examples widely used are the Lawton Instrumental Activities of Daily Living Scale developed by Lawton & Brody (Lawton & Brody, 1969) and

the Pfeffer's Functional Activities Questionnaire (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) to measure iADL; the Katz Activities of Daily Living (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) to measure bADL; and the Advanced Activities of Daily Living scale (Reuben, Laliberte, Hiris, & Mor, 1990) to measure aADL. Using report scales is the most convenient and practical way to measure ADL, and evidence shows they are usually correlated to cognitive scores (S. Miller, Brown, Mitchell, & Williamson, 2013).

But there are also downsides to this type of assessment. There is evidence indicating that informant- and self-report often differs substantially within dementia samples (Clare et al., 2012; DeBettignies, Mahurin, & Pirozzolo, 1990; Mograbi et al., 2017). Self-report also does not always correspond to objective measures of cognitive functioning (Michon, Deweer, Pillon, Agid, & Dubois, 1994; Tierney, Szalai, Snow, & Fisher, 1996), and there is considerable variability in the degree to which dementia individuals and their caregivers differ regarding their report (Reed, Jagust, & Coulter, 1993; Tierney et al., 1996). One potential issue leading to heterogeneity of results may be that individuals with dementia do not fully acknowledge the extent to which they have functional impairments. This lack of awareness about the diagnosis and its consequences, also termed anosognosia (Mograbi & Morris, 2018), is common in dementia (Mograbi et al., 2012). Although findings are mixed, it has been shown that people with MCI may also have limited awareness about their abilities (Tabert et al., 2002). This could suggest that the use of informant-based measures may be a better option when assessing functional abilities, but studies show informants can underestimate abilities due to stress and caregiver burden (Okonkwo et al., 2008).

In this context, performance-based measures can provide more objective data when compared to report scales (Mlinac & Feng, 2016). The assessment by performance-based measures requires various ADL activities to be performed in front of the examiner (Schmitter-Edgecombe, Woo, & Greeley, 2009). However, direct measures permit observation of only a small excerpt of real-world performance and are quite time consuming (Jekel et al., 2015). Actually, when compared to real-life monitoring, performance-based measures present different results (Lussier et al., 2019). Other downsides that can influence individual

performance are the novelty of the environment and even the presence of the evaluator (Lussier et al., 2019). Examples of performance-based tools used to assess functional capacity in older adults are the UCSD Performance-based Skills Assessment (UPSA), whose results have correlation to cognitive measures and evaluates 5 domains (comprehension and planning, finance, communication, transportation and household chores) (Becattini-Oliveira, Portela Câmara, Dutra, Sigrist, & Charchat-Fichman, 2019); and the Revised Observed Test of Daily Living, which evaluates medication management, using the telephone and managing finances, but does not have correlation to cognitive performance (Schmitter-Edgecombe & Parsey, 2014b). All types of assessment have downsides and benefits, and the evaluator must be aware of them to choose the best option for a given objective and interpret the results correctly, whereas for diagnosis purposes or for intervention planning.

1.3.2.2 Activities of daily living awareness

One issue regarding measures that are not objective is that lack of awareness may produce an inaccurate result. Is it well known that individuals with dementia are usually not fully aware of their functional disabilities (Mograbi et al., 2017). Because of that, objective measures would be more recommended to this kind of patient. Nevertheless, ADL performance is assuredly compromised in dementia (American Psychiatric Association, 2013), so detecting functional impairment may be less of a challenge in this condition. When investigating MCI or other initial cognitive decline, it becomes more important that the assessment is precise and able to detect subtle changes (Mlinac & Feng, 2016).

Generally, studies investigating the topic use the comparison between self-report and informant-report, or self-report and performance-based measures, to answer if individuals with MCI are aware of their deficits (Farias, Mungas, & Jagust, 2005; S. Miller et al., 2013; Mograbi et al., 2017; Okonkwo et al., 2008; Suchy, Kraybill, & Franchow, 2011). Both comparisons have advantages and disadvantages. While performance-based measures are more objective, they are not perfect when estimating real life performance (Lussier et al., 2019). Comparisons to informant-report scales, on the other hand, may be influenced by caregiver burden (Okonkwo et al., 2008), but studies show its results are correlated to

patient's cognitive function and more accurate than self-reports (S. Miller et al., 2013). Findings are mixed, and therefore needs further investigation. This variation may be partially explained by some confounding variables, such as depression (Suchy et al., 2011) and cognitive level within MCI samples (Jak et al., 2009).This dissertation will use the comparison between self-report and informant-report to address awareness, while controlling for depression and educational level to minimize the impact of confounding variables, as well as using a MCI criteria (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006) that embraces even light levels of cognitive deficit in the cognitive profile classification.

1.3.3 Reaction time and activities of daily living awareness

The two variables under investigation, reaction time and awareness of ADL performance, are not only relevant to the concept of MCI, but may also be connected. This connection relies on the relation between reaction time, executive functions, and functional performance. As mentioned, reaction time is one of the many measures of processing speed (Booth et al., 2019), and processing speed is a subcomponent of executive functions (Cornelis et al., 2019). Different studies describe the relations between processing speed, under the measures of reaction time or others, and ADL performance (Gulde, Schmidle, Aumüller, & Hermsdörfer, 2019; McAlister, Schmitter-Edgecombe, & Lamb, 2015; McDougall, Han, Staggs, Johnson, & McDowd, 2019). One study used instruments such as Trail Making Test and Animal Fluency test, both dependent on time performance, to investigate its relation to functionality, and found that ADL are more impaired in people with higher executive deficits in these instruments (Cornelis et al., 2019). Other studies related error reaction time (Chen, Weng, Hsiao, Tsao, & Koo, 2017), intravariability in reaction time (Haynes, Bauermeister, & Bunce, 2017), alterations in action initiation and reaction time of decision making (Andriuta et al., 2019), or even walking speed (Hackett, Davies-Kershaw, Cadar, Orrell, & Steptoe, 2018) to deficits in executive functions and ADL performance.

There are some definitions that can help deepen the topic. In general, evidence suggests that executive functioning is the best predictor of functional capacity (Cornelis et al., 2019; Okonkwo et al., 2006), but there is also evidence that deterioration in the ability to perform everyday tasks could be related to a general

cognitive impairment (Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008). To understand this difference, it is useful to differentiate between commission errors (performing a step incorrectly during a task) and omission errors (not performing a step at all). Actually, evidence shows only the latter error is related to a deficit in general cognitive resources (Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008). Besides general impairment, other studies found that omission errors seem to be also linked to memory impairment (Giovannetti, Bettcher, Brennan, Libon, Burke, et al., 2008; Schmitter-Edgecombe & Parsey, 2014a). Therefore, comission and omission errors would be different components of ADL impairment, and could be uncorrelated since dependents on different cognitive domains (Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008).

With regards to processing speed specifically and both types of errors, omission errors – not performing a step – might actually decrease the time spent in a task, but might also prevent it from being completed correctly. Commission errors, instead, can increase time spent in an activity, because a step is, for example, performed more than once or in a less proper way because of executive functions' deficits (Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008). Therefore, the task can be completed, but in more time, because some types of errors generate longer responses, either because of a longer reaction time in the step of decision making (Andriuta et al., 2019), or because the individual needs more time to do the same task (Okonkwo et al., 2006). If reaction time increase is part of ADL performance decline, the awareness of this decline may also be related to cognitive performance. Looking at the literature with regard to awareness of deficits, one study found that anosognosia is linked to memory impairment due to a lack of updating of personal information (Mograbi, Brown, & Morris, 2009), and another study results showed that individuals with poorer global cognitive performance overestimated their functional performance (Okonkwo et al., 2008).

