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Clinical Validation of Alzheimer's Disease Assessment Scale – cognitive sub-scale (ADAS-Cog) – for the Portuguese population

Joana Nogueira (e-mail: joananogueira.f@gmail.com)

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[1] Serviço de Neurologia do Centro Hospitalar e Universitário de Coimbra, Faculdade de Medicina da Universidade de Coimbra (FMUC).
[2] Perception and Recognition of Objects and Actions Laboratory (PROACTION Lab), Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra (FPCEUC).
[3]Centre for Neuroscience and Cell Biology (CNC); Centro de Investigação do Núcleo de Estudos e Intervenção Cognitivo Comportamental (CINEICC); Psychological Assessment Lab, Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra (FPCEUC).

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RESUMO

INTRODUÇÃO: A Escala de Avaliação da Doença de Alzheimer – subescala cognitiva (ADAS-Cog; Mohs, Rosen, & Davis, 1983; Rosen, Mohs, & Davis 1984; Guerreiro, Fonseca, Barreto, & Garcia, 2008) avalia a severidade do défice cognitivo na Doença de Alzheimer (DA), sendo uma medida de eficácia requerida pela *European Medicines Agency* (EMA) em ensaios clínicos em DA para aprovação de fármacos. Pretende avaliar os seguintes domínios cognitivos: memória, orientação, linguagem, praxia e capacidade construtiva.

OBJECTIVOS: Elaboração de um estudo de validação psicométrica e clínica no espectro da DA, incluindo um grupo com Défice Cognitivo Ligeiro (DCL) e um grupo com DA. Neste âmbito, pretende-se a exploração das propriedades psicométricas do teste, da sua capacidade discriminativa e o estabelecimento de pontos de corte e dados normativos para a população portuguesa.

METODOLOGIA: A amostra é composta por 743 participantes (Grupo Controlo: n=223, Grupo DCL: n=250; Grupo DA: n=270). Os grupos clínicos cumprem os respetivos critérios de diagnóstico internacionais estandardizados. O grupo de controlo é constituído por participantes cognitivamente saudáveis residentes na comunidade, submetidos ao seguinte procedimento avaliativo previamente à administração da versão portuguesa da ADAS-Cog: *Mini Mental State Examination, Montreal Cognitive Assessment* e Inventário de Avaliação Funcional de Adultos e Idosos.

RESULTADOS: A amostra apresenta uma média de idades de 70.03 (±8.81) anos e de 6.82 (±4.49) anos de escolaridade, sendo 456 (61.4%) participantes femininos. A pontuação total na ADAS-Cog difere significativamente entre os três grupos (p<.001: Controlo<DCL<DA) quando controlado o efeito das covariáveis. A ADAS-Cog apresentou boa acuidade diagnóstica para o grupo de DA. Para DCL obteve-se um ponto de corte >9 pontos (AUC=0.839), para DA >12 pontos (AUC=0.996) e na distinção entre ambas as condições >15 pontos (AUC=0.924). O tamanho do efeito foi maior para o grupo DA (η^2=.64), revelando o uso apropriado deste teste para esta condição clínica. Foram estabelecidas as normas a população Portuguesa.

CONCLUSÕES: Os resultados sugerem que a ADAS-cog é uma escala de avaliação da progressão da DA sensível à presença de défice nos desempenhos cognitivos, com pontos de corte a considerar na prática clínica e de investigação.

Palavras chave: ADAS-Cog, Doença de Alzheimer, Défice Cognitivo Ligeiro, Avaliação Neuropsicológica, Validação Clínica.

Title of dissertation *Clinical Validation of Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) – for the Portuguese Population*

ABSTRACT

INTRODUCTION: The *Alzheimer's Disease Assessment Scale – cognitive sub-scale* (ADAS-Cog; Mohs, Rosen, & Davis, 1983; Rosen, Mohs, & Davis 1984; Guerreiro, Fonseca, Barreto, & Garcia, 2008) is a brief battery developed to assess cognitive performance in AD patients. The ADAS-Cog was also used as an outcome measure required by Eurpean Medicines Agency (EMA) in clinical trials for AD, as a way to index the global level of cognitive functioning in response to therapies or drugs. The ADAS-Cog was developed according to the core characteristics of cognitive decline in AD: memory, language, praxia, constructive ability and orientation.

OBJECTIVES: Clinical validation and psychometric study of the European Portuguese version of ADAS-Cog for clinical groups with MCI and AD. Exploratory analysis on its psychometric properties, the establishment of discriminant cut-off points between clinical groups and the normative values for the Portuguese population.

METHODOLOGY: The Portuguese version of ADAS-Cog was administrated to 743 participants, divided into healthy control group (n=223), MCI group (n=250), and AD group (n=270). The clinical group fullfil the standard international diagnostic criteria. The control group was composed by healthy cognitive participants actively integrated in community. The neuropsychological assessment protocol administrated before the ADAS-Cog was composed by: Mini Mental State Examination, Montreal Cognitive Assessment and Adults and Older Adults Functional Assessment Inventory.

RESULTS: The age mean of the sample was 70.03 (±8.81) years, the education mean was 6.82 (±4.49) years, and the sample was composed by 456 (61.4%) female participants. The ADAS-Cog scores significantly differ between three groups (p<.001: Control<MCI<AD), controlling the covariables effect. The ADAS-Cog presented good diagnostic accuracy for AD group. The cut-off point for DCL was >9 points (AUC=0.839), for AD was >12 points (AUC=0.996) and between DCL and DA was >15 points (AUC=0.924). We found a better effect size for AD (η^2=.64), which corroborated the proper use of this test for the assessment of this clinical condition. The normative data was established for the Portuguese population.

CONCLUSIONS: The results suggested the sensitivity of ADAS-Cog to detect cognitive impairments in AD patients, with cut-off points to consider in clinical and research contexts.

Key Words: ADAS-Cog, Alzheimer's Disease, Mild Cognitive Impairment, Neuropsychological Assessment, Clinical Validation.

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Content

Introduction

The percentage of elderly individuals in the population, and overall life expectancy have been rising steadily worldwide. Parallely, we have witness an increase in the prevalence of age-related diseases, and specifically of neurodegenerative diseases and dementia (e.g. Alzheimer's Disease). A major societal challenge is then to effectively address the social and health-related issues that emerge from healthy and pathological aging. One such challenge is to validate neuropsychological assessment scales that can assess and monitor the progression of dementia, and thus ensure effective and timely prevention and treatment. The main goal of the present work is to clinically validate the Alzheimer's Disease Assessment Scale – cognitive sub-scale (ADAS-Cog) for the Portuguese population. This is of the utmost importance because the ADAS-Cog is required by the drug regulatory agencies as an efficacy assessment measure for all approved clinical trials on dementia.

We will start by introducing the main topics in aging and aging-related disease. We will then outline the procedures and materials used to validate this scale. This section will be followed by the Results section, where we will describe the statistical analysis used and the results obtained. In the Discussion section we will examine the results in the context of the current literature. Finally, we will discuss the goals achieved and limitations of the present work, and will briefly propose a set of future studies that could potentially be developed.

I – Background

Aging in Portugal

Most of the developed countries accepted the concept of elderly after the chronological age of 65 years old (WHO, 2015). By default, the range between 60 and 65 years old is today widely accepted as the main criteria to be "older", because it is the point from when active contribution is no longer feasible (EuroHealthNet, 2012).

Currently there is a demographic aging phenomenon occurring worldwide. Demographic projections indicate that by 2050 the world population above 60 years old will be over 2 billion, comparing with the 841 million in 2013. Moreover, by 2047 elderly people will exceed the number of children (Chatterji, Byles, Cutler, Seeman, & Verdes, 2015).

The aging phenomenon extends to Portugal. Due to its accelerating curve (Carvalho, 2012) and the impact over the social structure, the social aging problem has been a dominant issue debated within social and health professionals, and by policy makers. Indeed, the aging process is expected to have a strong negative impact in the social and the economic systems in the upcoming years. This demographic challenge is threatening the responsiveness of the social assistance in general and of the health care system in particular, leading to its needed adjustments (WHO, 2015).

The number of patients with neurodegenerative diseases are expected to grow due to the increase in life expectancy. In Portugal, the prevalence of Mild Cognitive Impairment (MCI), between 2003 and 2008, was 12.3% (Nunes, Silva, & Silva, 2008; Nunes et al., 2010). In 2012, the number of deaths caused by Alzheimer's Disease (AD) reached a total of 1740 (the majority of which were women with 83.1 years old in average; INE, 2014). AD was, in fact, the cause of 1.6% deaths in Portugal, a total of 16.6 deaths per 100000 people (Santana, Farinha, Freitas, Rodrigues, & Carvalho, 2015). According to these data, to find effective responses for the challenges brought by aging in its physic, cognitive and social characteristics it is demanding (Cabral, Ferreira, Silva, Jerónimo, & Marques, 2013; WHO, 2015).

Healthy Aging

Aging is an extremely complex process (Aboderin & Beard, 2015). Healthy elderly individuals should not present with any disease, but in spite of that should show natural age-related changes. They also could show high cognitive and functional capacity, as well as engage in an active life (WHO, 2015; Rowe & Kahn, 1997). Importantly, normal age-related changes, such as the gradual molecular/cellular damage and the reduction of physiologic reserves, can lead to a higher likelihood of disease (Christensen, Doblhammer, Rau, & Vaupel, 2009). Although age-related decline is influenced by individual predisposition and life style, in general elderly people experience a decrease in their abilities. The aging process shows inter-individual differences, and depends on multiple factors such as lifetime experience, practical competence, mental capacities, cognitive reserve, physical activity, and life context (Lezak, Howieson, Bigler, & Tranel, 2012). Moreover, and particularly in developed countries, advanced health care systems and facilities have shifted the balance between biological and chronological age, making it difficult to predict the course of biological aging from an individual's chronological age. That is, the interaction between body deterioration and age, as well as between biologic and chronologic age are no longer the same (WHO, 2015).

Typical physical and neural changes in healthy aging

Healthy aging typically leads to certain non-pathological changes at the neural, cognitive and vasculature level. The most prevalent aspect of healthy aging is an age-related cognitive decline. Age-associated cognitive decline occurs in specific domains, such as memory, reasoning, executive functions and speed of processing. These are some of the central functions underlying fluid intelligence. Importantly, fluid intelligence is the cognitive function that ensures autonomy in daily-live activities and at the same time is the most affected by aging (Deary et al., 2009).

Neuroanatomical changes

To some extent there is a normal and expected atrophy pattern that characterizes the healthy aging process influencing several cognitive changes (Lezak et al., 2012). The volume of the brain increases linearly until

adulthood, reaches a *plateau* in adulthood and declines considerably in the elderly (Muller et al., 1998; Raz & Rodrigue, 2006; Lezak et al., 2012). This pattern involves mostly white matter (Jernigan & Gamst, 2005), especially in temporal and prefrontal regions. Whether white matter abnormalities lead to poorer cognitive performance is still under debate (Lezak et al., 2012). Some authors suggest that white matter abnormalities lead to poor performance in cognitive and fine motor abilities (e.g. Gunning-Dixon & Raz, 2000). Others found no correlation between cognitive impairment and hyperintensities in white matter (e.g. Schmidt, Fazekas, Kapeller, Schmidt, & Hartung, 1999; Wahlund, Almkvist, Basun, & Julin, 1996). Recently, a longitudinal study by Silbert and colleagues (2008) suggested the association with white matter hyperintensity progression and cognitive impairment over time.

