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Verbal Memory and Visual Perception in early Alzheimer's disease: Contribution of new diagnostic tools for new classification criteria

Tese de doutoramento em Psicologia, especialidade em Neuropsicologia, sob orientação da Professora Doutora Maria Isabel Jacinto Santana e co-orientação do Professor Doutor Mário Manuel Rodrigues Simões e do Professor Doutor Miguel de Sá e Sousa de Castelo-Branco e apresentada à Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra

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The studies presented throughout this thesis were carried out at the Neurology Department of the Centro Hospitalar e Universitário de Coimbra and at the Visual Neuroscience Laboratory at IBILI (Instituto de Imagem Biomédica e Ciências da Vida), Faculty of Medicine, University of Coimbra, Portugal, and were funded by a PhD studentship (SFRH/BD/74070/2010) from the Fundação para a Ciência e Tecnologia (FCT) – Portugal, by FCT grants (PIC/IC/83206/2007, UID/NEU/04539/2013, and UID/NEU/04539/2013-2020) and grant "From Molecules to Man" CENTRO-07-ST24-FEDER-00205).

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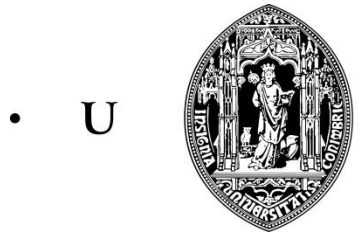

Verbal Memory and Visual Perception in early Alzheimer's disease: Contribution of new diagnostic tools for new classification criteria

Thesis presented to obtain a PhD degree in Psychology in the domain of Neuropsychology at the Faculty of Psychology and Educational sciences of the University of Coimbra

Tese de Doutoramento apresentada à Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra para prestação de provas de Doutoramento em Psicologia, especialidade em Neuropsicologia

Raquel Maria Baptista de Lemos Guerra de Oliveira

2015

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Para a minha família

"Parecia-lhe que a vida era aprender, saber sempre mais e mudar para aceitar sempre mais."

In *O Filho de Mil Homens*, VALTER HUGO MÃE

"*The pure and simple truth is rarely pure and never simple*."
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Contents

List of frequently used abbreviations

AD	Alzheimer´s Disease
3D	Three-Dimensional
ADAS-Cog	Alzheimer Disease Assessment Scale-Cognitive
ADL	Activities of Daily Living
aMCI	Amnestic Mild Cognitive Impairment
ApoE	Apolipoprotein E
AUC	Area Under the Curve
Aβ	Amyloid Beta
BLAD	Battery of Lisbon for the Assessment of Dementia
CDR	Clinical Dementia Rating
CS	Contrast Sensitivity
CSF	Cerebrospinal Fluid
CT	Cortical Thickness
DA	Doença de Alzheimer
DCL	Defeito Cognitivo Ligeiro
DR	Delayed Recall
DSM	Diagnostic and Statistical Manual of Mental Disorders
FFA	Fusiform Face Area
FCSRT	Free and Cued Selective Reminding Test
fMRI	Functional Magnetic Resonance Imaging
GDS	Global Deterioration Scale
GDS-30	Geriatric Depression Scale
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
IR	Immediate Recall
IWG	International Working Group
LM	Logical Memory
MCI	Mild Cognitive Impairment
MMSE	Mini-mental State Examination
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
NIA-AA	National Institute on Aging–Alzheimer's Association

NINCDS–ADRDA	National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders
NPV	Negative Predictive Value
p	p-value
PCA	Posterior Cortical Atrophy
FDG-PET	Fluorodeoxyglucose – Positron Emission Tomography
PiB-PET	Pittsburgh compound B – Positron Emission Tomography
PPV	Positive Predictive Value
ROC	Receiver Operating Characteristics
SFM	Structure-From-Motion
SPECT	Single-photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences
SRT	Selective Reminding Test
TR	Total Recall
TRSLG	Teste de Recordação Selectiva Livre e Guiada
VIF	Variance Inflation Factor
VPAL	Verbal Paired-Associate Learning
WAIS	Wechsler Adult Intelligence Scale
WM	White Matter
WMS	Wechsler Memory Scale