Considering the latter cognitive correlates of unawareness, and that only omission errors are related to global cognitive decline and memory impairment (Giovannetti, Bettcher, Brennan, Libon, Burke, et al., 2008; Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008; Schmitter-Edgecombe & Parsey, 2014a), therefore only those would be linked to overestimation of performance. Comission errors, linked to executive deficits - such as reaction time – would still be perceived

and reported by individuals during assessments because this type of cognitive impairment does not seem to be linked to anosognosia (Starkstein, Sabe, Cuerva, Kuzis, & Leiguarda, 1997; Suchy et al., 2011). These are all theoretical propositions of relations between reaction time and ADL performance awareness that need further investigation. But, since both are part of a context influenced by executive functioning, global functioning, errors in tasks and task completion, it is not unlikely that the variables cross its paths considering cognitive functioning and the processes it generates. This relation will be further explored in the conclusion of this work.

2. OBJECTIVES

According to the theoretical background presented, this dissertation is composed of two studies with the following objectives:

- To verify the diagnostic accuracy of CompCog's variables for mild cognitive impairment (MCI).
    - Check the sensitivity and specificity of each CompCog task for the diagnosis of MCI.
    - Check the sensitivity and specificity of the CompCog test set for the diagnosis of MCI.
- To verify activities of daily living impairment awareness in different profiles of cognitive impairment.
    - Analyze the awareness of impairment in instrumental activities of daily living through the difference in perception between informant- and self-report in Lawton's Instrumental Activities of Daily Living Scale.

3. ARTICLES SECTION

ARTICLE 1

Marques, L; Martorelli, M; Balboni, Giulia; Araujo, V; Charchat-Fichman, H. Discrepancies between self- and informant-report in a functionality measure in three neuropsychological profiles (in preparation).

Discrepancies between self- and informant-report in a functionality measure in three neuropsychological profiles (in preparation)

1. Introduction

The aging of the population has dramatically increased in recent decades (The United Nations Population Division, 2019), and age is the strongest risk factor for dementia (Alzheimer's Disease International, 2018). Currently, more than 45 million people live with dementia, which has become a major public health challenge (Alzheimer's Association, 2018). The term *dementia* refers to a syndrome typical to a group of diseases of a chronic nature. It involves cognitive decline and loss of functional capacity (American Psychiatric Association, 2013). Functional capacity is the ability to perform basic, instrumental and advanced activities of daily living (ADL; World Health Organization, 2011). Everyday practical capacities are essential for the older adults to maintain their independence (Book, Luttenberger, Stemmler, Meyer, & Graessel, 2018). Basic ADLs (bADL) refer to self-maintenance skills such as feeding and dressing, while instrumental ADLs (iADL) refer to more complex self-care tasks such as cooking, using the telephone, housekeeping, and managing medication regimes (Book et al., 2018). There is also the concept of advanced ADLs (aDL), that includes more social activities and hobbies (De Vriendt et al., 2012).

When considering ADL and its measurement in neurodegenerative condition, dementia is known to have an impact on ADL differently according to its level of complexity. It is common to see impairments in iADL at early stages of cognitive decline, for example in mild cognitive impairment (MCI), but bADL are affected later in the course of the condition (Mlinac & Feng, 2016; Njegovan et al., 2001). Nevertheless, this relationship may not be linear, with some evidence suggesting that iADL are less preserved than even some more aADL in some individuals (Takechi, Kokuryu, Kubota, & Yamada, 2012).In fact, the initial diagnostic criteria for MCI included intact everyday functional activities (Petersen et al., 1999). But later evidence (Winblad et al., 2004) proposed the inclusion of "preserved basic activities of daily living/some minimal impairment in complex instrumental function" in the diagnostic process. Ever since, the literature

demonstrating the presence of difficulties in everyday abilities in PwMCI groups has grown (Lee et al., 2019; Lindbergh et al., 2016).

The assessment of ADL is frequently done by using rating scales, which are administered either to the individual or a proxy (Albert et al., 1999; Okonkwo et al., 2008; Tabert et al., 2002). Another option is the assessment by performance-based measures, that requires various ADL to be performed in front of the examiner (Glosser et al., 2002; Jefferson, Paul, Ozonoff, & Cohen, 2006; Mariani et al., 2008; Schmitter-Edgecombe et al., 2009; Senanarong et al., 2005; Tuokko, Morris, & Ebert, 2005). Both options bring benefits and downsides. Direct measures permit observation of only a small excerpt of real-world performance and are quite time consuming (Jekel et al., 2015). Other downsides that can influence individual performance are the novelty of the environment and even the presence of the evaluator (Lussier et al., 2019). With regard to scales, self-report does not always correspond to objective measures of cognitive functioning (Michon et al., 1994; Tierney et al., 1996), and, there is considerable variability in the degree to which people with dementia (PwD) and their caregivers differ regarding their report (Reed et al., 1993; Tierney et al., 1996). Usually, this is interpreted as if individuals with dementia are not aware of their impairment (Mograbi et al., 2017).

With regard to MCI, there is controversy about the ability of individuals with the condition to rate themselves adequately, as they also may lack awareness of ADL deficits and overestimate their functional capacity (Albert et al., 1999; Okonkwo et al., 2008; Tabert et al., 2002). Typically, research that investigate this topic uses comparisons between self- and informant-report of scales assessing iADL to achieve the goal of understanding awareness of functional deficits in people with MCI (PwMCI) (Farias et al., 2005; Suchy et al., 2011). This study will follow the same pattern and analyze differences between self-report and caregivers report in iADL measures. The chosen instrument, the Lawton Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969) is the most common iADL questionnaire for the older adults (Sikkes, De Lange-De Klerk, Pijnenburg, Scheltens, & Uitdehaag, 2009), is broadly used in Brazil (Santos & Virtuoso Júnior, 2008), and has both self- and informant-report. The comparison will be made considering three independent neuropsychological profiles classified by cognitive performance: PwD, PwMCI and control participants.

2. Methods

Setting and procedures

The participants of the present study were obtained after participating in a larger study under an agreement between Pontifical Catholic University of Rio de Janeiro and a social program offered by the government of Rio de Janeiro (Casas de Convivência e Lazer para Idosos) (Araujo et al., 2018). The program offers daily activities for older adults during the day, in houses located in different neighborhoods of Rio de Janeiro. Some examples of activities are physical exercises, stretching, yoga, dance, cognitive stimulation, crafts, theater, etc. The project aimed to define, through a cognitive screening and with no diagnostic intent, neuropsychological and functional profile of the population.

To do so, older adults were evaluated through a brief neuropsychological assessment. The evaluation was done by researchers and psychologists, who were supervised weekly. It lasted one hour and was held in a quiet room in the houses where the social program commonly took place. During the assessment, cognitive tests and scales were used to assess cognition and depressive symptoms. Lawton Instrumental Activities of Daily Living Scale was used to assess functionality (Araujo et al., 2018; Brucki, Nitrin, Caramelli, Bertolucci, & Okamoto, 2003; Nitrini et al., 1994). The latter was filled out by the individuals and an accompanying person who were indicated by the individual. All instruments are described in the corresponding section below. After this first stage, individuals that went through the entire assessment were selected to the present study. Cognitive tests results were used to classify the individuals in different neuropsychological profiles, and the Lawton Instrumental Activities of Daily Living Scale results were used in the comparative analyses.

Participants

The original sample consisted of 470 older adults. The inclusion criteria were: (1) participants who were older than 60 years old, (2) who agreed to participate in the study, (3) and who understood and signed an informed consent form. The exclusion criteria from the original study were severe hearing or visual impairment that would make communication difficult.