Some cortical regions are also particularly sensitive to the aging process, for example, a longitudinal study by Raz (2004, cited in Raz & Rodrigue, 2006), showed that the size of the hippocampus is associated with chronological age in that, on average, the older an individual is the more pronounced is the reduction in volume (atrophy) at the hippocampus. Interestingly, although both the hippocampus and the entorhinal cortex showed age-related volume loss, the hippocampus was more pronounced (Raz & Rodrigue, 2006). This is particularly important because medial temporal cortex – namely the hippocampus and the entorhinal cortex – plays a central role in memory and are pathological targets in dementia (e.g. AD). Also, the volume of prefrontal cortex seems to suffer an age-related shrink. This volume loss of lateral prefrontal cortex was correlated with changes in fluid intelligence, which comprises reasoning and problem solving (Salthouse, 2011; Rog & Fink, 2013). Similarly, brain changes also play a central role in the course of degenerative disorders, as Frontotemporal Dementia (FTD; Lezak et al., 2012).

In sum, the main age-related changes in the brain occur in the frontal and temporal lobes, and are related with aging-specific cognitive changes, that we will explore next.

Cognitive Changes

Longitudinal studies have suggested an enhancement in cognitive functioning up to 60 years of age – using acquired knowledge as a proxy (Salthouse, 2010a; Salthouse, 2010b; Salthouse, 2011). Then, a linear decline from the adulthood to aging is observed in what concerns the efficiency and effectiveness of processing (Salthouse, 2011). However, within the normal aging process there is great heterogeneity and one must take into account the individual's personal history (e.g.: education level, life experiences, other pathologies, etc.), when assessing cognitive decline and interpreting these changes as healthy or pathological.

The memory system is the most affected by the aging process (Lezak et al., 2012). Memory is the ability to encode and explicitly or implicitly recall information about recent or distant past experiences. Memory can be divided into hierarchical taxonomic modules. Such modules are defined according to the duration the retention interval and the type of information to be retrieved

(Brickman & Stern, 2009). Specifically, long-term memory can be divided into declarative (or explicit) and non-declarative (or implicit). The declarative subcomponent relates to the ability to recall facts or general knowledge (semantic memory), recall events (episodic memory) or recall perceptual information (perceptual memory) in a conscious way (Squire, 2004). The non-declarative subcomponent relates to the implicit recall of information (Brickman & Stern, 2009). Within the declarative memory subcomponent, episodic memory is the most affected by aging – manifested by an impaired recall of past events (Peters, 2006). In contrast, semantic memory is relatively stable across the adult lifespan, and is minimally affected by normal aging. In fact, even under mild pathological aging, semantic memory remains less impaired than it episodic counterpart (Brickman & Stern, 2009). Nevertheless, a difficulty to recall names of common objects or other well-learned information can happen with aging, demonstrating that "crystalized intelligence" – which corresponds to over-learned and familiar knowledge and abilities – can also be compromised in aging (Brickman & Stern, 2009; Lezak et al., 2012).

Some studies suggest that the most generalized change that comes with aging is a progressively slower processing speed (Lezak et al., 2012), influencing simultaneously memory, retention, concentration, learning and psychomotor speed (Lezak et al., 2012). For example, attention in aging is closely affected by task complexity. That is, tasks that recruit large amounts of attentional processes result in poorer performance. Similarly, tasks demanding divided attention show increased reaction times (Hartley, Jonides, & Sylvester, 2011). Normal aging is also accompanied by sustained and selective attention deficits, which again, can affect the ability to function adequately and autonomously in everyday life (Glisky, 2007).

Age-related prefrontal lobe atrophy is known to be responsible for some of the cognitive changes that occur with aging – typical frontal-lobe dependent tasks are very susceptible to aging (MacPherson, Phillips, & Sala, 2002). Impaired executive functions, particularly planning, attention, problem solving and reasoning, reduce the individual's autonomy and compromise specific aspects of her/his behavior. For example, Rhodes and Kelley (2005) found that deficits in strategic thought and controlled processing in encoding and retrieval are associated with aging. These deficits lead to vulnerabilities in tasks that require mental manipulation of material, as for example the recall of a short list of words. Similarly, changes in word fluency are also explained by executive dysfunctions (e.g. difficulty in recalling names, lapses in speech and difficulties in word finding; Lezak, Howieson, & Loring, 2004: Lezak et al., 2012).

However, not all cognitive functions suffer deterioration with age. Good examples of such are language, comprehension and vocabulary, all apparently remaining stable throughout the aging process (WHO, 2015).

Functional changes in daily living

During the aging process there are changes in cognitive functioning that affect the daily routine and limit autonomy. In this period of life, physiologic

losses (e.g. decline of sensory and sensitivity acuity, visual acuity, motor functions, decline in hearing, balance problems, etc.) interfere with activities of daily living (ADLs; e.g. daily hygiene care, feeding, care home, etc.) and instrumental activities of daily living (IADLs; e.g. medication monitoring, safety rules, bill payment, etc.; Lezak et al., 2012). Also, the age effect is more evident in IADLs than ADLs, where the age-related changes follow a linear relationship regarding disability levels. Actually, measuring these changes in the individual capability of autonomous functioning allow the detection of social care needs and the anticipation of dependence in the future (WHO, 2015). Indeed, measuring functionality is one of the most important assessments when detecting and monitoring cognitive deterioration and extends to the evaluation of elderly people autonomy and safety (Stineman et al., 2016). For example, longitudinal studies suggest that an increased functional impairment with age is related with objective cognitive impairments (Hajek & König, 2016). Similarly, most functionality changes are related to health conditions. Thus, due to an increased life expectancy, most developed countries have today an increasing number of elders with health conditions that affect their functionality and autonomy on daily living (Chatterji et al., 2015).

Pathological Aging

Throughout the aging process several structural and functional changes within the prefrontal cortex and the hippocampus may occur, which could eventually result in pathological conditions. Specifically, volume loss in the hippocampus, and decline in attentional processes, working memory, executive functions, and memory recall are seen as important markers of pathological aging. However, other cognitive functions may remain preserved, such as language, semantic memory, and visuospatial functions (Gazanova et al., 2012).

Pathological aging is also characterized by neuronal loss or vascular changes, which are frequently associated with neurodegenerative diseases. How a particular neurodegenerative disease is clinically expressed depends on the structural and functional changes at play. That is, each etiological entity presents particular patterns of neuronal loss and specific anatomical distribution of cortical atrophy, which leads to more or less well-defined cognitive performance deficits and behavioral symptoms (Peña-Casanova, Sánchez-Benavides, Sola, Manero-Borrás, & Casals-Coll, 2012).

Establishing cognitive impairment profiles is useful to characterize different etiological entities and will better inform on diagnosis and potential intervention. According to Peña-Casanova (2012) the neurological, cognitive and neuropsychiatric symptoms allows the understanding of complex interplay occurring pathologic aging (Peña-Casanova et al., 2012). Furthermore, knowing that the degree of cognitive impairment has differents impacts on functional autonomy (ADL), the assessment of the cognitive impairment profile is crucial for diagnose and the establishment of adequate intervention programs for each dementia syndrome (McKhann et al., 2011).

Dementia

Alzheimer's Disease

Alzheimer's Disease (AD) is the most common cause of dementia with insidious and progressive features. Early decline in episodic memory characterizes AD and is related to an early cortical atrophy that occurs in the medial temporal lobe (MTL) – including the hippocampus and the entorhinal cortex (Cunha, Guerreiro, Mendonça, Oliveira, & Santana, 2012). In AD, according to Brickman and Stern (2009), long-term memory suffers gradual and progressive loss in its functioning. However, previous studies suggest a heterogeneous cortical atrophy within the medial temporal lobe, always mostly pronounced in the hippocampus (Gazanova et al., 2012).

Moreover, to diagnose AD the presence of other biomarkers, besides anatomical changes and memory loss, have been suggested. For example, according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984) deficits regarding executive functions, attentional processes, visuospatial abilities, language, and working memory must be taken into account. In sum, the major clinical criteria for AD is memory loss, and the presence of particular biomarkers' evidence, as deposition of amyloid-beta (Aß) protein, low Cerebrospinal Fluid (CSF) $Aß_{42}$, positive PET[1] amyloid imaging, and neuronal degeneration (McKhann et al., 2011).

Finally, one key aspect to diagnose AD is a comprehensive neuropsychological assessment to study patients cognitive profile. Neuropsychological assessment is an useful tool to characterize the specific deficits within each cognitive domain, and helps to establish structural and functional relations between specific brain structures recruited by the cognitive function affected. Furthermore, neuropsychological assessment enables monitoring the progression of the disease (Peña-Casanova et al., 2012).

Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is a heterogeneous clinical condition, that lays between healthy aging and dementia, where some cognitive abilities suffer decline (Ribeiro, Mendonça, & Guerreiro, 2006). This clinical condition is characterized by memory complaints and impaired performance on memory tasks, with a relative sparing of general cognitive functioning (Belleville et al., 2006). However, other cognitive domains, such as executive functions, language, attention and visuospatial abilities, can be affected. MCI is distinct from dementia because ADL is preserved and patients are still able to be independent. However, a mild decline in more complex instrumental activities of daily living (IADL) is common in this diagnosis.

[1] Positron emission tomography.

Recently, Peterson and colleagues (2014) suggested the need for longitudinal studies to clarify and characterize MCI profiles according to the cognitive domains affected - amnestic MCI (a-MCI) vs. nonamnestic MCI (na-MCI) – and according to the number of cognitive domains affected - MCI single domain and MCI multiple domains. Four clinical MCI subtypes are possible: a-MCI single domain, na-MCI single domain, a-MCI multiple domain and na-MCI multiple domain. The diagnosis of nonamnestic MCI is dependent on the presence of impaired performance on neuropsychological tests in cognitive domains other than memory (e.g. executive functions, visuospatial abilities and language). The amnestic type occurs when episodic memory is the most affected cognitive domain. Each clinical subtype is closely associated with the later development of specific dementias (Petersen et al., 2014).

The amnestic MCI subtype is the most studied and prevalent. Epidemiological, clinical and neuropathological research, suggest this subtype to be a pre-symptomatic form of Alzheimer's (Petersen et al., 1999; Morris & Price, 2001; Mitchell et al., 2002; Santana, 2003). Furthermore, other MCI subtypes seem to be related also with pre-symptomatic stages of other diagnosis (Small et al., 1997), such as Fronto-Temporal Dementia, Dementia with Lewy bodies, diseases manifested through parkinsonism symptoms and cognitive impairments (Santana, 2003).