Summary

Ageing of the population, as a result of the increase of life expectancy, is followed by the growth of age-related neurodegenerative diseases and dementia. Amongst all neurodegenerative diseases, Alzheimer's disease (AD) is the most prevalent, affecting 5 to 7% of people over the age of sixty and comprising about 60% to 70% of all the dementia cases. Dementia in general, and AD in particular, are considered public global health priorities regarding their high prevalence, their high dependence, their economic cost and their impact on caregivers. The clinical interest in establishing an early diagnosis has led to a concept of a transitional state between normal and dementia known as Mild Cognitive Impairment (MCI). This stage was operationalized as a higher cognitive impairment, particularly in memory, than the one expected for the age and education levels, but not sufficient to establish dementia. MCI subjects, particularly the amnestic subtype (aMCI), present a heightened risk of conversion to dementia, particularly AD. Combining both the interest in capturing the earliest stages of AD and the new available biomarkers of the illness, the International Working Group on AD developed and published new diagnostic criteria for AD. The core diagnostic criterion includes the evidence of a significant and progressive episodic memory impairment confirmed by objective testing, thus suggesting the use of cued recall measures based on encoding specificity such as the Free and Cued Selective Reminding Test (FCSRT). The FCSRT is a memory test that controls attention and cognitive processing, requiring subjects to search, in the learning process, for items in response to their semantic category cues; moreover, these same category cues are later used to elicit recall of the items not retrieved on free recall, coordinating acquisition and retrieval.

Considering both the interest in the standard implementation of the IWG criteria and the usefulness of the suggested diagnostic tools, the main purpose of the first chapter of the current thesis aims at adapting the FCSRT and validating its usefulness, on a memory clinic basis, to the Portuguese population. Our specific purposes were to show that: 1) AD patients do not improve with cueing or, at the very least, improve significantly less than patients with other dementing and non-dementing conditions; 2) aMCI patients display an intermediate pattern of severity between healthy ageing and

AD; 3) this paradigm is more accurate at identifying people affected by AD than other declarative memory tests with no support for encoding or cue for retrieval; 4) a great predictive value for conversion to AD is detectable among MCI patients that exhibit a similar profile of impairment to AD.

After the FCSRT transcultural adaptation process, we started a validation set of studies that tried to cover both psychometric and clinical validity in AD spectrum disorders (MCI and mild AD). A longitudinal study, i.e., prediction of conversion to AD, revealed that an impaired FCSRT has a great predictive value of conversion. We showed also that this test enables the isolation of an amnestic syndrome of the hippocampal type as representative of typical-AD, through the inclusion of a group of behavioural variant of frontotemporal dementia patients that showed to benefit from this paradigm when compared to AD. All these studies corroborate the arguments of the IWG in favour of the use of the FCSRT in the objective assessment of memory in AD spectrum disorders.

By adapting and validating the FCSRT, we also contributed to the increase of Portuguese-adapted neuropsychological instruments' availability and to present a different paradigm of verbal memory evaluation.

Apart from the objective episodic memory deficit, additional brain systems may be altered in the AD spectrum surpassing the medial temporal lobes and involving the medial and lateral parietal cortices, thus leading to impairment in other cognitive domains. Sensory and motor impairments, which focus on age-related and neuropathological changes, have been reported as preceding the well-known AD cognitive alterations.

AD neuropathological findings have been reported in the visual cortex, thus contributing to distinct forms of visual impairment in AD. These deficits range from contrast sensitivity and colour perception deficits to impairments in higher-order visual functions, including motion, object and face perception and visual attention, as well as visual memory and learning.