To the present study, another exclusion criterion was added: the absence of informant-report in Lawton's Instrumental Activities of Daily Living Scale. This last criterion was responsible for eliminating 233 individuals, leaving a sample of 237 older adults that were divided in three groups – as explained in Neuropsychological profile section below. In order to pair the groups with respect to sex, age, depressive symptoms and educational level (in years), 12 individuals were randomly eliminated – as explained in Statistical analysis section below. The resulting sample consisted of 225 individuals, divided in control group (CG), people with mild cognitive impairment cognitive profile (PwMCI) and people with dementia cognitive profile (PwD).

Of the 225 individuals, 73 were classified as CG, with mean age 72,12 (6,40), mean years of education 9,01 (4,16), mean number of depressive symptoms 2,47 (2,82) and 89% women; 107 were classified as PwMCI, with mean age 72,28 (6,55), mean years of education 7,84 (4,52), mean number of depressive symptoms 2,91 (3,33) and 87,9% women; and 45 classified as PwD, with mean age 74,71 (7,01), mean years of education 7,17 (4,82), mean number of depressive symptoms 2,88 (2,46) and 86,7% women.

Instruments

The evaluation used to determine the neuropsychological profile of the older adults was done through the Brief Cognitive Screening Battery (BCSB; Nitrini et al., 1994). This tool is commonly used in Brazil for cognitive screening, and it is not greatly affected by education (Araujo et al., 2018), an important feature for LMIC or even regions for developed countries populations that may have individuals with different educational backgrounds. The battery is adapted to Brazilian population and norms are available. It consists of the Figure Memory test, Semantic Verbal Fluency test (animals' category), Clock Drawing test, Lawton Instrumental Activities of Daily Living Scale, Pfeffer Functional Activities Questionnaire, and Geriatric Depression Scale (GDS-15). The Mini Mental State Examination (MMSE) was used to measure general cognitive functioning. Lawton Instrumental Activities of Daily Living Scale and Geriatric Depression Scale were not used to define neuropsychological profiles since the first was the dependent

variable of the analysis and the later was used to confirm the absence of difference between groups regarding number of depressive symptoms.

The Figure Memory test (Araujo et al., 2018; Nitrini et al., 1994) consists of a sheet of 10 simple drawings of common objects (i.e., shoe, house, comb, key, airplane, bucket, turtle, book, spoon, and tree) that are named by the examiner and then recalled immediately by the individual. The individual is then presented with the drawings two more times and then asked each time to remember and say as many drawings as possible. After an interval of 5 minutes, when other tests are performed, the individual is asked again to remember and say the figures names. Finally, the recognition task is performed with a sheet of paper that contains the 10 figures first seen and 10 other distracting figures. The individual is asked to recognize which figures were presented previously.

In the Semantic Verbal Fluency test (animals' category), the individuals are asked to say as many animals as possible, as quickly as possible, in 1 minute (Araujo et al., 2018; Nitrini et al., 1994; Tombaugh, Kozak, & Rees, 1999).

In the Clock Drawing test, the individuals are asked to draw a clock with all the numbers and the watch hands marking 2:45 (2 hour and 45 minutes). Scores are calculated based on the criteria adapted from Sunderland and coworkers (Araujo et al., 2018; Nitrini et al., 1994; Sunderland et al., 1989).

The MMSE is widely used to assess global cognitive function in Brazil (Brucki et al., 2003). In the present study, we used the score of 30 (MEEM-30; Araujo et al., 2018; Folstein, Folstein, & McHugh, 1975).

Lawton's Instrumental Activities of Daily Living Scale and the Pfeffer Functional Activities Questionnaire assess the independence of the older adults with regard to instrumental activities of daily living (Lawton & Brody, 1969; Pfeffer et al., 1982; Sanchez, Correa, & Lourenço, 2011; Santos & Virtuoso Júnior, 2008). For the Lawton scale, the older adults and their companion answered the questionnaire. Both the self- and the informant-report have to answer, in a scale between 1 and 3, how independent the person is when using the telephone, using transportation, preparing food, handling medications, handling finances, doing housekeeping and shopping. Results range from 7 - completely impaired - to 21 –

completely functional. Differences between the two results were calculated to create the variable *perception discrepancy.* Although the Pfeffer questionnaire is also part of the BCSB, results were not used because it assesses the same variable and could influence the main analysis.

The GDS-15 is a shortened version of the original 30-item instrument, which has presented good sensitivity and specificity for screening depressive symptoms (Paradela, Lourenço, & Veras, 2005; Yasavage & Sheikh, 1986).

Neuropsychological profile

The neuropsychological profiles were defined based on the performance in the BCSB (Araujo et al., 2018; Nitrini et al., 1994). The variables used can be seen in table 1. After calculating the Z scores with Brazilian norms (Araujo et al., 2018) for each variable, individuals were classified in three neuropsychological profiles (CG, PwMCI, PwD) by the MCI modified criteria proposed by Busse et al. (Busse et al., 2006).

Table 1 – Variables used in neuropsychological profile definition

Test	Variables	Cognitive function
MMSE	Global score	Global cognition measure
Figure Memory test	Naming, incidental memory, immediate memory, learning, late memory, and recognition	Memory
Semantic Verbal Fluency test	Global score	Fluency
Clock Drawing test	Global score	Executive function

Ethics

This study was approved by the Research Ethics Committee (opinion no. 965.264). The volunteers participated in the study by signing a free and informed consent form, according to the resolution 196/96 of the National Health Council of Brazil, which deals with guidelines and standards for research involving human individuals. Participation in this survey was voluntary, so the participants did not

receive any payment. The study did not bring any risk to the health of volunteers and they could refuse and/or withdraw consent to participate in the study at any time.

Statistical analysis

All data entry and analyses were carried out with the Statistical Package for Social Sciences (SPSS, version 22). Descriptive statistics were done regarding each neuropsychological profile separately. The main comparisons were done after verifying if the data was parametric through Shapiro–Wilk test. Only the variable age was normal and compared with One-Way ANOVA. Kruskal Wallis followed by Mann-Whitney tests were performed to compare non-parametric data: years of education, number of depressive symptoms and each pair, in raw scores, considering (1) self-report in Lawton's Instrumental Activities of Daily Living Scale, (2) informant-report in the same scale and (3) the difference between these two, named perception discrepancy. A chi-square test verified the difference between groups regarding gender. P values under 0.05 were considered significant.

3. Results

There were no significant differences between groups regarding sex ($H(2) = .153$; $p = .926$), age ($F2{,}222 = 2{,}581$, $p = .078$), educational level ($H(2) = 5.552$; $p = .062$) and number of depressive symptoms ($H(2) = 2.198$; $p = .333$). Performance in neuropsychological assessment normative mean scores and raw means scores in Lawton's Instrumental Activities of Daily Living Scale can be seen in table 2 for each neuropsychological profile. Comparisons between self-, informant-report and perception discrepancy are reported on table 3.