In Portugal there is lack of epidemiological studies in dementia spectrum, beyond Nunes and colleagues' studies (2008; 2010), being that estimates and prevalences might not be consistent with reality.

Neuropsychological Assessment

Neuropsychological Assessment aims to understand cognition, brain function and behavior. In the beginning of the 21st century, neuropsychological assessment as an applied science was concerned about the behavioral expression of the brain dysfunction (Lezak et al., 2004). In the last years, neuropsychologists have been developing instruments to measure cognitive functioning within specific domains. The aim is to identify behavior and cognitive dysfunctions, leading to an increasingly diagnosis efficiency (Lezak et al., 2012).

As Lezak referred in 1983, the "*direct observation of the fully integrated functioning of living human brains will probably always be impossible*" (1983, p. 15, cited in Lezak et al., 2012). However, neuropsychological assessment techniques have been in constant development and improvement, overcoming administration, scoring and interpretation shortcomings. The 21st Century computer-based neuropsychological assessment tools, albeit not yet the dominant methods, have been showing to be powerful and to lead to an efficient prediction of brain functioning. The computer-based approach has proven to overcome administration, scoring, analysis and data storage bias. However, computerization is limited in the sense that it lacks the needed patient-clinician relationship, known to be an essential feature of neuropsychological assessment (Lezak et al., 2012).

Neuropsychological assessment should be integrative. That is, it should be applied along with other methods that together support diagnosis accuracy (e.g. combining neuropsychological assessment with functional neuroimaging, to observe the relationship between brain activation patterns with tests scores; Lezak et al., 2012). Furthermore, we must be aware of how well the neuropsychological assessment scores reflect reliable information about the brain functioning of patients. Thus, in this work we will explore the validity and diagnostic accuracy of Alzheimer Disease Assessment Scale – cognitive subscale (ADAS-Cog) for the Portuguese population, beginning with the following battery definition.

The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog)

The *Alzheimer's Disease Assessment Scale – cognitive sub-scale* (ADAS-Cog; Mohs, Rosen, & Davis, 1983; Rosen, Mohs, & Davis 1984; Guerreiro, Fonseca, Barreto, & Garcia, 2008) is a brief battery developed to assess cognitive performance in AD patients. The ADAS-Cog was also used as an outcome measure in clinical trials for AD (e.g. Davis et al., 1992; Birks, 2006), as a way to index the global level of cognitive functioning in response to therapies or drugs (Skinner et al., 2012). Indeed, from 1992 onwards, drug regulatory agencies as the Food and Drug Administration (FDA) requires the ADAS-Cog as an efficacy measure for clinical trials in AD, as well as a primary cognitive outcome (Davis et al., 1992; Doraiswamy et al., 1997; Vellas, Andrieu, Sampaio, Coley, & Wilcock, 2008; Schneider & Sano, 2009). Moreover, in the last years the ADAS-Cog has been used as a surrogate or a monitoring measure in clinical trials on Mild Cognitive Impairment (MCI; Skinner et al., 2012), but with poor efficacy (Sano et al., 2011).

The ADAS-Cog was developed according to the core characteristics of cognitive decline in AD: memory, language, praxia, constructive ability and orientation (Lezak et al., 2004). The ADAS-Cog is divided in two formal evaluation parts: the first is a brief interview that aims to assess several spontaneous language features (as fluency in speech, naming, comprehension and quality of speech); the second is a battery of tests that aim to assess multiple cognitive domains. This battery is composed by the following tasks: Word recall; Naming; Commands; Constructional Praxis; Ideational Praxis; Orientation; Word Recognition; Remembering Test Instructions; Spoken Language Ability; Word finding difficulty and Comprehension of oral language (Connor & Schafer, 1994). The total score in original version of ADAS-Cog may range between 0 and 70 points, where higher scores reflect poor performances or greater cognitive impairment (Lezak et al., 2004).

The ADAS-Cog shows high sensitivity, in that it can distinguishing between treatment and placebo groups in clinical trials (Skinner et al., 2012). However, Sano and colleagues (2011) suggest that ADAS-Cog is somehow limited in distinguishing MCI groups, due to its short form and ceiling effects in some items. Moreover, in faster stages of decline, the accuracy of the ADAS-Cog seems to be better, in contrast with slower stages as MCI conditions. At the end, the authors defend that the ADAS-Cog lacks

responsiveness as a cognitive measure in MCI's clinical trials (Skinner et al., 2012).

Connor and Sabbagh (2008) put forth a survey on rater's experience with ADAS-Cog administration. Their results show that there is significant variance in administration procedures (e.g.: explanations of instructions), scoring rules (e.g.: consider or not a subject error), and materials (e.g.: quality of word cards) across raters. This variance seems to compromise inter-raters agreement. The systematic review performed by Appels and Scherder (2010) on the diagnostic accuracy ADAS-Cog shows moderate to high inter-raters agreement (*r* range between .65-.95).

Patients' performances on ADAS-Cog seem to be influenced by demographic variables such as age and level of education. The results show a positive correlation between ADAS-Cog scores and age, and a negative correlation between ADAS-Cog scores and level of education. That is, the ADAS-Cog scores increase with age, and hence cognitive decline, mainly in subjects with low level of education (Doraiswamy et al., 1997; Doraiswamy, Kaiser, Bieber, & Garman, 2001).

Regarding extant similar tools, the ADAS-Cog is less expensive and requires simple administration and scoring procedures. Albeit its short-form, sensitivity and specificity of ADAS-Cog are good, and the battery has been suggested to be an adequate tool to predict the conversion to AD (Monllau et al., 2007). However, previous studies hinted at particular limitations of the ADAS-Cog, namely the undervaluation of critical functions in AD, such as attention, working memory and executive functions (Karin et al., 2014). For this reason, most authors and practitioners suggest the use of complementing neuropsychological tools to adequately assess all cognitive domains (Zec et al., 1992).

Recently, the responsiveness of the ADAS-Cog has been improved. Some studies suggested the redefinition of the items weighting system (Llano, Laforet, & Devanarayan, 2011; Wouters, van Gool, Schmand, & Lindeboom, 2008). Similarly, Skinner and colleagues (2012) suggest additional content to overcome the limitations of the ADAS-Cog. That is, this author suggests increasing the ADAS-Cog accuracy in detecting differences by adding new factors (e.g. number cancellation to assess frontal cognitive domains). Thus, the development of an extended version for ADAS-Cog has been under discussion, especially in what regards the assessment of mild conditions of dementia as is MCI (Skinner et al., 2012).

In Portugal, the ADAS-Cog was translated, adapted and transculturally validated by Guerreiro and colleagues (2008). The validation study of the Portuguese version of the ADAS-Cog used a control group from which preliminary cut-off values by age and level of education (including illiterate individuals) were defined (Guerreiro et al., 2008). The Portuguese version of the ADAS-Cog is available to clinicians monitor the progression of AD.

II – Objectives

The present study aims to validate the European Portuguese version of ADAS-Cog for the Portuguese population, considering the cognitively healthy elderly and the clinical groups with MCI and AD (mild to moderate severity). More specifically, we aim to present an exploratory analysis on its psychometric properties, analyze the cognitive performance of the study groups (Control Goup vs. MCI, Control Group vs. AD and MCI vs AD) and determine the respective diagnostic accuracy. Furthermore, we aim to update and extend the existing normative data, by including a larger control group (CG).

III – Methodology

Sample characterization

The Control Group was composed by healthy elderly people actively insert in community. The recruitment was made in Senior Universities (Universidade Sénior da Nazaré – USN), associations for elderly people (National Association of Elderly Support – ANAI, Coimbra), and patients' caregivers and companions of Dementia appointments in Memory Clinic of the Neurology Department of University Hospital of Coimbra. The inclusion criteria comprise Portuguese as native language, age equal or more than 50 years, absence of current history of psychiatric or neurologic disease and taking no medication with interference in normal function of cognitive domains. The exclusion criteria include illiteracy, people with functional deficits with influence in daily living autonomy (assessed with Adults and Older Adults Functional Assessment Inventory – IAFAI), presence of depressive symptomatology (assesses throughout clinical interview and items with emotional dependence in IAFAI), and performance's values outside of the normative range by age and education level in cognitive screening tests (e.g. Mini Mental State Examination – MMSE; Montreal Cognitive Assessment – MoCA), according to the normative values defined for the Portuguese population (Freitas, Simões, Alves, & Santana, 2011; 2014). These neuropsychological tests will be described in Procedures and Materials.

We recruited the participants for the clinical groups (MCI and AD) from the Memory Clinic of the Neurology Department of University Hospital of Coimbra. The patients were referred upon a detailed collection of self-reported history and report from reliable informant. Additionally, all patients underwent through a medical exam by a neurologist; presence of complementary diagnostic exams (e.g.: laboratory analysis – with genotype study of Apolipoprotein E, APOE –structural imaging exams – by axial computed tomography and magnetic ressonance – and functional – SPECT[2]); presence of other complementary medical exams (e.g.: PET[3] analysis and Cerebrospinal fluid – CSF – analysis through Lumbar Puncture);

[2] Single-photon emission computed tomography.

[3] Positron emission tomography.

Neuropsychological Assessment battery, with *Bateria de Lisboa para a Avaliação das Demências* (Guerreiro, 1998), presence of a Neuropsychological Assessment battery used to assess the progression of this clinical condition also integrated in a longitudinal study in MCI and described in Procedures and Materials of the present work. Final diagnosis was established by a multidisciplinary team following the international criteria to MCI conditions of Petersen's workgroup and Albert (Petersen et al., 1999; Albert et al., 2011) and the international criteria to probable AD of NINCDS-ADRA (McKhann et al., 2011). The MCI group included all patients presenting sub-clinical conditions, such as MCI amnestic single-domain and MCI amnestic multi-domain. The AD group included patients presenting mild to moderate Alzheimer's Disease.

Procedures

Control Group

The evaluation protocol was composed by: the Informed Consent Form; a Structured Clinical Interview; the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro et al., 1994), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Simões et al., 2008), the Adults and Older Adults Functional Assessment Inventory (IAFAI; Sousa, Vilar, & Simões, 2013), and the Alzheimer's Disease Assessment Scale – cognitive sub-scale (ADAS-Cog; Mohs et al., 1983; Rosen et al., 1984; Guerreiro et al., 2008). The assessment procedure was performed individually within one-hour session through a fixed order of tests.