The main focus of the second chapter of this thesis is the investigation of the visuospatial processing in MCI and AD patients. In particular, we considered the performance of these pathological groups in psychophysical tasks, hence assessing both the dorsal and the ventral pathways.

Our results corroborated the existence of AD visual deficits among the two visual pathways and showed specific impairments on motion perception and integration as early as in the MCI stage. The important and specific role of the ventral pathway for face stimuli was confirmed by structure-function correlation analysis, suggesting that the ventral pathway provides the substrate for information re-routing and reorganization in the presence of dorsal stream vulnerability in MCI.

In sum, the work presented in this thesis allowed us to confirm the FCSRT as a valid and accurate memory test, as well as a useful tool, in the objective characterization of the amnestic syndrome associated with AD. Moreover, we suggest the assessment of visual functions as an additional diagnostic tool for improving the knowledge of AD spectrum disorders, and consider that future interventions can be designed to compensate for visual problems in these pathologies, such as using higher contrast or larger stimuli.

Sumário

O envelhecimento da população, como consequência do aumento da esperança média de vida, tem sido acompanhado de um incremento na prevalência das doenças neurodegenerativas. A doença de Alzheimer (DA) é a forma mais prevalente, afectando 5 a 7% das pessoas com mais de 60 anos e sendo responsável por 60 a 70% de todos os casos de demência. A demência em geral, e a DA em particular, são consideradas áreas de intervenção prioritária em saúde pública tendo em conta o número de doentes, a elevada dependência, os custos directos e indirectos, e o impacto nos cuidadores. A evolução no sentido de um diagnóstico precoce permitiu identificar um estádio de transição entre o envelhecimento normal e a demência conhecido como Defeito Cognitivo Ligeiro (DCL). Foi operacionalizado como um compromisso cognitivo, particularmente da memória, desadequado à idade/escolaridade, mas insuficiente para constituir demência. Os sujeitos, especialmente do subtipo amnésico (DCLa), apresentam um risco elevado de conversão para demência, em particular para DA. Aliando o interesse em caracterizar as fases precoces da DA à valorização de novos biomarcadores da doença, o "International Working Group on Alzheimer´s Disease" (IWG) desenvolveu e publicou novos critérios de diagnóstico para a DA. Como critério major de diagnóstico propõe-se a evidência de um défice de memória significativo e progressivo confirmado objectivamente em testes de memória, sugerindo para esse efeito a utilização de medidas de evocação guiada baseadas em codificação específica, tal como o *Teste de Recordação Selectiva Livre e Guiada* (TRSLG). O TRSLG é um teste de memória que controla a atenção e o processamento cognitivo, durante o processo de aprendizagem, ao impor aos sujeitos a codificação dos itens em resposta à sua categorização semântica; além disso, os itens não reproduzidos livremente são facilitados através da utilização das mesmas pistas, coordenando assim a aprendizagem e a evocação.

Considerando o interesse na implementação estandardizada dos novos critérios de diagnóstico IWG, e utilizando as ferramentas propostas, o principal objectivo do primeiro capítulo desta tese prende-se com a adaptação e validação do TRSLG para o diagnóstico precoce da DA, num contexto de clínica de memória, para a população portuguesa. Pretendíamos comprovar que: 1) os doentes com DA não beneficiam da

utilização de pistas semânticas, comparativamente ao que acontece noutros tipos de demência; 2) os sujeitos com DCLa revelam um padrão de desempenho de severidade intermédia entre o envelhecimento normal e a DA; 3) este paradigma é mais preciso na identificação de sujeitos com DA do que outro tipo de testes de memória; 4) os sujeitos com DCL que apresentam um perfil de alteração da memória equivalente aos DA estão em maior risco de conversão para esta.