Table 2 – Neuropsychological assessment and Lawton's Instrumental Activities of Daily Living Scale mean scores

Neuropsychological profile	CG (N=73) M (SD)	PwMCI (N=107) M (SD)	PwD (N=45) M (SD)
MMSE30	0,20 (0,91)	-0,52 (0,83)	-0,89 (0,87)
Nomination	-0,07 (1,29)	0,17 (0,35)	-0,13 (0,95)

Incidental memory	0,25 (0,88)	-0,15 (1,04)	-0,72 (1,16)
Immediate memory	0,25 (0,78)	-0,45 (1,09)	-1,15 (1,16)
Learning	0,26 (0,66)	-0,39 (0,94)	-1,35 (1,35)
Delayed recall	0,32 (0,65)	-0,39 (0,78)	-1,33 (1,12)
Recognition	0,26 (0,34)	-0,16 (0,69)	-1,08 (2,03)
Clock drawing test	0,27 (0,96)	-0,47 (0,90)	-0,58 (1,01)
Verbal Fluency	0,04 (0,80)	-0,63 (0,90)	-0,88 (0,72)
Lawton Self-report	20.46 (1.13)	20.19 (1.26)	19.53 (2.37)
Lawton Informant-report	20.35 (1.47)	20.06 (1.34)	18.77 (2.92)
Perception discrepancy	-0.11 (0.85)	-0.13 (1.19)	-0.756 (1.68)

Table 3 – Comparisons between groups in self- and informant-report and their differences

	All groups	**PwMCI and CG**	**PwD and CG**	**PwD and PwMCI**
Self-report	*H*(2) = 20.363; *p* = .005**	*U* = 3307.0; *Z* = -2.034; *p* = .042*	*U* = 1147.5; *Z* = -3.157; *p* = .002**	*U* = 2015.0; *Z* = -1.739; *p* = .082
Informant-report	*H*(2) = 10.424; *p* < .000**	*U* = 3210.0; *Z* = -2,278; *p* = .023*	*U* = 921.5; *Z* = -4.375; *p* < .001**	*U* = 1706.5; *Z* = -3.004; *p* = .003**
Perception discrepancy	*H*(2) = 6.065; *p* = .048*	*U* = 3782.0; *Z* = -.430; *p* = .667	*U* = 1314.0; *Z* = -2,079; *p* = .038*	*U* = 1904,0; *Z* = -2,237; *p* = .025*

*p < .05; ** p < .01

4. Discussion

Looking at the data and considering the continuum CG>PwMCI>PwD for cognitive decline, some important points can be raised. There seems to be initial difficulties regarding iADL in PwMCI that both individuals and informants agree to. The difficulties get worse in PwD, but individuals no longer perceive them the same way their informants do. Results have shown a gradual decrease in the informant-report through the continuum between CG, PwMCI and PwD, with significant differences between all groups. Regarding self-report, the differences

between groups were significant only in the first two comparisons (PwMCI and CG; PwD and CG). PwD and PwMCI did not perceive their IADL performance differently. Perception discrepancy showed an opposite pattern than self-report. PwMCI and CG perception discrepancy did not differ. Further on in the disease continuum, the discrepancy increased and became significantly different in the other two comparisons (PwD and CG; PwMCI and CG). It is also interesting to notice that, although significantly different, there is only a small decline in scale's results between all groups, suggesting the decline in functional capacity is very sutble.

In the comparisons between PwMCI and healthy controls of CG, self-report and informant-report were significantly different. But the discrepancy between perceptions were not significant. This result suggests that there already is a decrease in iADL regarding people with neuropsychological profile of MCI in comparison to healthy individuals. This is backed by literature (Giovannetti, Bettcher, Brennan, Libon, Burke, et al., 2008; Lindbergh et al., 2016), although at first the MCI construct did not involve any ADL deficits (Petersen, 2016). It is well established that functional deficits are caused by cognitive decline, so some impairment in ADL in PwMCI is expected. Looking at the neuropsychological assessment means (table 2), it is possible to see in the present sample that performance in executive functions have a bigger decrease from CG to PwMCI than from PwMCI to PwD. Memory has a different pattern, with a more gradual decrease in the continuum. In general, day-to-day functioning is linked to executive performance (Cornelis et al., 2019). But, as seen in other studies (Starkstein et al., 1997; Suchy et al., 2011), light executive deficits does not seem to be linked to lack of awareness and anosognosia. Thus, even if there are some initial functional and executive deficits in the MCI condition, individuals are as aware of it as their caregivers. The cognitive decline responsible for decrease of functional capacity in this group may not be severe enough to affect awareness, as it is in dementia (Mograbi et al., 2017).

But this is not true when cognitive impairment reaches the threshold of dementia. PwD and PwMCI did not differ considering self-report. In line with the above, there is some perception of functional decline in the continuum between healthy aging and dementia, but results suggest consciousness decreases when

PwMCI convert to the latter. Again, this follows the literature (Farias et al., 2005; Mograbi et al., 2017). Caregivers continue to perceive the gradual decline, as can be seen considering the significant difference in informant-report between PwD and PwMCI. This also creates a discrepancy between both measures, again suggesting that a lack of awareness begins only with the onset of dementia.

In the comparisons between the beginning and the end of the cognitive impairment continuum, PwD and CG differed in all analyses. Self-report, informant-report, and discrepancy between both showed significant differences. Functional decline is well established in PwD (Parra et al., 2018; Slachevsky et al., 2019), so differences were expected. It is interesting to notice that differences were also found regarding self-report. Normally, as said, PwD do not have consciousness about their functional disability (Mograbi et al., 2017). Thus, one may think there should be no significant differences between conditions considering self-report. This result can be explained, however, by the fact that in the continuum between healthy aging and dementia there is the MCI condition. As seen above, PwMCI perceived a decrease in their iADL abilities. The awareness of these *specific deficits* continues in dementia condition even though *new deficits* developed latter may remain unnoticed.

To summarize, results imply deficits in iADL begin to take place already in MCI neuropsychological profiles and are perceived both by the older adults and their caregivers, even though some cognitive impairment has already taken place. After conversion to dementia, however, the discrepancy increases and a lack of awareness of the functional decline follows. This results help to solidify three important definitions to pathological aging: first, that individual with initial cognitive deficits, characterizing an MCI neuropsychological profile, already have some functional deficits, are aware of then and it can be measured with instruments as simple as report scales, either for diagnostic purposes or for planning interventions; second, informant-report or other instruments are more recommended then self-report when assessing individuals with dementia ADL performance; and third, that functional assessment is useful as part of an evaluation when screening for dementia and prodromal dementia.

Therefore, screening for MCI and assessing functionality with an instrument as simple as a self-report can be part of the screening for initial cognitive impairment and part of early intervention planning that would not only affect life quality, but also patients' costs. An estimation predicted a 10% reduction in life cost of individuals with dementia with an early intervention addressing functionality difficulties during one year (Jutkowitz et al., 2017). Additionally, a meta-analysis with 30 studies concluded cognitive training has an effect in ADL performance (Chandler, Parks, Marsiske, Rotblatt, & Smith, 2016). Functional impairment was also shown to impact on the quality of life of the, their family members and society in general (Kasper et al., 2020; Lindbergh et al., 2016).

One limitation of conclusions here presented is the absence of medical diagnosis. The battery used to define the neuropsychological profile and the chosen algorithm, however, tried to balance this limitation while still considering application time. Besides that, another limitation refers to the kind of scale used to assess ADL. Literature shows that informant and self-report can be influenced by some variables, such as depression and caregiver burden (Jekel et al., 2015). Although groups were paired concerning depressive symptoms, caregiver burden was not measured. Other potential problem is the absence of data about the informants. Since it is not known the relation between individuals and their informants, or how present the companion or caregiver were in the life of the participant, it is possible that data is not accurate. This and other confounding variables could be measured in future studies, as well as performance-based measures could be used to verify if the same results are obtained.

ARTICLE 2

Marques, L; Martorelli, M; Balboni, Giulia; Souza, R; Charchat-Fichman, H. CompCog's diagnostic accuracy: sensitivity and specificity of reaction time as a screening measure for mild cognitive impairment (in preparation).