MCI Group

Annually, all MCI patients of the Memory Clinic of the Neurology Department of University Hospital of Coimbra go through a comprehensive neuropsychological evaluation integrated in a more extensive longitudinal study. Here, we will retrospectively use part of the data collected for each patient within these extensive longitudinal study, in theirs last annual assessment. The neuropsychological protocol is composed by: the MMSE (Folstein et al., 1975; Guerreiro et al., 1994), the MoCA (Nasreddine et al., 2005; Simões et al., 2008), the ADAS-Cog (Mohs et al., 1983; Rosen et al., 1984; Guerreiro et al., 2008), the Subjective Memory Complaints (SMC; Schmand, Jonker, Hooijer, & Lindeboom, 1996; Ginó, Guerreiro, & Garcia, 2008), the Geriatric Depression Scale (GDS-30; Yesavag et al., 1983; Barreto, Leuschner, Santos, & Sobral, 2008; Simões & Firmino, 2013), the Hamilton, the Clinical Dementia Rating (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993; Garret et al., 2003), the Neuropsychiatric Inventory (NPI; Cummings et al., 1994; Cummings, 1997; Leitão & Nina, 2008), the Blessed Dementia Scale (Blessed, Tomlinson, & Roth, 1968; Garcia, 2008) and the Disability Assessment for Dementia Scale (DAD; Gelinas, Gauthier, McIntyre, & Gauthier, 1999; Leitão, 2008). Additionally, our participants also signed an Informed Consent Form authorizing the use of their data within the aims of the present thesis.

AD Group

The AD Group patients are assessed by the administration of a comprehensive Portuguese neuropsychological battery for dementias' assessment: the "Bateria de Lisboa para a Avaliação das Demências" (Guerreiro, 1998). For the present work, AD patients and its caregivers consent the participation with the Informant Consent's signature. Besides the typical evaluation made in this clinical condition, the participants were submitted to the ADAS-Cog scale. As well as the MCI group, the AD group was also composed in a retrospective way by part of data collected in previous studies with the ADAS-Cog scale.

Materials

In this topic "Materials", we will describe the three main cognitive tests (ADAS-Cog, MMSE and MoCA) subject to statistical analysis for the results of the present thesis, although the extensive neuropsychological protocol used for the inclusion and exclusion of patient in each group.

Alzheimer Disease Assessment Scale – Cognitive subscale (ADAS-Cog)

The Portuguese version of the ADAS-Cog (Guerreiro et al., 2008; Mohs et al., 1983; Rosen et al., 1984) was composed by the following subtasks. The total score in portuguese version of ADAS-Cog may range between 0 and 68 points.

Word Recall

In the Word Recall subtask 10 words printed in block letters on white cards are presented, in three trials. In each trial, the same 10 words are presented, although in different orders. In each trial, the participant is instructed to read the words out loud and to memorize them. Right after, the rater asks the participant to recall the words previously presented. Reinforcement is given when the participant is nervous or seems to be willing to give up. However, no recall clues are offered.

The score is the sum of the non-recalled words on the three trials divided by 3. The score range is between 0 (zero; i.e. all words were recalled) and 10. In general, this task assesses the ability to retain verbal material (Connor & Schafer, 1994).

Naming

In the Naming subtask the participant is asked to name 12 common objects. These objects are divided into three categories according to their lexical frequency (or familiarity): high frequency objects, medium frequency objects and low frequency. The participant is instructed to name the objects that are presented by the rater. If there is no response from the participant, the rater offers a standard clue for the specific item. If there is no response after the clue or if the participant provides an incorrect response, the rater moves to the next object. In these cases, the rater considers the presence of visuo-perceptional deficits. After the completion of this object naming task, the

participant is asked to name the fingers of his/her dominant hand. Correct responses are accepted according to specificities regarding cultural traditions and level of education.

The scoring is the sum of incorrect answers (for objects and for fingers) and ranges between 0 (zero; until two incorrect answers) and five points (between 15 and 17 incorrect answers). The Naming subtask assesses naming abilities, and the influence of the cultural background on the performance of the participant (Connor & Schafer, 1994).

Commands

In the Commands subtask the rater reads five commands, each at a time, to be performed by the participant. For two of the commands, three objects are needed (pencil, card and watch), for example: "put the watch on the other side of the pencil and then turn over the card". Each object represents a single step of the whole command, given in a row. If the participant shows hearing problems or attentional deficits, the rater instructs and captures the participant attention before reading the full command. It is important to ensure that a command is not given more than twice (first reading and one additional reading).

The score is the sum of errors in performing the commands and ranges between 0 (zero; no command was incorrectly performed) and five (all commands were incorrectly performed). The goal of this subtask is to assess receptive language (Connor & Schafer, 1994).

Constructional Praxis

In Constructional Praxis four images of different geometric figures are presented (circle; two overlapping rectangles; diamond or rhombus and cube). The geometric figures have distinctive shape complexity degrees, starting with a circle and ending with a cube. The figures are presented once at a time and the participant has two attempts to draw each shape. A second attempt is only offered when the participant indicates a problem with her/his drawing (the valid drawing is always the second one). If the participant is not able to reproduce a given geometric figure within two attempts, the rater moves to the next figure. The rater gives a pencil to the participant, informs her/him that she/he is not allowed to erase the drawing and that there is no time limit to draw each geometric shape.

To score the drawings small gaps in lines or size differences are not considered as errors, given that the whole shape was reproduced. The score ranges between 0 (zero; no incorrect drawings) and five (applied when the participant does not draw anything or writes words instead of forms). The Constructional Praxis subtask assesses the ability to copy four geometric forms and visual planning (Connor & Schafer, 1994).

Ideational praxis

In Ideational Praxis the participant is asked to execute a familiar action - to send a letter to someone. This task has 5 components, where each one represents a single step underlined in the whole instruction. If any of the steps

is missing, the rater repeats the instruction. If one step is overlooked, the rater reminds the participant of the next component.

The scoring codes for whether the participant is able to successfully perform the task of sending a letter (e.g., it should contain the name; street; city; and the zip code is not necessary). Wrong positioning of the address or stamp (represented by an "X" on the envelope) is scored as error. The total score ranges between 0 (zero; no errors) and 5 (a failure to complete the all 5 components). In general, the Ideational Praxis assess the ability to perform an overlearned task with an increasing complexity in its components (Connor & Schafer, 1994).

Orientation

In the Orientation subtask, the participant is instructed to answer a set of questions regarding time and space at the present moment: name, year, month, date, day of the week, season, place and time of the day. Each component has a right or wrong answer. However, some exceptions are accepted: incomplete name, one delayed hour regarding time the partial name of the place (for example: partial name of the hospital), and within one week prior to the onset of each season or two weeks after its offset. The remainder must be exact to be scored as correct (the day of the week, the month, the year and the participant's first and last names).

The total score is the sum of incorrect responses and ranges between 0 (zero; no incorrect responses) and 8 points (all answers are incorrect). The Orientation subtask determines how well oriented (time and space) is the participant at the moment of the assessment (Connor & Schafer, 1994).

Word recognition

In the Word Recognition subtask, the participant is instructed to read out loud the twelve words that are presented by the rater and try to learn them in one trial. Right after, the rater presents 3 sets of words composed by 24 words, in three trials. In each new set of 24 words 12 were within the first set and 12 are new ones. The participant is instructed to identify the words of these sets according to its presence or absence from the first set of words. That is, when the rater presents a word that was part of the first set, the participant should answer "yes". When, the participant is not able to recall the task instructions or gives the same answer repeatedly (e.g., saying "yes" or "no" to every word), the rater repeats the instructions and takes a note about the repetition of the instructions. These notes will be useful to score the next task that regards "remembering test instructions".

The score is the sum of word recognition errors over the three trials divided by 3. The total score ranges between 0 (zero; no errors) and 10 points (all answers are incorrect). If the result is higher than 10, the rater considers the maximum score. This subtask assesses the ability to recognize words or recently learned material (Connor & Schafer, 1994).

Remembering test instructions

This item assesses the ability of the participant to remember the instructions to perform the Word Recognition Task. The rater should know how many extra times the instructions were given to the participant for him/her to complete the subtask. The scoring ranges between 0 (zero; "no need for extra reminders") and 5 points ("severe – reminded 7 or more times"; Connor & Schafer, 1994).

Spoken Language Ability

This function is assessed throughout the session and regards narrative quality, fluency, clarity and difficulty of the participant's speech. Also, the introductory conversation before the beginning of the word recall subtask, allows for assessing spoken language abilities. The rater must be aware of the idiosyncratic speech and score accordingly. The total score ranges between 0 (zero; "no difficulty to understand the participant") and 5 points ("severe – e.g. one or two words utterance; fluent, but empty speech; mute"; Connor & Schafer, 1994).

Word finding difficulty

The presence or absence of impairments regarding expressive speech – the degree of difficulty to find the right word to explain some content – is assessed here. Therefore, this evaluation is taken during the whole session, according to the easiness of the participant to communicate verbally. The Naming subtask must be not included. The total score ranges between 0 (zero – "no evidence of word finding difficulty in spontaneous speech") and 5 points ("severe – near total loss of content of words; speech sound empty; 1 – 2 word utterances"; Connor & Schafer, 1994).

Comprehension of oral language

How well the participant understands the rater's speech during the assessment session is consider here. The Commands subtask must not be included. The total score ranges between 0 (zero – "no evidence of poor comprehension") and 5 points ("severe – the participant barely give appropriate answers, and that is not due to poor speech"; Connor & Schafer, 1994).

Mini Mental State Examination (MMSE)

The Mini Mental State Examination (MMSE; Folstein et al., 1975; Guerreiro et al, 1994) is the brief cognitive screening instrument most often used in clinical, research and epidemiological contexts (Freitas, Simões, Alves, & Santana, 2015a). This instrument assesses six cognitive domains: orientation; repetition; verbal recall; attention and calculation; language and visual construction. The administration of the test takes 5-10 minutes with total test scores ranged between 0 to 30 points, wherein high scores mean better cognitive performances (Freitas, Simões, Alves, & Santana, 2015b).

Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Simões et al., 2008) is a brief cognitive screening instrument developed

specifically for the assessment of milder forms of cognitive impairment, namely for the identification of mild cognitive impairment (MCI) patients (Freitas et al., 2011). This instrument assesses six cognitive domains: executive functions; visuospatial ability; short-term memory; language; attention; concentrarion and working memory; and temporal and spatial orientation (Freitas et al., 2011; Freitas, Simões, Alves, & Santana, 2015c). The administration of MoCA takes 10-15 minutes and the scores ranged between 0 to 30 points, where high scores mean better cognitive perfomances (Freitas et al., 2015c).

Ethical considerations

Both clinical groups were assessed according to their clinical condition, fully completing the currently adopted evaluation and research protocol by the Memory Clinic of the Neurology Department of University Hospital of Coimbra. The participants in the control group were individually identified and contacted after the agreement of the institutions that collaborated. All participants were volunteers and completed the Informed Consent Form after being conveniently informed about the study, its aims and procedures. To perform the assessments, facilities of the institutions were made available with appropriate rooms and fixed schedule slots. The participants were invited to individually and autonomously use one of these assessment slots if he/she wished to integrate the study. No payment was available to participants.