Após o processo de adaptação transcultural do TRSLG para a população portuguesa, desenvolveu-se um conjunto de estudos de validação que confirmaram as qualidades psicométricas, bem como a utilidade clínica do TRSLG, nas perturbações do espectro da DA (DCL e DA ligeira). Um estudo longitudinal, de predição da conversão de DCL para DA, mostrou que uma alteração no TRSLG revela um elevado valor preditivo de conversão. Confirmámos ainda que o teste permite isolar o síndrome amnésico de disfunção do hipocampo característico da DA típica, através da inclusão de um grupo de demência frontotemporal (variante comportamental) que mostrou beneficiar deste paradigma comparativamente ao da DA. No seu conjunto, estes estudos corroboram a proposta do IWG em favor da utilização do TRSLG na avaliação objectiva da memória nas patologias no espectro da DA. Com a adaptação e validação do TRSLG contribuímos ainda para aumentar o leque de instrumentos neuropsicológicos adaptados para a população portuguesa, nomeadamente com a introdução de um paradigma alternativo na avaliação da memória verbal.

Além do declínio da memória episódica relacionado com as estruturas mesiais do lobo temporal, outros sistemas cerebrais podem sofrer alterações na DA, tais como o córtex parietal medial e lateral, produzindo alterações noutros domínios cognitivos. Estudos de envelhecimento normal e patológico descrevem alterações sensoriais e motoras precedendo as alterações da memória e os achados neuropatológicos no córtex visual, que podem ser precoces nalguns doentes, corroborando a importância do compromisso visual na DA. Nestes défices incluem-se a redução de sensibilidade ao contraste e percepção da cor, alterações em funções de processamento visual superior como a percepção do movimento e atenção visual, bem como o declínio da memória e aprendizagem visuais.

O enfoque principal do segundo capítulo desta tese é a investigação do processamento visuoespacial no DCL e na DA utilizando tarefas psicofísicas integrativas, vocacionadas para avaliar tanto a via dorsal como a via ventral.

Os resultados corroboraram a presença de défices visuais nas duas vias visuais, na DA, salientando-se as alterações específicas na percepção e integração do movimento no estádio precoce de DCL. Foi ainda possível, através de análises de correlação estrutura-função, confirmar um papel importante e específico da via ventral no processamento de estímulos faciais, levando-nos a sugerir que a via ventral fornece o substrato para reencaminhar e reorganizar a informação na presença da vulnerabilidade da via dorsal no DCL.

Em suma, o trabalho desenvolvido fundamenta a utilização do TRSLG como um teste de memória válido e útil na caracterização objectiva da síndrome amnésica associada à DA em contexto de consultas de memória. Além disso, contribui para alargar o conhecimento das perturbações cognitivas noutros domínios, confirmando que as funções visuais estão afectadas precocemente, levando-nos a propor intervenções que compensem as alterações visuais destas patologias recorrendo, por exemplo, à utilização de maior contraste ou de estímulos maiores.

General Introduction

In this general introduction, we describe the historical evolution and the clinical and neurocognitive characteristics of the pathologies of the Alzheimer's disease (AD) spectrum. We depict the evolutionary criteria for the diagnosis of these conditions, as well as its biological footprints – the biomarkers. Our main focus of attention is the impairment of episodic memory as the cognitive hallmark of AD. In addition, we deepen our research arena into the visuospatial processing of AD spectrum disorders in trying to look for new biomarkers. The general outline of this thesis is presented at the bottom of this introduction.

Background

Ageing of the population, as a result of the increase average of life expectancy, is followed by the growth of age-related neurodegenerative diseases. Among ageing disorders, dementia is one of the most significant. Its prevalence increases exponentially with age, beginning at about 1% at age 60 years, and doubles every 5 years after the age of 65 (Alzheimer's Disease International, 2009). Amongst all types of dementia, AD is the most common, comprising about 60% to 70% of all the dementia cases (World Health Organization & Alzheimer's Disease International, 2012). It is already a huge health problem of the elderly, comparable in incidence to the risk of myocardial and/or cerebral infarction, and it has become one of the leading causes of death in modern societies. Dementia in general and AD in particular, is considered a public global health priority considering its high prevalence, economic impact, and associated stigma and social exclusion (World Health Organization & Alzheimer's Disease International, 2012). In Portugal, a very recent study suggests that about 5.9% of the population aged ≥60 years suffers from dementia, and probably more than 80.000 persons have AD (Santana, Farinha, Freitas, Rodrigues, & Carvalho, 2015).