CompCog's diagnostic accuracy: sensitivity and specificity of reaction time as a screening measure for mild cognitive impairment (in preparation)

1. Introduction

The American Academy of Neurology acknowledged the utility of the diagnosis of mild cognitive impairment (MCI) as proposed by Petersen (Petersen, 2016). Its utility is related to the higher rate of conversion of individuals diagnosed with MCI to dementia compared to those not diagnosed (Petersen et al., 2001) and to the possibility of early interventions improving quality of life (Kasper et al., 2020; Ritchie et al., 2017). The diagnosis of MCI has evolved throughout the years. Today, it includes subtypes with different etiologies and prognostics (Petersen, 2016). Thereby, it is a heterogeneous construct that can involve a subtle cognitive impairment of several functions, not always detectable by commonly used screening tests (Breton et al., 2019). It is a challenge to detect MCI in its early years, before it has progressed to severer forms of cognitive decline like dementia. Although research is making progress, it is usually more focused on (1) forms of MCI related to Alzheimer Disease (e.g. Tsoi et al., 2017; Van Giau, Bagyinszky, & An, 2019), and (2) techniques using technologies not always accessible or used in screening processes, like neuroimaging and biomarkers (Knopman & Petersen, 2014; Parra et al., 2018).

In search for an easier way to screen for MCI, evidence suggest that some cognitive variables can represent non-invasive and affordable first step regarding screening for cognitive decline (Oliveira & Brucki, 2014; Razak et al., 2019). One cognitive variable that seems to be affected throughout many types of cognitive decline caused by neurodegenerative conditions is reaction time (Andriuta et al., 2019; Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008; Phillips et al., 2013; Salthouse, 2000). Although it can be measured by traditional neuropsychological assessment, paper and pencil neuropsychological tests rarely have precise reaction time measurements that are able to detect the subtle changes that occur in the first stages of pathological aging (Ferreira et al., 2015; Levinson, Reeves, Watson, & Harrison, 2005). One viable option is to use computerized tests.

These can be successful in this task because they have precise measures of reaction time (Charchat et al., 2001).

Using computerized tests brings also other benefits, such as the more precise control over the administration and scoring of tests; the dynamic and colorful interfaces which add a new form of interaction; the possibility of more accurately measuring response times throughout the evaluation process; the superior control of time and order of presentation of stimuli; the possibility of developing several forms of the same test; the reduction of financial costs, with the reduction of the use of papers and the time of administration and training of professionals when compared to traditional tests; and the reduction of possible bias in the examiner's application and the possibility of errors on the part of the examiner thanks to automatic correction (Miller & Barr, 2017). This is especially true for low- and middle-income countries, where resources are limited and there is a need for methods that are fast, cheap, and amenable to a large-scale application (Parra et al., 2018).

The present research uses the computerized battery CompCog to investigate if its measures of reaction time are useful to discriminate between MCI and healthy individuals. The battery uses an iPad interface, and all responses are issued using a touchscreen. During each test, the type of response and reaction time in milliseconds are recorded. A previous version of the same test is already known to distinguish between healthy individuals and individuals with Alzheimer Disease (Fichman et al., 2008). Thus, CompCog is expected to be a useful tool for the detection of MCI and abnormal aging.

2. Methods

Setting and procedures

The participants of the present study were invited after participating in a larger study under an agreement between Pontifical Catholic University of Rio de Janeiro and a social program offered by the government of Rio de Janeiro (Casas de Convivência e Lazer para Idosos) (Araujo et al., 2018). The program offers daily activities for older adults during the day, in houses located in different neighborhoods of Rio de Janeiro. Some examples of activities are physical

exercises, stretching, yoga, dance, cognitive stimulation, crafts, theater, etc. The first study evaluated older adults through a brief neuropsychological assessment done by researchers and senior neuropsychologists, who were supervised weekly. It lasted one hour and was held in a quiet room in the houses where the social program commonly took place. During the assessment, cognitive tests and scales were used to assess cognition, depressive symptoms, and functionality. They are all described in the corresponding section below.

Participants of the larger study were then invited to the present study. The ones who accepted it went through another session of neuropsychological testing and a medical appointment with a doctor. The former consisted of (1) an anamnesis with the objective of knowing the clinical and sociodemographic aspects of the individuals and confirming the inclusion and exclusion criteria for recruitment and (2) CompCog application. The average session time was 1h15, and it was carried out at the Applied Psychology Service of the Pontifical Catholic University of Rio de Janeiro. Medical appointments aiming for a diagnosis were carried out in the same place or in the Ambulatory of the Department of Medicine of the same University.

The evaluation of the cases and diagnosis were done by geriatricians and based on clinical history, neuroimaging when available and the initial neuropsychological protocol that included the following tests and scales: 1) Mini Mental State Examination (MMSE, Brucki et al., 2003); 2) Cognitive Brief Screening Battery (Araujo et al., 2018; Nitrini et al., 1994). This latter battery consists of the following tests: Figure Memory Test (MFT); The Categorical Verbal Fluency Test (VF); Clock Drawing Test (CDT); Geriatric Depression Scale (GDS-15); The Functional Activities Questionnaire (FAQ) and The Lawton Instrumental Activities of Daily Living.. Although the FAQ is also part of this battery, it was not used due to a high rate of absence of data in relation to completing the questionnaire.

Participants

Seventy older adults (above 60 years old) were recruited for this study. Among them, 40 were classified as healthy older adults - individuals with no changes in cognitive performance tests and without functional impairment. - and 30 diagnosed as older adults with MCI. Exclusion criteria eliminated 6 individuals

between people with MCI group (PwMCI) and 2 individuals from the control group (CG). The exclusion criteria were: (1) presenting other conditions other than MCI that affect cognition (e.g., stroke); (2) recent history of alcohol or other drug dependence; (3) high depressive symptoms assessed by score on depression scale; (4) visual or hearing disorders without correction; (5) being illiterate and/or (6) use of medications that could affect reaction time (e.g., benzodiazepines).Among CG, 10 cases were randomly excluded until the variables years of education, sex, age, number of health issues, depressive symptoms and number of medications in use were paired. The resulting sample consisted of 24 PwMCI and 28 individuals in the CG. PwMCI mean age was 73.9 (6,9), mean years of education 11.6(5.3) and 70.8% women. CG mean age was 71.4(5.7), mean years of education 14.1(3.3) and 82.1% women.

Instrument

CompCog is a computerized cognitive screening battery with 8 subtests, listed in Table 1 with respective evaluated variables. The hole battery presents 50 variables in total. All answers are issued using a touch screen and recorded. All tests generate reaction time measures that are registered in milliseconds for each touch and are presented by total time and median to eliminate eventual discrepant data through each test. Furthermore, correct responses percentage, errors, and differences in reaction time between errors and correct answers are also registered. All stimuli tests are visuospatial, except for one test – the Stroop Test, which contains written words in order to maintain the original paradigm (Stroop, 1935).