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS), Version 21 for Windows. Descriptive statistics were used for the sample's characterization. Differences within subgroups according to sociodemographic variables were analyzed using Student's *t* test and analyses of variance (ANOVA). To assess the internal consistency of ADAS-Cog was considered Cronbach α index. The construct validity was explored through correlations between items, subtasks and total scores of ADAS-Cog (*r;* Cohen, 1988). The convergent validity was determined using Pearson correlation coefficients between ADAS-Cog, MoCA, and MMSE scores (*r;* Cohen, 1988). The estimates of effect size were also calculated through analysis of eta squared (η^2; Cohen, 1988). The diagnostic accuracy of the ADAS-Cog for the identification of MCI and AD patients was assessed with the receiver operating characteristics (ROC) curve analysis. In this analysis, larger areas under the curve (AUC) reflect better diagnosis accuracy. The optimal cut-off points were determined by Youden index formula, where higher Youden index indicating maximization of the sensibility and specificity. For each cut-off point we calculated the sensitivity (the probability for subjects with disease to have a positive test), specificity (the probability for subjects without disease to have a negative test), positive predictive values (PPV; the probability of disease in subjects who have a positive test), negative predictive value (NPV; probability of the classification "without disease" in subjects who have a negative test), and classification accuracy (probability of correct classification of subjects with or without disease). The influence of sociodemographic characteristics, as age and education level, in ADAS-Cog

scores was addressed with multiple linear regression (MLR) analysis. Finally, the normative values of ADAS-Cog were stratified and determined according to the sociodemographic variables most significantly associated with ADAS-Cog scores showed by MLR analysis. The normative values are expressed through the means ± standard deviations (*SDs*), and the distributions of means below 1 *SD*, 1.5 *SDs*, and 2 *SDs*.

IV - Results

Sociodemographic characterization of the study sample

The present study's sample was composed by 743 participants, subdivided into 223 participants of the control group and 520 participants of the clinical group (MCI group: *n*=250: AD group: *n*=270). Table 1 presents sociodemographic characterization of the study sample and in more detail of the all subgroups. For this description were considered the following variables: sample size, age, educational level, and gender.

Table 1. Sociodemographic characterization of the study groups.

	Total Sample	**Control Group**	**Clinical Group**	**MCI Group**	**AD Group**
n	743	223	520	250	270
Age					
(M±SD)	(70.03±8.81)	(69.15±8.68)	(70.41±8.84)	(69.94±8.24)	(70.85±9.36)
[Min-Max]	[50 – 98]	[50 – 88]	[50 – 98]	[50 – 98]	[50 – 91]
Education					
(M±SD)	(6.82±4.49)	(8.22±4.87)	(6.21±4.18)	(6.68±4.46)	(5.79±3.87)
[Min-Max]	[1 – 21]	[2 – 18]	[1 – 21]	[1 – 21]	[1 – 17]
Gender	Female	Female	Female	Female	Female
F (%)	456 (61.4%)	130 (58.3%)	326 (62.7%)	149 (59.6%)	177 (65.6%)

We analyzed the existence of statistically significant differences in the sociodemographic variables with more influence on cognitive performance: age and education. The results suggested no statistical significant age differences between groups, except in control and AD groups, as presented on table 2.

Table 2. Age differences between groups.

	Age			Differences between groups
Control Group vs Clinical Group	(69.15±8.68) [50 – 88]		(70.41±8.84) [50 – 98]	$t_{(1, 741)}$=-1.80, p=.07
Control vs MCI	(69.15±8.68) [50 – 88]		(69.94±8.24) [50 – 98]	$t_{(1,471)}$=-1.02, p=.31
Control vs AD	(69.15±8.68) [50 – 88]		(70.85±9.36) [50 – 91]	$t_{(1, 491)}$=-2.07, p=.04
MCI vs AD	(69.94±8.24) [50 – 98]		(70.85±9.36) [50 – 91]	$t_{(1, 518)}$=-1.17, p=.24
Control Group vs MCI vs AD	(69.15±8.68) [50 – 88]	(69.94±8.24) [50 – 98]	(70.85±9.36) [50 – 91]	$F_{(2, 740)}$= 2.30, p=.10

We also analyzed the existence of significant differences in educational level between groups. It was observed statistical significant differences in all group comparisons, as presented on table 3.

Table 3. Education differences between groups.

	Education			Differences between groups
Control Group vs Clinical Group	(8.22±4.87) [2 – 18]		(6.21±4.18) [1 – 21]	$t_{(1, 741)}$=5.70, p<.01
Control vs MCI	(8.22±4.87) [2 – 18]		(6.68±4.46) [1 – 21]	$t_{(1, 471)}$=3.60, p<.01
Control vs AD	(8.22±4.87) [2 – 18]		(5.79±3.87) [1 – 17]	$t_{(1, 491)}$=6.19, p<.01
MCI vs AD	(6.68±4.46) [1 – 21]		(5.79±3.87) [1 – 17]	$t_{(1, 518)}$=2.44, p=.02
Control Group vs MCI vs AD	(8.22±4.87) [2 – 18]	(6.68±4.46) [1 – 21]	(70.85±9.36) [50 – 91]	$F_{(2, 740)}$=19.01, p<.01

In these preliminary results, we observed differences between groups in educational level. According to the fact that age and education level are the main influent variables in cognitive performance on neuropsychological assessment instruments, we opted to reduce the sample size in an attempt to matching the groups in those variables and thus minimized the influence of these individual variables on results. Therefore, with these matched groups, we obtain equivalent educational level between control, MCI and AD groups.

On table 4 we present sociodemographic characteristics results of the matched sample. After reducing the sample, we acquire 605 participants, 198 in control group and 407 in clinical groups. For this description were considered the following variables: sample size, age, educational level, and gender.

Table 4. Sociodemographic characterization of control and clinical groups in matched sample.

	Total Sample	Control Group	Clinical Group	MCI Group	AD Group
N	605	198	407	207	200
Age					
(M±SD)	(69.46±9.15)	(69.32±8.85)	(69.53±9.30)	(69.90±8.75)	(69.14±9.84)
[Min-Max]	[50 – 98]	[50 – 88]	[50 – 98]	[50 – 98]	[50 – 91]
Education					
(M±SD)	(6.96±4.31)	(7.34±4.35)	(6.78±4.28)	(6.81±4.50)	(6.74±4.05)
[Min-Max]	[2 – 17]	[2 – 17]	[2 – 17]	[3 – 17]	[2 – 17]
Gender	Female	Female	Female	Female	Female
F (%)	364 (60.2%)	117 (59.1%)	247 (60.7%)	122 (58.9%)	125 (62.5%)

Comparing these matched groups (control, MCI and AD groups), no differences were observed at level of mean age, as presented on table 5.

Table 5. Age differences between matched groups.

	Age			Differences between groups
Control Group vs Clinical Group	(69.32±8.85) [50 – 88]		(69.53±9.30) [50 – 98]	$t_{(1, 603)}$=-.26, p=.79
Control vs MCI	(69.32±8.85) [50 – 88]		(69.90±8.75) [50 – 98]	$t_{(1,403)}$=-.66, p=.51
Control vs AD	(69.32±8.85) [50 – 88]		(69.14±9.84) [50 – 91]	$t_{(1,396)}$=.19, p=.85
MCI vs AD	(69.90±8.75) [50 – 98]		(69.14±9.84) [50 – 91]	$t_{(1, 405)}$=.82, p=.41
Control Group vs MCI vs AD	(69.32±8.85) [50 – 88]	(69.90±8.75) [50 – 98]	(69.14±9.84) [50 – 91]	$F_{(2, 602)}$=.38, p=.68

We also compared the mean education level of the matched groups, where no differences between control, MCI and AD groups was obtained, as presented on table 6.

Table 6. Education differences between matched groups.

	Education			Differences between groups
Control Group vs Clinical Group	(7.34±4.35) [2 – 17]		(6.78±4.28) [2 – 17]	$t_{(1, 603)}$=1.51, p=.13
Control vs MCI	(7.34±4.35) [2 – 17]		(6.81±4.50) [3 – 17]	$t_{(1, 403)}$=1.20, p=.23
Control vs AD	(7.34±4.35) [2 – 17]		(6.74±4.05) [2 – 17]	$t_{(1, 396)}$=1.42, p=.16
MCI vs AD	(6.81±4.50) [3 – 17]		(6.74±4.05) [2 – 17]	$t_{(1, 405)}$=.17, p=.87
Control Group vs MCI vs AD	(7.34±4.35) [2 – 17]	(6.81±4.50) [3 – 17]	(6.74±4.05) [2 – 17]	$F_{(2, 602)}$=1.15, p=.32

Cognitive characterization of groups

In an attempt to characterize the global cognitive performance of participants, table 7 presents the results of each group in MMSE and MoCA in matched sample.

Table 7. Characterization of the global cognitive performance of the matched groups.

	Total Sample	Control Group	Clinical Group	MCI Group	AD Group
N	605	198	407	207	200
MMSE					
(*M*±*SD*)	(25.96±4.07)	(28.97±1.04)	(24.49±4.18)	(27.19±2.26)	(21.70±3.86)
[Min-Max]	[12 – 30]	[25 – 30]	[12 – 30]	[19 – 30]	[12 – 29]
N	*605*	*198*	*407*	*207*	*200*
MoCA					
(*M*±*SD*)	(19.77±5.74)	(23.38±3.20)	(16.96±5.71)	(19.85±4.69)	(10.27±3.60)
[Min-Max]	[4 – 29]	[15 – 29]	[4 – 29]	[7– 29]	[4 – 19]
N	*210*	*92*	*118*	*92*	*26*

It was observed statistically significant differences between control, MCI and AD groups of the matched sample on MMSE performance ($F_{(2, 602)}$ =409.26, p<.01, η^2=.58) and MoCA performance ($F_{(2, 207)}$ =115.26, p<.01, η^2=.54). As expected, according to the post-hoc tests, the control group showed better cognitive performance than both clinical groups and the MCI group revealed significant higher results than the AD group.

Psychometric properties

Internal Consistency of ADAS-Cog

The Cronbach's alpha is the most common estimate of the internal consistency. According to retrospective characteristic of the present study, it was not possible to collect the data of ADAS-Cog items of all participants, thus the Cronbach's alphas were computed on more restricted subgroups. The total subgroup (n=274) showed a Cronbach's alpha of α=.58, the control subgroup (n=150) obtained a Cronbach's alpha of α=.56, the clinical group (124) obtained a Cronbach's alpha of α=.62, the MCI group (n=59) with a Cronbach's alpha of α=.58 and the AD group (n=65) with a Cronbach's alpha of α=.52. Regarding the analysis of ADAS-Cog items that could be eliminated to increase consistency, the results indicated that none should be excluded in any group.

Even if it was not possible to collect the ADAS-Cog items of all participants, we collected the most part of ADAS-Cog subtasks (e.g.: word recall task, naming task, commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test instructions, spoken language ability, word finding difficulty and comprehension of oral language). Consequently, we also examine the internal consistency of this cognitive subtasks that in set resulted in ADAS-Cog total score. It was obtained a

Cronbach's alpha of α=.81 for the subtasks in the total sample (n=742), the control group (n=223) obtained a Cronbach's alpha of α=.33, the clinical group (519) obtained a Cronbach's alpha of α=.78, the MCI group (n=249) obtained a Cronbach's alpha of α=.53 and the AD group (n=270) obtained a Cronbach's alpha of α=.71. Once again, the results indicated that the internal consistency do not revealed improvement with the exclusion of any items/subtasks.