Alzheimer's disease

AD is an age-related neurodegenerative brain disorder that is the main cause of memory impairment and global cognitive decline in the elderly. It was first described with this denomination in 1906 by the German psychiatrist Alois Alzheimer after

examining the brain of August D., a fifty-year-old woman that “had been suffering for a long time from weakness of memory, psychopathological manifestations, and that was no longer capable to do any physical or mental work” (Weiner, 2009). This constellation of symptoms, typical of the well-known “senile dementia”, affecting a young woman, raised many questions concerning nosological classification. It took several years to assume both the early and late forms as the same histological entity.

The disease is characterized by neuronal death, loss of synapses, and the abnormal accumulation of neuritic plaques and neurofibrillary tangles, first in strategic areas and later in more widespread regions of the cortex (Braak & Braak, 1997; Terry, Katzman, & Bick, 1994). The identification of these histological alterations is still mandatory for a definitive diagnosis, according to the most recent diagnostic criteria. Clinical-AD diagnosis is generally based in the history and in the neurological examination, complemented by neuropsychological evidence of cognitive dysfunction (Blennow, de Leon, & Zetterberg, 2006), mainly in memory domain. The evidence of an early memory deficit in this condition is supported both by neuropathological and imaging findings due to a pronounced damage in the hippocampus and related structures (such as the entorhinal cortex). Other brain regions (frontal, temporal, and parietal association cortices) become increasingly involved as the disease progresses (Braak & Braak, 1997). In general, primary motor and sensory cortices and most subcortical structures are spared (Salmon, 2000). Apart from the prominent amnesia, additional deficits occur in language and semantic knowledge (i.e. aphasia), abstract reasoning and other executive functions, attention, constructional and visuospatial abilities (Salmon, 2000).

Despite the fact that a definitive diagnosis can only be achieved on the basis of brain biopsy or autopsy, the clinical diagnosis of AD is usually classified as “possible” or “probable” (Mckhann et al., 1984) according to the two most widely used and accepted sets of criteria: the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA; Mckhann et al., 1984), and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR; American Psychiatric Association, 2000). As such, the clinical approach to accomplish a differential diagnosis relies on information from a variety of sources, fulfilled in a two-step diagnostic process where a dementia syndrome is initially identified and then

criteria apply based on the clinical features of the AD phenotype (Dubois et al., 2007). Impairment on activities of daily living (ADL) has come to define the threshold for the diagnosis of dementia beyond the identification of a cognitive abnormality (Dubois et al., 2007) on the two criteria sets; and both underline that the cognitive deficits are not due to, and not better accounted for, any other systemic or brain condition. The DSM-IV-TR criteria require the presence of memory impairment and disturbances in at least one additional cognitive domain, both of which cause significant impairment in social function or ADL; the course of the disease is characterized by gradual onset and continuing cognitive decline (American Psychiatric Association, 2000). The NINCDS–ADRDA clinical criteria do not require evidence of cognitive interference with social or occupational functioning on its criteria, but refers impaired ADL as a support for the diagnosis of probable AD; it includes deficits in two or more areas of cognition, a progressive worsening of memory and other cognitive functions, and includes the specification that the onset of AD is insidious (Mckhann et al., 1984).

The great amount of research within AD is justified not only by its clinical and pathological complexity, but also by the imperative need to establish an early and accurate diagnosis that is crucial for intervention, namely to develop effective treatment strategies and also to plan assistance and economical resources.