Table 1 – CompCog tests and variables

Test	Cognitive functions involved and how they are evaluated	Variables
Simple Reaction Time (SRT)	Processing speed. As soon as a white square appears in the middle of the screen, the person should touch the rectangle in the bottom of the screen.	Median reaction time
Choice Reaction Time (CRT)	Processing speed. As a white or orange square appears in the middle of the screen, the person should touch the rectangle of the same color in the bottom of the screen.	Median reaction time, correct answers, revised median reaction time (choice reaction time - simple reaction time)

Implicit Learning Test (ILT)	Implicit learning. As one of ten gray squares distributed in the screen turns white, the person must press it. There is a fixed sequence of 25 squares that is repeated 4 times and one last random sequence.	Median reaction time in each of five tasks, Implicit learning (median reaction time in sequence 4 – median reaction time in sequence 1)
Visual and Spatial Short-Term Memory (STM)	Working memory. There are, as ten gray squares distributed on the screen. One will become white at a time, making a sequence that must be reproduced.	Correct answers, direct order SPAN, reaction time in direct order, inverse order SPAN, reaction time in direct order.
Face Recognition and Memory (FRM)	Episodic memory. Ten drawings of unknown faces are presented for 30 seconds. Then the participant should choose, between ten pairs of faces, which one was among those initially shown for memorization in 4 attempts.	Correct answers and median reaction time for each of the four tasks.
Inhibitory Control Test (ICT)	Attention, Inhibitory control Squares of different colors will appear in the middle of the screen for one second each, the white ones should be avoided.	Median reaction time, correct answers, correct answers median reaction time, errors median reaction time, and errors.
Stroop Test (StT)	Attention, Inhibitory control. All tasks have 4 colored rectangles located at the bottom of the screen. The person should touch the one matching the stimuli that appears in the middle of the screen considering its color without (task 1) and with distracters (task 2 and 3).	Interference, median reaction time and errors for each of the three tasks.
Survey Test (ST)	Attention. Squares of different colors will appear in the middle of the screen for one second each. Participants should press the white ones on the first tasks, whites and blues on the second and also yellow ones at the third.	Median reaction time, correct answers, reaction time of correct answers, errors and reaction time of errors for each of the three tasks.

Ethics

This study was approved by the Research Ethics Committee (opinion no. 965.264; CAAE: 39381514.3.0000.5285). The individuals participated in the study by signing a free and informed consent form, according to the resolution 196/96 of the National Health Council of Brazil, which deals with guidelines and standards for research involving human individuals. Participation in this survey was voluntary, so the participants did not receive any payment. The study did not bring

any risk to the health of the participants and they could refuse and/or withdraw consent to participate in the study at any time.

Statistical Analysis

All analyses were conducted with Statistical Package for Social Sciences (SPSS, version 22). After verifying if the data was parametric through Shapiro–Wilk tests, differences between groups were tested with T Tests for normal distributions or Mann-Whitney Tests for non-normal distributions. A chi-square test was used in the case of sex. Receiver Operating Characteristic (ROC) analysis was performed for each CompCog variable. The ROC curves were plotted in order to determine the degree to which subtests discriminated between controls and MCI. These analyses show the sensitivity versus one minus the specificity for each possible cutoff point. Areas under the curve (AUCs), with its 95% confidence intervals, were used as an indicator of the ability of the measures in differentiating individuals. To create a model with the least number of variables to predict MCI, the variables with higher sensitivity in ROC analysis were then used in a logistic regression model with the stepwise forward method.

3. Results

Sample characteristics

Participants' performance in neuropsychological assessment, demographic and clinical characteristics are described in Table 2. There were no significant differences between groups regarding age ($t(50) = -1.414$; $p = .164$), educational level in years ($t(37.486) = 2.008$; $p = 0.052$), number of health problems ($t(40.60) = -0.0846$; $p = .403$), number of medications in use ($t(50) = 0.203$; $p = .840$), number of depressive symptoms ($t(50) = -1.234$; $p = .224$) and sex (x^2 (1)= 0.931; $p = .335$).

There were differences regarding cognition in immediate memory ($t(50) = 3.562$; $p = .001$), learning ($t(50) = 3.572$; $p = .001$), delayed recall ($t(50) = 2.914$; $p = .005$), and verbal fluency ($t(50) = 0.732$; $p = .002$). Functionality also differed between groups ($U = 1440$; $Z = -4{,}257$; $p < .001$). Tests did not show differences in nomination ($U = 308$; $Z = -1{,}542$; $p = .123$), incidental memory ($t(50) = -1.764$; $p = .084$), recognition ($U = 332{,}5$; $Z = -0{,}087$; $p = .930$), clock drawing test ($t(50) = 1.141$; $p = .259$), and MMSE ($t(50) = 1.873$; $p = .067$).

Table 2 – Clinical characteristics of the sample

Variable	**CG** (n = 28) Mean (SD), Range 95% confidence interval	**MCI** (n = 24) Mean (SD), Range 95% confidence interval	**Total** (n = 52) Mean (SD), Range 95% confidence interval
Health problems	1.5 (1.0), 0–3	1.7 (1.4), 0–4	1.6 (1.2), 0–4
Medications in use	2.0 (1.9), 0-6	1.9 (2.0), 0-6	2.0 (1.9), 0–6
Depressive symptoms	2.8 (1.9), 0–6	3.6 (2.6), 0-9	3.1 (2.3), 0–9
Nomination	10.0 (0.0), 10-10	9.8 (4.4), 8–10	9.9 (0.3), 8–10
Incidental memory	5.9 (1.2), 4–8	5.2 (1.5), 3–8	5.6 (1.3), 3–8
Immediate memory**	8.5 (1.1), 6–10	7.2 (1.4), 5–10	7.9 (1.4), 5–10
Learning**	9.3 (0.8), 8–10	8.3 (1.1), 6–10	8.8 (1.1), 6–10
Delayed recall**	8.6 (1.5), 4–10	7.2 (1.6), 4-10	8.0 (1.7), 4–10
Recognition	9.7 (0.4), 9–10	9.5 (0.9), 7–10	9.6 (0.7), 7–10
Clock drawing test	6.2 (2.2), 4–10	5.5 (2.5), 1–10	5.9 (2.3), 1–10
Verbal fluency**	20.7 (4.3), 13–30	16.6 (4.6), 8-26	18.8 (4.9), 8–30
MMSE30	27.0 (2.1), 22–30	25.7 (2.7), 21-29	26.4 (2.5), 21-30
Functionality	20.9 (0.2), 20–21	19.6 (1.6), 15–21	20.3 (1.2), 15-21

* # female/male, ** significant differences between groups

ROC curve

ROC curves with AUC above 0.8, its sensitivity, specificity and cutoff points can be seen in Table 3. As proposed by the literature (Breton et al., 2019), sensitivity was prioritized instead of specificity since we are proposing a screening measure, and therefore false positives would be better than false negatives in order to continue clinical investigation.

In general, measures of reaction time in cognitive tasks of lower complexity (e.g., choosing between colors) and in memory tasks were the variables that best discriminated between CG and MCI. Simple reaction time, reaction time in the

Stroop effect and working memory, and reaction time regarding errors and its quantity did not differentiate between CG and MCI.

Table 3 – AUC, cutoff points, sensitivity and specificity for significant variables

Test	AUC, Range 95% confidence interval	Cut-off point (milliseconds)	Sensitivity/ specificity
Choice Reaction Time Test			
MRT*	.915, .837-.993	689.813	91.7%/89.3%
Implicit Learning Test			
MRT 1	.839, .721-.957	688.125	83.3%/75%
MRT 2	.836, .720-.953	651.531	75%/75%
MRT 3	.823, .703-.943	628.612	70.8%/71.4%
MRT 4	.829, .710-.948	618.139	75%/71.4%
MRT 5	.804, .674-.933	664.784	75%/75%
Face Recognition and Memory			
MRT*	.896, .799-.993	1580.791	83.3%/85.7%
MRT 1	.823, .703-.943	1905.385	75%/71.4%
MRT 2	.881, .781-.981	1506.316	91.7%/75%
MRT 3	.872, .767-.977	1430.946	87.5%/75%
MRT 4	.813, .693-.932	1486.333	79.2%/71.4%
Inhibitory Control Test			
MRT*	.884, .782-.976	664.447	87.5%/78.6%
CAMRT	.871, .774-967	663.279	83.3%/78.6%
Stroop Test			
MRT 1	.847, .732-.962	814.839	87.5%/75%
Survey Test			
MRT 1	.818, .703-.934	637.844	79.2%/71.4%
CAMRT 1	.818, .703-.934	637.844	79.2%/71.4%
MRT 2	.829, .714-.944	663.004	79.2%/75%
CAMRT 2	.835, .721-.949	663.004	79.2%/75%
MRT 3	.823, .707-.939	653.629	83.3%/71.4%
CAMRT 3	.826, .711-.941	664.223	83.3%/75%

MRT = median reaction time; CAMRT = correct answers median reaction time; best accuracy*; all $p < .001$

Regression models

The final model correctly classified 92.3% of individuals, with 92.9% specificity and 91.7% sensitivity, and included 4 variables. All variables concerned reaction time, but in 4 different tasks: in the first task of the Stroop test, in the inhibitory control test, in the second task of the memory test and in the second sequence of the implicit learning test. The final model had a chi-square value of 46.183 (4), $p < .001$. The -2 Log likelihood was 25.597, with Cox & Snell R Square of 0.589 and 0.786 Nagelkerke R.