Construct Validity

In order to explore indicators of construct validity, we explored a set of correlations: items vs items, items vs subtasks, items vs ADAS-Cog total score and subtasks vs ADAS-Cog total score, for total study sample as well as for each subgroup. For total study sample, the correlation coefficients values between items ranged between -.67 and 1 (p<.01); the correlations between items and subtasks showed coefficients values ranging between -.83 and .92 (p<.01); the correlations between items and ADAS-Cog total score ranged between -.49 and .80 (p<.01); and the correlations between subtasks and ADAS-Cog total score ranged between .50 and .82 (p<.01). For the control group, the correlation coefficients values between items ranged between -.26 and 1 (p<.01); the correlations between items and subtasks showed coefficients values ranging between -.85 and .81 (p<.01); the correlations between items and ADAS-Cog total score ranged between -.38 and .60 (p<.01); and the correlations between subtasks and ADAS-Cog total score ranged between .11 and .73 (p<.01). For the clinical group, the correlation coefficients values between items ranged between -.59 and 1 (p<.01); the correlations between items and subtasks showed coefficients values ranging between -.80 and .90 (p<.01); the correlations between items and ADAS-Cog total score ranged between -.62 and .76 (p<.01); and the correlations between subtasks and ADAS-Cog total score ranged between .43 and .76 (p<.01). For the MCI group, the correlation coefficients values between items ranged between -.50 and 1 (p<.01); the correlations between items and subtasks showed coefficients values ranging between -.83 and .86 (p<.01); the correlations between items and ADAS-Cog total score ranged between -.60 and .74 (p<.01); and the correlations between subtasks and ADAS-Cog total score ranged between .16 and .72 (p<.01). Finally, for the AD group, the correlation coefficients values between items ranged between -.43 and .76 (p<.01); the correlations between items and subtasks showed coefficients values ranging between -.78 and .88 (p<.01); the correlations between items and ADAS-Cog total score ranged between -.47 and .68 (p<.01); and the correlations between subtasks and ADAS-Cog total score ranged between .36 and .65 (p<.01).

Convergent Validity

The convergent validity was explored through the correlations between the three applied cognitive tests (MMSE, MoCA and ADAS-Cog). The results suggested significant negative correlations between the total scores of ADAS-Cog and MMSE (r=-.86, p<.01, n=743), as with MoCA (r=-.80, p<.01,

n=248). The result between MoCA and MMSE total scores was a significant positive correlation (*r*=.80, *p*<.01, *n*=248). We also performed the same analysis to each group, where in the control group was observed a significant negative correlation between the total scores of ADAS-Cog and MoCA (*r*=-.42, *p*<.01, *n*=103), as with MMSE (*r*=-.37, *p*<.01, *n*=223). The result between MoCA and MMSE total scores was a significant positive correlation (*r*=.50, *p*<.01, *n*=103). In the MCI group, the results suggested a significant negative correlation between the total scores of ADAS-Cog and MoCA (*r*=-.68, *p*<.01, *n*=110), as with MMSE (*r*=-.63, *p*<.01, *n*=250). The result between MoCA and MMSE total scores was a significant positive correlation (*r*=.61, *p*<.01, *n*=101). Finally, the AD group showed significant negatives correlations between the total scores of ADAS-Cog and MoCA (*r*=-.54, *p*<.01, *n*=35), as with MMSE (*r*=-.67, *p*<.01, *n*=270). The result between MoCA and MMSE total scores was a significant positive correlation (*r*=.50, *p*<.01, *n*=35).[4]

Differences between groups in ADAS-Cog performance

According to the main objective of the present study, we test the differences between the matched groups in ADAS-Cog performance. On Table 8 we presented the ADAS-Cog performance in matched sample, in more detail of the all subgroups, and the performance in each ADAS-Cog subtasks.

Table 8. Characterization of the ADAS-Cog performance of the matched groups

	Total Sample	Control Group	Clinical Group	MCI Group	AD Group
n	605	198	407	207	200
ADAS-Cog					
(M±SD)	(12.69±8.01)	(6.22±2.53)	(15.84±7.87)	(10.82±4.03)	(21.03±7.51)
[Min-Max]	[0 – 50]	[0 – 13]	[3 – 50]	[3 – 31]	[7 – 50]
n	*605*	*198*	*407*	*207*	*200*
WRT					
(M±SD)	(5.09±1.89)	(3.63±1.38)	(5.80±1.65)	(4.90±1.42)	(6.73±1.31)
[Min-Max]	[0 – 10]	[0 – 7]	[2 – 10]	[2 – 10]	[3 – 10]
n	*605*	*198*	*407*	*207*	*200*
NT					
(M±SD)	(0.31±0.56)	(0.09±0.28)	(0.43±0.62)	(0.32±0.54)	(0.54±0.68)
[Min-Max]	[0 – 5]	[0 – 1]	[0 – 5]	[0 – 4]	[0 – 5]
n	*605*	*198*	*407*	*207*	*200*
COM					
(M±SD)	(0.49±0.76)	(0.21±0.45)	(0.55±0.86)	(0.26±0.51)	(0.85±1.02)
[Min-Max]	[0 – 5]	[0 – 2]	[0 – 5]	[0 – 3]	[0 – 5]
n	*605*	*198*	*407*	*207*	*200*

[4]The retrospective characteristic of the present study justifies these differences in sample size for each cognitive test.

	Total Sample	Control Group	Clinical Group	MCI Group	AD Group
n	605	198	407	207	200
CP					
(M±SD)	(0.78±0.83)	(0.41±0.60)	(0.96±0.87)	(0.63±0.61)	(1.31±0.96)
[Min-Max]	[0 – 4]	[0 – 4]	[0 – 4]	[0 – 3]	[0 – 4]
n	*605*	*198*	*407*	*207*	*200*
IP					
(M±SD)	(0.36±0.61)	(0.09±0.30)	(0.49±0.68)	(0.32±0.53)	(0.67±0.77)
[Min-Max]	[0 – 4]	[0 – 2]	[0 – 4]	[0 – 2]	[0 – 4]
n	*605*	*198*	*407*	*207*	*200*
OR					
(M±SD)	(1.07±1.65)	(0.08±0.29)	(1.56±1.81)	(0.48±0.92)	(2.67±1.83)
[Min-Max]	[0 – 7]	[0 – 2]	[0 – 7]	[0 – 5]	[0 – 7]
n	*605*	*198*	*407*	*207*	*200*
WR					
(M±SD)	(3.82±2.80)	(1.75±1.35)	(4.84±2.77)	(3.50±2.02)	(6.22±2.77)
[Min-Max]	[0 – 12]	[0 – 7]	[0 – 12]	[0 – 10]	[0 – 12]
n	*605*	*198*	*407*	*207*	*200*
RTI					
(M±SD)	(0.42±1.03)	(0.03±0.19)	(0.62±1.20)	(0.20±0.56)	(0.36±0.89)
[Min-Max]	[0 – 5]	[0 – 2]	[0 – 4]	[0 – 3]	[0 – 4]
n	*605*	*198*	*407*	*207*	*200*
SPA					
(M±SD)	(0.13±0.55)	(0±0)	(0.19±0.66)	(0.03±0.20)	(0.38±0.98)
[Min-Max]	[0 – 5]	[0 – 0]	[0 – 5]	[0 – 2]	[0 – 5]
n	*605*	*198*	*407*	*207*	*200*
WFD					
(M±SD)	(0.14±0.60)	(0±0)	(0.21±0.73)	(0.04±0.23)	(1.06±1.49)
[Min-Max]	[0 – 5]	[0 – 0]	[0 – 5]	[0 – 2]	[0 – 5]
n	*605*	*198*	*407*	*207*	*200*
COL					
(M±SD)	(0.10±0.46)	(0±0)	(0.15±0.55)	(0.01±0.12)	(0.29±0.75)
[Min-Max]	[0 – 4]	[0 – 0]	[0 – 4]	[0 – 1]	[0 – 4]
n	*605*	*198*	*407*	*207*	*200*

ADAS-Cog = total score; WRT = Word Recall Task; NT = Naming Task; COM = Commands; CP = Constructional Praxis; IP = Ideational Praxis; OR = Orientation; WR = Word Recognition; RTI = Remembering Test Instructions; SLA = Spoken Language Ability; WFD = Word Finding Difficulty; COL = Comprehension of Oral Language.

We analyzed the existence of statistically significant differences in the ADAS-Cog performances in matched sample. The results suggested significant statistical differences between groups: clinical vs control group, control vs MCI group, control vs AD group and MCI vs AD group, as presented on table 9.

Table 9. Differences in ADAS-Cog between matched groups.

	Differences between groups
Control Group vs Clinical Group	$F_{(1, 603)}$=112.55, p<.01, η^2=.32
Control vs MCI	$F_{(1, 403)}$=26.41, p<.01, η^2=.33
Control vs AD	$F_{(1, 396)}$=102.67, p<.01, η^2=.64
MCI vs AD	$F_{(1,438)}$=45.38, p<.01, η^2=.43

Validity and Diagnostic Accuracy of ADAS-Cog

To evaluate the diagnostic accuracy of ADAS-Cog in the discrimination of MCI and AD patients from healthy elderly controls, as well as between MCI and AD patients, we performed the ROC curve analysis presented in figures 1, 2 and 3.

The AUC for the MCI was 0.839 [95% confidence interval (CI)=0.801-0.876]. For AD we obtained an AUC of 0.996 [95% (CI)=0.992-1.000]. We also calculated the discriminant potential of ADAS-Cog between MCI and AD, with an AUC of 0.924 [95% (CI)=0.898-0.949]. On table 10 we described the optimal cut-off point for maximum accuracy (according to Youden index) and the respective values of sensitivity, specificity, PPV, NPV, and classification accuracy. The optimal cut-off point for the ADAS-Cog total score above 9 allows identify MCI patients discriminating from the healthy elderly controls. With this cut-off point, ADAS-Cog had a sensitivity of 58%, a specificity of 91%, a PPV of 87%, a NPV of 67%, and a classification accuracy of 74%. To AD, the cut-off point above 12 in ADAS-Cog total score allows the discrimination between AD and controls, with a sensitivity of 94%, a specificity of 98%, a PPV of 98%, a NPV of 94%, and a classification accuracy of 96%. To distinguish MCI and AD patients, the cut-off point above 15 in ADAS-Cog total score presented a sensitivity of 76%, a specificity of 91%, a PPV of 88%, a NPV of 79%, and a classification accuracy of 83%.

Figure 1. ROC (receiver operating characteristics) curve analysis of the ADAS-Cog to detect MCI.