This clinical interest in establishing an early diagnosis associated with the fact that the progression to AD is gradual, has led to the suggestion of a transitional state between normal ageing and dementia (Petersen, 2003; Petersen et al., 1999; Santana, 2003). The concern about the characterization of this intermediate state between healthy ageing and dementia has been attempted by diverse designations and definitions.

Towards an early diagnosis – concept development

The first definition of a memory deficit, in normal adults, is endorsed to Kral (1962) who used the designation of “benign senescent forgetfulness” (BSF) to categorize age-associated changes in memory. Nevertheless, he did not operationalize the concept. Importantly, BSF was characterized as an age-related problem that did not cross a pathological onset, even though Kral ensured that it was likely a mild form of the same

process which gave rise to the “malignant senescent forgetfulness” (Davis & Rockwood, 2004).

Further definitions were influenced by changing viewpoints on cognitive disorders, and an important conceptual advance was to recognize dementing disorders as disease processes that are distinct from healthy ageing (Blessed, Tomlinson, & Roth, 1968; Wells, 1971). Thus the term “senility” was eventually rejected in favour of “dementia” as the former implied only an ageing process, whereas the latter was meant to signify a syndrome or state of illness-health, caused by a number of diseases, mainly AD (Davis & Rockwood, 2004).

After Kral’s BSF, in an attempt to characterize the phenomenon more precisely, a workgroup of the National Institute of Mental Health suggested the term "age-associated memory impairment" (AAMI; Crook et al., 1986). Its criteria included: the presence of complaints of gradual memory loss in everyday problems in persons over the age of 50 years, objective evidence of impairment on a standardized memory test as compared to young adults (1 standard deviation – SD – below the mean test value norms), evidence of adequate intellectual function, and absence of dementia or any medical condition that could produce cognitive deterioration (Crook, Bahar, & Sudilovsky, 1987-1988).

These first two definitions carried out the same conceptual and methodological errors, i.e., they adopted patterns of normality that did not account for age (Santana, 2003) and did not specify individualized memory tests what, depending on the instrument used, could classify almost all elderly subjects on the AAMI category (Petersen, 2003). Likewise, the criteria do not necessarily represent decline, which is a point central to the assumptions both of age-relatedness and of illness (Davis & Rockwood, 2004). Moreover, the clinical course of AAMI was not known, and it had been debated whether it could be viewed as an intermediary state in a continuum from normal ageing to dementia (especially AD), or just a representation of an increased variability of cognitive performance in the elderly population (Hänninen, 1996). Consequently, milder stages of dementia performed similarly to AAMI when assessed with memory tests or with cognitive and behavioural scales (Brayne, 1994).

Blackford and La Rue (1989) altered Crooks criteria by adding an upper age limit of 79 years, requiring standardized self-report memory questionnaires, and using results on

a battery of four or more tests of memory to define categories of impairment based on both young adult and age-matched norms: AAMI, age-consistent memory impairment (ACMI), or late-life forgetfulness (LLF). They also required preserved general intelligence and revised the exclusion criteria (Davis & Rockwood, 2004).

Levy (1994) reviewed the AAMI concept and suggested the definition of "ageing-associated cognitive decline" (AACD) with specific diagnostic criteria. The novelty of this concept was the adoption, on its classification, of age and education specific cut-off points on neuropsychological tests, the requirement of a broader assessment of cognitive domains (memory and learning, attention and concentration, thinking, language, and visuospatial functioning), and the notion of progression over time (Santana, 2003).

These attempts in trying to enable a clearer distinction between healthy and pathological ageing expanded to clinical setting instruments and, in 1982, two clinical staging scales, were published: the clinical dementia rating (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993) and the global deterioration scale (GDS; Reisberg, Ferris, de Leon, & Crook, 1982). The CDR allows to distinguish a stage of “questionable dementia” (CDR 0.5), from people termed healthy (CDR 0) and those with dementia (CDR 1 = mild, CDR 2 = moderate, CDR 3 = severe). Individuals at CDR 0.5 have mild consistent forgetfulness and doubtful or mild impairment on functioning of instrumental ADL (IADL) (Morris, 1993). Similarly, stages 2 and 3 of the GDS account for mild cognitive decline: very mild in the former (subjective memory complaints, but no objective evidence of memory deficit on clinical interview), and mild in the latter (earliest clear-cut deficits with manifestations in more than one area, objective evidence of memory deficit on interview, decreased performance in demanding employment and social settings) (Reisberg et al., 1982).