4. Discussion

Sample characteristics are different between paper and pencil and computerized tests

First thing to notice is the sample neuropsychological profile. Regarding the paper and pencil traditional assessment, groups differed only in tests evaluating episodic memory and verbal fluency - highly dependable on memory (Ross, O'Connor, Holmes, Fuller, & Henrich, 2019). This profile is usually categorized as the amnestic subtype of MCI. Meanwhile, reaction time in CompCog tasks involving memory, attention and executive functions had good accuracy in discerning between PwMCI and CG. This suggests a potential benefit of using computerized tests. They are able to track a greater number of impairments than the ones typically measured by traditional paper and pencil assessment. Besides that, if one looks specifically at memory performance in CompCog, the number of correct answers did not discern well between groups, whereas reaction time did.

When comparing specifically the CompCog memory task and the paper and pencil test, there are differences. Comp Cog's task uses recognition, and not recall, as the paper and pencil test does. This suggests CompCog task is easier than the later. Two benefits can be extracted from this information. The first is the possibility of evaluation without generating performance anxiety and frustration (Kit, Mateer, Tuokko, & Spencer-Rodgers, 2014) – since correct answers are similar between groups. The second is the ability to distinguish between groups before errors start to be committed. One hypothesis is that a slower reaction time is one of the first cues of cognitive impairment. Other studies have already shown a decrease in

processing speed as one of the signals of cognitive decline (Chen et al., 2017). There is also evidence of a correlation between reductions in processing speed and cognitive performance (Chen et al., 2017). It is interesting to note that a reduction in processing speed is also related to subjective memory complaint (Brailean, Steptoe, Batty, Zaninotto, & Llewellyn, 2019). Although it is not possible to draw any conclusions on the individual, reaction time measures may be useful to investigate if it is possible that a slower reaction time is related to subjective memory complaint. Results of a meta-analysis suggest people with subjective memory complaints have twice as high risk of developing MCI and dementia compared to older adults people who have no complaints (Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014). But their condition is difficult to measure with traditional memory tasks because individual's performances are similar to controls (Jorm et al., 2004).

ROC curve: reaction time is useful as a screening measure for MCI under certain conditions

In general, ROC curve results showed that reaction time measures in different cognitive processes were good at distinguishing between healthy individuals and PwMCI. Measures of the number of errors and correct answers, instead, did not have good accuracy. Normal aging is known to have a correlation with slower reaction time (Salthouse, 2000). But the results show signs that this slowing might be even larger under *certain* circumstances in pathological conditions. These circumstances involve reaction time of cognitive processes of low and moderate complexity are the best measures for screening. This can be seen in numerous comparisons, but mostly between the first two subtests: (1) simple reaction time – which is not good at distinguishing – and (2) choice reaction time – the best one, with AUC as high as 0.9. Literature has mixed results regarding the topic. Some studies investigated reaction time in simple tasks, and also found a good accuracy at discerning between PwMCI and controls (Memória, Yassuda, Nakano, & Forlenza, 2014; J. H. Park et al., 2018; Tornatore, Hill, Laboff, & McGann, 2005). One study (Gorus, De Raedt, Lambert, Lemper, & Mets, 2008) investigated the effect of increasing complexity stimulus and proposed a division of reaction time in a movement and a cognitive component. Only the cognitive component was sensitive to cognitive impairment, proposing that although lower

complexity tasks may be useful to the matter, at least some cognitive processing must be involved. That may explain why the test Simple Reaction Time was not able to discriminate between groups, but Choice Reaction Time was.

Nevertheless, the same study and also others (de Jager, Schrijnemaekers, Honey, & Budge, 2009; Haworth et al., 2016) found that more complex variables were better at distinguishing, which is the opposite finding. One hypothesis for the opposite findings is it the fact that these studies used only the amnestic subtype of MCI. Using one subtype creates a more homogeneous sample in relation to cognitive impairment. So, perhaps, using more subtypes would produce different results. For example, cognitive impairment in complex cognitive processes would be more heterogeneous and reaction time in simple cognitive tasks would still be homogenously impaired in the sample as a whole.

Another common problem in research that may cause divergence is the intraindividual variability. Some studies suggest that intraindividual variability is higher in individuals going through cognitive decline and, therefore, PwMCI (Anstey et al., 2007; Gorus et al., 2008). Because of that, results from one or few trials might not be a good measure of comparison. CompCog does not have this problem since it uses the median reaction time derived from multiple trials. This would eliminate the variability problem that affects the MCI sample and does not affect the control sample. Besides the benefit of some computerized tests mentioned right above, two more can be added in the same context. The variable being discussed, simple choice reaction time, is something that can be evaluated longitudinally and without learning effect. This makes possible a longitudinal follow-up in which the individuals will be compared to themselves for the detection of a decline since the very beginning, with the consequent possibility of early interventions.

The simpler the cognitive task, the better accuracy the reaction time measure has

The other tests also follow this pattern of the simpler the cognitive task, the better accuracy the reaction time measure. This is especially evident when looking at variability intratest. For example, reaction time measures in Implicit Learning subtest got less discriminating in each subsequent block. That is, the more the

cognitive process of implicit memory was activated, the less reaction time differentiated between groups. But the best way to see this effect is to look at results regarding the Stroop Test. Accuracy was good only in the first task, where there is no influence of the Stroop effect. The next blocks were not able to predict individuals' conditions and are highly influenced by executive functions. Episodic memory tasks and Survey test followed the same pattern.

Discrepancies and variables without good accuracy

Finally, another two interesting pieces of data should be examined. The first finding is the inability of working memory to discern between groups. This might not be a surprise since the sample did not show a difference in working memory when looking at paper and pencil test performance. Also, the working memory subtest is not spared from the intratest variability performance. This specific test does not have a lot of trials due to its construct, being highly affected by one error or an outlier performance. Because of that, intratest variability can affect the results. The second finding relates to the comparison between errors reaction time and correct answers reaction time. The latter was good at discerning PwMCI, but not the former. The separation is not common in studies and needs to be further investigated. Few errors were committed in the present study, making it hard to analyze the matter properly. A lot of computerized tests are available nowadays, but not all of them use reaction time measures, and specially not reaction times in errors and correct answers separately. Many still use the same measures used by paper and pencil tests, like errors and total scores. The tests that do investigate reaction time, do it mainly focused on attention processes (J.-H. Park & Park, 2018; Schweiger, Doniger, Dwolatzky, Jaffe, & Simon, 2003), probably because of the cognitive process' construct, highly relatable to processing speed.