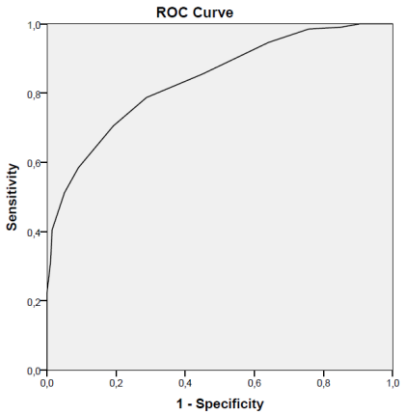

Figure 2. ROC (receiver operating characteristics) curve analysis of the ADAS-Cog to detect AD.

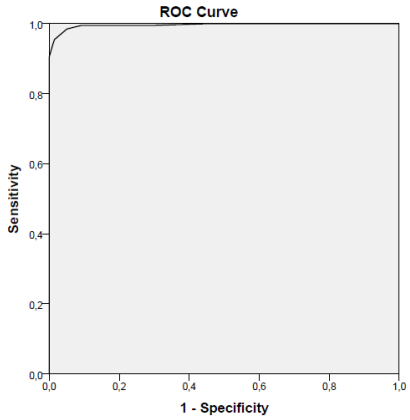

Figure 3. ROC (receiver operating characteristics) curve analysis of the ADAS-Cog to distinguish MCI of AD.

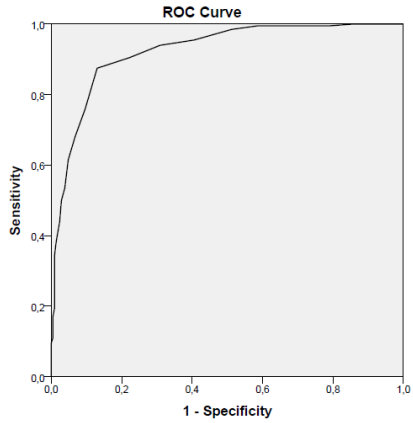

Table 10. Diagnostic Classification Accuracy

ADAS-Cog	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	Classification Accuracy
MCI	>9	0.839	58	91	87	67	74
AD	>12	0.996	94	98	98	94	96
AD/MCI	>15	0.924	76	91	88	79	83

Sensitivity, specificity, PPV, NPV, and classification accuracy values were expressed in percentage. Cut-off points indicate the minimum score required for presence of signal.
AUC: area under the operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value.

Normative Values

Influence of the sociodemographic variables on ADAS-Cog performance

Statistically significant correlations were observed between the ADAS-Cog scores and age (r=.13, p<.01) and educational level (r=-.27, p<.01) considering the total sample (n=743). We also calculated these correlations coefficients for each group. The results suggested significant positive correlation coefficients between ADAS-Cog and age in control group (r=.35, p<.01) and MCI group (r=.21, p<.01), while the AD group did not show this significant positive correlation (r=.03, p<.65). Significant negative correlation coefficients between ADAS-Cog and educational level were found to control group (r=-.16, p<.05), MCI group (r=-.26, p<.01), and AD group (r=-.18, p<.01).

MLR analysis was performed to examine the contribution of these significant variables (age and education) to the ADAS-Cog scores, observing the interactions that could explain the variance of performances. We performed the regression model ($F_{(2)}$=18.567, p<.001), where we consider the two variables combined age (ß=.343, t=5.491, p<.001) and education (ß=-.146, t=-2.333, p=.021). The beta weights indicated that age was the major contributor to the prediction of the ADAS-Cog scores, nevertheless education level also had contribution to the prediction. To this model, the adjusted R^2 value was .137, which means that 13.7% of the variance on the ADAS-Cog scores was explained by both variables.

Including only the variable age ($F_{(1)}$=13.199, p<.001, ß=.351, t=5.57, p<.001). The adjusted R^2 value was .119, which indicates that 11.9% of the variance on the ADAS-Cog scores was explained by age. We also performed a regression model to education level ($F_{(1)}$=6.173, p=.014) where we obtained a ß=-.165, t=-2.485, p=.014. The adjusted R^2 value was .023, which indicates that 2.3% of the variance on the ADAS-Cog scores was explained by education level.

Normative values

According to the results of MLR analysis, age and education level were considered in the development of the normative values of the ADAS-Cog for the Portuguese population. To obtain these normative values we stratified the sample according to the distribution properties of education level and age. The

ADAS-Cog scores are expressed through the means and standard deviations (M±SD) by education levels and age. On table 11 we present the normative values of ADAS-Cog according to both age and education level.

Table 11. Normative values of ADAS-Cog according to age and education level.

Age		Education (years)			
		Primary (1-4)	Middle (5-9)	High (≥10)	All education
50-64	***n***	27	17	21	65
	M±SD	5.48±2.17	5.41±2.21	3.67±2.08	4.88±2.28
	***SD*[1]**	8, 9, 10	8, 9, 10	6, 7, 8	7, 8, 9
65-75	***n***	47	17	33	97
	M±SD	6.85±2.57	5.89±1.93	6.06±1.62	6.41±2.20
	***SD*[1]**	9, 11, 12	8, 9, 10	*8, 8, 9*	9, 10, 11
+75	***n***	27	11	23	61
	M±SD	7.15±2.84	7.09±2.26	6.70±2.46	6.97±2.57
	***SD*[1]**	10, 11, 13	9, 10, 12	*9, 10, 12*	*10, 11, 12*
All age	***n***	101	45	77	223
	M±SD	6.56±2.61	6.00±2.17	5.60±2.34	6.12±2.46
	***SD*[1]**	*9, 10, 12*	*8, 9, 10*	*8, 9, 10*	*9, 10, 11*

[1]ADAS-Cog values above 1 *SD*, 1.5 *SDs*, and 2 *SDs*, respectively

V - Discussion

The main objective of this study was to validate the ADAS-Cog for MCI and AD patients, as a brief method for evaluate the global cognitive status and its impairments in AD. The analysis of group differences reports that the ADAS-Cog are able to distinguish between clinical and control groups. Also within clinical groups, the ADAS-Cog shows a discriminative capacity between MCI patients and AD patients. According to Cohen (1988) this differences had a large effect size (>.25) represented by eta squared values (η^2), reflecting the degree to which researchers could believe in H0 as a false hypothesis (Cohen, Swerdlik, & Smith, 1992). The reliability and validity of neuropsychological tests should be tested to ensure the "quality" of the neuropsychological assessment process (Strauss, Sherman, & Spreen, 2006). To ensure an optimal use of the ADAS-Cog in clinical field, we explored its psychometric characteristics. We tested the coherence of ADAS-Cog components through internal consistency using Cronbach's alpha which is the most commonly used measure, and as well as an attempt to enhance the comparability between studies (McCrae, Kurtz, Yamagata, & Terracciano, 2011). This measure tested the way that each item within a test mesure the same cognitive domain (Strauss et al., 2006). We obtained values below the recommended minimum of .70, however international studies in psychometric field also had this limitation in internal consistency of ADAS-Cog (e.g. Karin et al., 2014). Actually, within psychometricians community some issues about low value of Cronbach's alpha are still without a consensual explanation, as well as questions about its sufficiency as a reliability's measure (Karin et al., 2014). Thus, we could point out several variables, as sample size of items and

the population's features, which contribute to this low Cronbach's alpha value. Indeed, theoretically the Loevinger's hypothesis (1954) about the attenuation paradox is a relevant explanation about the limitation of predictive utility, due to narrow content and its consequently threats, for instance the item redundancy (McCrae et al., 2011). Additionally, it is common the observation of low reliability coefficients within population with high response variability, for instance elderly people and individuals with brain disorders, similarly to the population recruited in this thesis (Strauss et al., 2006). Within psychometric field, as expected, we observed a high negative correlation between ADAS-Cog scores and both MMSE scores (r=-.86, p<.01, n=743) and MoCA scores (r=-.80, p<.01, n=248), which is indicative of convergent validity. The construct validity assessed correlations between items, subtasks, and total scores together, addressing important information related to partial and whole function of the test. The analysis between items, in control group, we found significant positive correlations between the components of the ideational praxis subtask (r=1, p<.01), the MCI group shown significant positive correlations (r=1, p<.01) between objects' names of the naming subtask, and the AD group shown significant positive correlations between fingers' names of the naming subtask (r=.76, p<.01, n=65). In all groups, we also found that all of the items were more highly positive correlated with their own respective subtask, for example: one trial of word recall had significant positive correlation with word recall subtask (r=.81, p<.01, n=151). The highly significant negative correlations were found between more complex items and its own subtaks, for example: the cube draw was negativetly correlated with constructional praxis subtak (Control group: r=-.85, p<.01, n=179), and the fifth command was negativetly correlated with commands subtask (MCI: r=-.83, p<.01; AD group: r=-.78, p<.01). We also analyze the correlations between subtasks and ADAS-Cog total score. In control group the highest significant positive correlation was between "word recall subtask" and ADAS-Cog total score (r=.73, p<.01, n=223) and the lower positive correlation was between "naming subtask" and ADAS-Cog total score (r=.11, p<.11, n=223); in MCI group the highest significant positive correlation was between "word recognition subtask" and ADAS-Cog total score (r=.72, p<.01, n=250) and the lower significant positive correlation was between "comprehension of oral language" and ADAS-Cog total score (r=.16, p=.01, n=250), and in AD group the highest significant positive correlation was between "comprehension of oral language" and ADAS-Cog total score (r=.65, p<.01, n=270) and the lower significant positive correlation was between "ideational praxis" and ADAS-Cog total score (r=.36, p<.01, n=270). The present results of construct validity reveal some important aspects of ADAS-Cog constitution. The perfect correlation between naming's items (e.g. pencil with ball) or between items of different substaks (e.g. month and pencil; first command and pencil) in control and MCI group means that these itens had a low discriminative power of the performance of the participants, where these use are meaningless. Indeed, these correlations corroborated the reported ceiling effect in some subtasks of ADAS-Cog, principally in naming subtask (Verma et al., 2015).

However, in AD group we did not observe perfect correlations between items, even in the same subtask, which means that the dificult level of these items are more adequate for this clinical group and moderate cognitive impairment. Finally, the highly correlated subtask with ADAS-cog total score was the "comprehension of oral language", revealing that the main characteristic that compromised the total score was the understanding of explanations given during the test's administration. Indeed, the high correlation between fifth command, which is the most complex command, and its own subtask shows this observed difficulty in the comprehension of oral language and complex instructions. Thus, in construct validity we observed the relationship between the information provided by each part of ADAS-Cog and its diagnostic purpose, that seems to be more realiable in AD group.