Regression models

The final model that better predicted MCI with the least number of variables included three reaction time measures regarding attention and one regarding memory, classifying correctly 92.3% of individuals. At last, and given all the above, it is not a surprise that the four variables chosen by the regression analysis were reaction time measures, and not errors, correct answers, or total scores. What we can infer from the 92.9% specificity and 91.7% sensitivity is that measures of

reaction time in CompCog, are a low-cost, efficient, and accurate way to screen for MCI. It is not our proposal to use the test as a diagnosis tool, but to use technology for a simple screening by doctors or caregivers in the threshold of old age. Depending on the results, more exams and investigation should be done to reach a diagnosis and indicate treatments.

Conclusions

In order to achieve the objective above, more evidence needs to be produced. This study and the literature in general have still a lot of blank spaces. To assess a cognition decline, it is important to compare the individuals to themselves (Knopman & Petersen, 2014), which is an aspect that this study was not able to cover. The best way to screen for MCI would be comparing the individuals results year over year. Studies with follow-up could provide more evidence of the utility of CompCog to MCI screening. Besides that, another limitation of the present study is the small sample. Although there is a need for bigger samples to achieve more reliable results, there is a lack of studies exploring all MCI subtypes together, so our findings are still influential. Although a lot of research linked to Alzheimer's Disease and amnestic MCI is available, other MCI subtypes are less investigated. Our results show it might be possible to create a protocol to screen for cognitive impairment regardless the etiology with simple measures of reaction time. To do so, a bigger sample is needed, as well as higher levels of evidence to define reaction time in low and moderate cognitive tasks as a good screening measure of cognitive impairment.

IV. GENERAL DISCUSSION

The present dissertation aimed to investigate the role of two variables that are important to the early screening, comprehension, or intervention planning in the context of MCI. The analysis of reaction time was hypothesized as an accessible, fast, and cheap way to screen for cognitive deficits in older adults. Besides that, the awareness older adults have about their ADL performance was also investigated. The proposal was not to offer a diagnosis instrument, but tools that can be part of a screening protocol that could be widely used to indicate those who need a more careful investigation in order to reach an early diagnosis. Diagnosis for MCI originally asked for: (1) cognitive complaint, (2) impaired cognition, and (3) preserved activities of daily living (Petersen et al., 2001). As already discussed throughout this work, the last criterion has been questioned after evidence was brought into light there would already be some ADL impairment in PwMCI.

The two variables that were investigated, reaction time in different cognitive tasks and activities of daily living performance awareness, are in connection with the later evidence and the original criteria for diagnosis. The first study brought evidence that there already is a small decline in functional capacity in MCI cognitive profiles, and that individuals are aware of this decline. The second study showed that reaction time assessed through CompCog is a better measure to differentiate between normal and pathological aging than errors. Although both were addressed separately here and there is still a need of studies considering both together, it is possible to draw some theoretical relations.

The theoretical relation between the two variables is based on the concept of different types of errors committed in the performance of ADL. There are commission errors (performing a step incorrectly – putting sugar twice in a recipe or baking it for longer), that are related to executive functioning and hinder, but do not prevent, the execution of a task (Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008), and omission errors (not performing a step – not using sugar or baking at all), related to a deficit in general cognitive resources or memory, and inability to complete the task (Giovannetti, Bettcher, Brennan, Libon, Burke, et al., 2008). Also, studies investigating cognitive correlates of anosognosia or, even more specifically, ADL deficits awareness, show that the conditions are usually related

to general cognitive decline (Okonkwo et al., 2008) or memory impairment (Mograbi et al., 2009).

If omission errors are more related to general cognitive impairment or memory deficits (Giovannetti, Bettcher, Brennan, Libon, Burke, et al., 2008; Giovannetti, Bettcher, Brennan, Libon, Kessler, et al., 2008; Schmitter-Edgecombe & Parsey, 2014a), and the same type of impairment is usually related to unawareness, therefore it is understandable that the error might not be perceived and, thus, reported. Alternatively, a commission error, where a step is performed with some difficulties and is linked to executive deficits rather than global deficits, might occur in the beginning of functional capacity decline, where global cognition is still preserved. This executive deficits does not seem to prevent perception by people involved (Starkstein et al., 1997; Suchy et al., 2011).

Observing the present work results, the data follows the same pattern. Reaction time in cognitive activities was a good measure to differentiate between PwMCI and controls, showing a decline in executive functions in PwMCI. Furthermore, ADL deficits awareness were, in the other study, different between PwMCI and PwD – and memory and executive impairment followed the same pattern proposed by the previously mentioned studies. Thus, it is possible to suggest that both variables – reaction time and ADL performance awareness – may decline in a tandem. Although this is only a hypothesis and more studies are needed, reaction time seems to be affected prior to omission errors, where global cognition is already impaired, some ADL cannot be completed and there is a lack of awareness of functional deficits. It is possible this effect in reaction time is linked to commission errors, and therefore to executive functioning and a preserved perception of ADL capacity.

Nonetheless, both variables are easily assessed, can be part of clinical routine tests and bring some benefits when compared to more expensive options not really suitable for all health care systems (Parra et al., 2018). For example, recent research has shown the possibility of using biomarkers and neuroimaging to detect neurodegenerative conditions in its prodromal or advanced stages (Petersen, 2018). But those options are not viable as a screening procedure, especially in low- and middle-income countries, where neuropsychological assessment is a more

accessible course of action (Parra et al., 2018). Results here presented showed ADL performance assessment done through self-report or informant-report scales for PwMCI, and through informant-report for PwD, brings information that can help to discriminate between cognitive profiles.

With regard to tests assessing cognitive processes, a recent meta-analysis (Breton, Casey, & Arnaoutoglou, 2019) analyzed diagnostic accuracy of different instruments. The Mini-Mental State (MMSE) and Montreal Cognitive Assessment (MoCA) appear to be the most used options, and both try to embrace assessment of all cognitive variables. Results of this meta-analysis report an AUC of 0.847 for MoCA and 0.735 for MMSE. Some alternatives focus only on memory recall and have a higher accuracy, such as Memory Alteration Test and Quick Screen (AUC 0.961) (Breton et al., 2019). One downside of focusing only on memory components is that it is only accurate for amnestic MCI. CompCog variables, 20 AUC varied from 0.804 (CI 0.674-0.933) to 0.915, (CI 0.837-0.993), higher than the option mentioned. Besides, CompCog does not have a total final score, and subtests can be used separately. The subtest with highest sensitivity and specificity – choice reaction time subtest – had 91.7% sensitivity and 89.3% specificity and can be done in 5 minutes. The logistic regression final model correctly classified 92.3% of individuals, with 92.9% specificity and 91.7% sensitivity, and included only 4 variables. Different combinations of subtests can be used depending upon the time available, but even a single subtest has been shown to be useful.

One thing that needs to be highlighted is that the proposal of the present work is not a diagnosis. Therefore, this sensitivity and specificity would only indicate those who need to go through a more comprehensive investigation to identify any pathological process taking place. Although reaction time seems to be affected before errors and hence before severe functional deficit, considering activities of daily living complaints of subtle changes simultaneously to CompCog's results could be of great utility. Activities of daily living scales are already used in clinical contexts, but an impairment in reaction time could suggest the use of ADL performance investigation even before the formal complaint arrives to the clinician.

Of course, there are some limitations to all these proposals. In order to confirm all of the conclusion here presented, both variables should be investigated together. This is also a project for subsequent studies. Additionally, studies should involve a diagnosis, which is a limitation of the first study here presented. Finally, probably the most important limitation and also recommendation for subsequent studies is the absence of intraindividual comparison, that is, evaluating the individual over time. Although cognitive impairment can be detected in comparison to normative data, cognitive decline can be defined with comparisons to oneself. Personal decline is the best way to screen for pathological aging, and both reaction time measures and awareness of ADL deficits can be easily evaluated and compared longitudinally.

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