According to the results of each subtask per group, an increased tendency of means could be observed. Actually, this results reveal the expected likelihood to have more errors in AD group than Control group in ADAS-Cog' subtasks. Furthermore, the tendency of error increased from Control Group to AD group. The Clinical group shown more tendency to error in memory subtasks (e.g. word recall and word recognition subtasks) as AD group, but MCI group showed lower error's means. Memory subtask shown high differences across the results of the three groups, which is not surprising considering its important role in cognitive characterization of AD. Based on preliminary descriptive analysis, we cannot assume the redundancy of subtasks of Portuguese version of ADAS-Cog, due to the lack of Item Response Theory (IRT) analysis in this present thesis. Studies in psychometric properties (e.g. Wouters et al., 2008; Benge, Balsis, Geraci, Massman, & Doosy, 2009) explore the information provided by ADAS-Cog assessment thought IRT analysis. Wouters and colleagues (2008) found that ADAS-Cog did not have good results in (IRT) analysis to the spectrum of cognitive dysfunction, which provide information about the way that items in a specific test are related to a latent construct. However, the same authors suggested that modifications in weighted scores could improve the instrument's performances and its responsiveness, especially for others clinical conditions as MCI (Wouters et al., 2008). Instead, but not completely, Benge and colleagues (2009) found that ADAS-Cog are better in the assessment of moderate levels of cognitive impairment in AD, wherein as a whole the magnitude of cognitive dysfunction was not equal across this test.

Recently the ADAS-Cog has been used as the standard measure of cognition in clinical trials with MCI patients, although its limited sensitivity to detect change in this early stages of the disease (Podhorna, Krahnke, Shear, Harrison, & the Alzheimer's Disease Neuroimaging Initiative, 2016). Studies suggested the importance of adding delayed recall memory task, due to its critical role in the assessment of preclinical stages, as MCI. Also, the inclusion of this task is frequently administered but without weight in final score of 70 points (Benge et al., 2009). Indeed, adding new sensitive subtasks to preclinical stages, also improves the responsiveness and psychometric properties of ADAS-Cog in cognitive dysfunction spectrum. Thus it is imperative to make adjustments in this battery to MCI groups avoiding lacks

in the assessment of cognitive functioning, despite the ability to discriminate clinical groups (MCI and AD). Indeed, our results suggest that ADAS-Cog are capable to distinguish patients between AD and MCI, but its sensitivity and specificity are better to AD group. We also reported a better effect size for AD (η^2=.64), which corroborated the proper use of this test for the assessment of this clinical condition.

Therefore, we explored the diagnostic validity of ADAS-Cog to our sample. As expected, the results of ROC analysis suggested a higher discriminant potential of ADAS-Cog for AD than for MCI patients. The optimal cut-off point for AD was above 12 of total score, and this value is close to other studies in diagnostic validity of ADAS-Cog (e.g. cut-off point of 15 by Youn and colleagues, 2002; cut-off point of 12 by Monllau and colleagues, 2007). For AD patients, the ADAS-Cog shown a high sensitivity of 94% and a specificity 98% in comparison with values already demonstrated by Monllau and colleagues (2007) with 89% and 89%. Indeed, our results for AD was closed to the values reported by Chu and colleagues (2000) with 90% and 95% respectively. In MCI patients, we obtained lower sensitivity (58%) and high specificity (91%) for a cut-off point of 9 with an AUC of 0.839, but similar with studies in ADAS-Cog validation for MCI patients (e.g. Papp, Pákáski, Drótos, & Kálmán, 2012) where the AUC was 0.875, the sensitivity was 95.6% and the specificity was 70.2%. These results confirm that the ADAS-Cog is a better cognitive battery to assess and monitoring AD conditions, with higher diagnostic accuracy for its patients than for MCI patients. Due to its capacity for discriminate both clinical conditions, the consideration of this cut-off points seems to be pertinent, as well as an useful tool for diagnosis conversion. It is important to highlight the careful use of ADAS-Cog in MCI population, due to its poor sensitivity (58%) and classification accuracy (74%), as an indicator of high likelihood to have false-negative cases. Nevertheless, in both clinical conditions (AD and MCI) the ADAS-Cog should be used as a progression assessment tool and never for a diagnostic tool. Additionaly, the progression between MCI and AD should be auxiliated by our cut-off point of 15 ADAS-Cog total score, with a sensitivity of 76%, a specificity of 91% and a classification accuracy of 83%.

Surprisingly, during the constitution of normative data, we realized that age was the major contributor to the prediction of ADAS-Cog scores, in comparison with education. Similarly, Graham and colleagues (2004) found no influence of ten or more years of education in their study, pointed out the hypothesis of a required threshold level of education to evaluate ADAS-Cog's performances with success. Indeed, the results of a study by Liu and colleagues (2002) suggested the possibility of influence just in very low education levels (e.g. zero to six years), which could explain the results of our MLR analysis since our education mean is above this range (8.22). Albeit the MLR analysis results of this study, we opted to considered both sociodemographic variables (age and education) for the constitution of normative values. Furthermore, several studies (Doraiswamy et al., 1997, 2002; Peña-Casanova et al., 1997; Schultz, Siviero, & Bertolucci, 2001) have been show the magnitude of the education effect in cognitive performances,

being criteria for the establishment of normative data. Instead, before normative values of ADAS-Cog by Guerreiro and colleagues (2008) for the Portuguese population, our normative data was established and stratified into more restricted education groups (primary: 1-4 years; middle: 5-9 years; high ≥10 years) and age groups (50-64; 65-75; +75). Thereby, we determined the means and standard deviations for each subgroup, crossing the several education levels and age. We also presented cut-off points of 1 *SD*, 1.5 *SDs*, and 2 *SDs* used to define the norms. Finally, we established the same norms to "all education levels" and "all age" to cover situations with lack of sociodemographic information.

The main limitation of the present study was the exclusion of the illiterate subjects. In illiteracy, cognitive evaluation needs to be adapted to ensure the reliability of the obtained scores. The education seems to have influence on cognitive processes, further than the ability to read or write. Studies suggested influence of education in cognitive batteries that apparently were free of schooling effects, like ADAS-Cog (Schultz et al., 2001; Brucki, 2010). Furthermore, illiteracy shows effects in language, praxis, and visuospatial abilities, which are three main components of ADAS-Cog. Thus, difficulties in naming can easily occur (e.g. illiterates have difficulties in naming fingers), commands (e.g. illiterates tend to omit sequences), ideational praxis (e.g. the subtask is composed by a familiar task for literates – sending a letter) and constructional praxis (e.g. illiterates show shortcomings in copying figures, especially in cube; Lezak et al., 2004; Ardila & Rosselli, 2007). Importantly, memory presents significant differences between illiterates and literates, where the main effect has been reported in words recall tasks (immediate or delayed recall). Indeed, illiterate people have few available strategies to process and to retain verbal material (e.g. they just can recruit auditory cortex to help in memorization, while literate can recruit visual processes – read – and auditory processes – when read out loud – to memorize). Finally, phonemic verbal fluency suffers the effect of education, as well as the speech, also assessed by ADAS-Cog (Ardila & Rosselli, 2007; Brucki, 2010). Thereby, we believe that ADAS-Cog needs to be adapted to this special populations, considering the structure, the items, the administration and the scoring system, to ensure the reliability of illiterate subjects' scores without bias. The use of same tests for literates and illiterates clearly penalizes illiterates, and the failure in development of appropriate tests lead to an overestimation of dementia (Lezak et al., 2004). The undertraining of the most part of tasks, unfamiliarity of concepts, difficulties in understanding some instructions, are a few examples of lacks in illiteracy, thus in somehow they are subject to more confounding variables in their scores. Methodologically, the retrospective strategy for collected some part of the data could be pointed out as one limitation. Actually, as we noted before during the "statistical analysis" point, this stategy could limited our interpretations due to the lack of equality of tests' items over the three groups. However, we did not detect any aspect that could be completely compromised in exploratory analysis on psychometric features of ADAS-Cog. Furthermore, the clinical validation and the normative data did not suffer any influence of

this retrospective strategy, due to the fact that all patients had sociodemographic and diagnostic informations collected, as well as the total score of ADAS-Cog. Finally, we could have pointed out as limitation the disuse of test for depression screening in control group. Nevertheless, before the administration of ADAS-Cog, we applied a clinical interview which allow the screening of recent psychiatric or psychological conditions and family clinical history. Also, we asked about the medication that was been taken at the time, wherin the purpose of the treatment could lead us to understand the mening of these intake. Knowing that the depression symptomatology could be present without any treatment or diagnosis, with the administration of IAFAI we could explore the aspects of functionality that could be affected by emotional causes. Thus, with the previous enterview report completed by the information collected with IAFAI, we could easly detect people with some depression features at the time. For the present study, without any outcome related with depression symptomatology, we assume that this strategy was sufficient to ensure no great influences on the main objectives.

Despite these limitatons, the present study also has a set of strengths. First, the sample size of 743 participants is an important strength to improve the validity of the present study. Additionally, the inclusion of a MCI group afforded the knowledge about the discriminant capacity of ADAS-Cog whitin the spectrum of Alzheimer's Disease. One of the most important strength of this study is the presence of ROC analysis with the establishment of a cut-off point of >9 for MCI (AUC=0.839), a cut-off point of >12 for AD (AUC=0.996) and a cut-off point of >15 between both clinical conditions (AUC=0.924), which allow the detection of some important aspects of the battery to clinical administration, as well as in research context. As noted before, this battery is widely used in clinical research by drug regulatory agencies, namely in AD clinical trials to drug approvement, and so it is also required into clinical research in Portuguese population. Thus this study has also the strength of reveal and update the knowledge about ADAS-Cog's properties in the Portuguese population, which could faciliates the interpretation of ongoing clinical trials and the setting up of new ones. Finally, the update of the existing normative data (Guerreiro et al., 2008), the exploratory analysis of psychometric properties, the analysis of discriminant validity, the establishment of optimal cut-off points and the respective diagnostic accuracy of ADAS-Cog are important goals achieved, that are an innovate contribution to the existing literature using ADAS-Cog in Portuguese population.

VI - Conclusions

The present thesis shows the importance of considering the administration of ADAS-Cog in AD populations, according to its role in monitoring the progression and conversion between disease's stages within the spectrum of Alzheimer's Disease. Likewise, we presented normative values to ensure the correct interpretation of ADAS-Cog scores, which are useful in both clinical and research contexts. The main results presented the

clinical validity of this test to classify AD, with cut-off points that assumes an important role in clinical field.

We believe that ADAS-Cog might become more useful in the diagnosis field, considering changes in its weighted scores and add new subtasks, covering the low sensitivity for milder forms of the diasease, mostly caused by either floor and ceiling effects (Verma et al., 2015). Future studies should consider the addition of delayed recall memory task, considered a cardinal feature to assess mild preclinical stages such as MCI (Skinner et al., 2012). Also, it is important to continue with studies in its psychometric properties, testing the present version of the scale and new versions. Specifically, future studies should proceed with analysis of Item Response Theory, exploring the responsiveness of the Portuguese version of ADAS-Cog as a whole, as well as testing new scoring methodologies. Similarly, the clinical validity of this scale should be explored in other clinical conditions within neurodegeneration spectrum. Future studies should consider the adaptation of this scale to illiterate population, proceeding with validity studies as well as normative studies.

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Annexes

The Portuguese version of ADAS-Cog (Guerreiro et al., 2008) can be consulted in "Escalas e Testes na Demência" (2nd Edition), with Alexandre de Mendonça, Manuela Guerreiro e Grupo de Estudos de Envelhecimento Cerebral as Editors, pages 41-68, as referenced in "References" topic.