The DSM-IV (American Psychiatric Association, 1994) comprised the notion of an “age-related cognitive decline” (ARCD) on the section “additional conditions that may be focus of clinical attention”, apart from dementia classification. This category refers to objective identified decline in cognitive functioning (memory or other cognitive functions impairment) consequent to the ageing process that is within normal limits given the person's age, that is not attributable to a specific mental disorder or neurological condition (American Psychiatric Association, 1994). Nevertheless, criticism

to this concept is related to its imprecision and to the fact that it does not address notions of healthy ageing and incipient disease (Petersen, 2003). When the cognitive impairment is better accounted for by the direct effects of a general medical condition than by a mental disorder, DSM-IV refers this entity as "mild neurocognitive disorder" (MND). It is assured, however, that individuals with ARCD may have similar levels of cognitive impairment to MND, but the decline is considered to be part of the normative aging process rather than attributable to a general medical condition (American Psychiatric Association, 1994). Nevertheless, the recent DSM-5 (American Psychiatric Association, 2013) included a subsection entitled neurocognitive disorders (ND) that distinguishes between "major" and "mild" ND. While the former replaces the previous DSM-IV's term "dementia or other debilitating conditions", the latter is defined by a noticeable decrement in cognitive functioning that goes beyond the normal changes of normal ageing and that may (or may not) progress to dementia.

The International Classification of Diseases, 10th revision (ICD-10; World Health Organization, 1993), suggested the concept of "mild cognitive disorder" (MCD), whose criteria include the report of a mild cognitive dysfunction (memory, learning and concentration) quantified by formal neuropsychological testing, that was not believed to be due to dementia or other nervous system conditions but, rather, as secondary to systemic illness or impairment. MCD is applicable to people of all ages, and early attempts to apply its criteria to population studies of elderly people have been unsuccessful (Ritchie & Touchon, 2000). As a result, the validity and usefulness of MCD as a separate nosological entity was questioned (Christensen et al., 1995).

Finally, the Canadian Study of Health and Aging developed the concept of "cognitive impairment, no dementia" (CIND), including both early disease and age-related problems (Graham et al., 1997). This category was meant to encompass a variety of conditions which, while giving rise to cognitive impairment, did not meet the criteria for dementia (Davis & Rockwood, 2004). The concept divides conditions towards the likelihood of progression to dementia: disorders such as AAMI, depression, alcoholism, vascular, and delirium, are likely to be "pre-dementia" syndromes; while in others (tumours, schizophrenia and mental retardation) a diagnosis of dementia is effectively excluded (Davis & Rockwood, 2004; Gauthier et al., 2006; Petersen, 2003). In general, subjects diagnosed with CIND have a higher rate of progression to dementia than

those without cognitive impairment (Tuokko et al., 2003). Nonetheless, CIND subjects revealed a high rate of dependence in one or more ADL in the Italian Longitudinal Study on Aging (Di Carlo et al., 2000). As a consequence, the impact of functional impairment needs to be taken into account thereafter in all classifications of cognitive states in older adults (Davis & Rockwood, 2004).

Findings of longitudinal population studies, evaluating the outcomes of a variety of definitions of cognitive impairment, have shown a prevalence in the general elderly population between 3% and 19%, with an incidence of 8–58 per 1000 per year, and a risk of developing dementia of 11–33% over 2 years (Ritchie, 2004), and about 8–10% per year over 5 years (Fisk, Merry, & Rockwood, 2003). Fisk et al. (2003) showed that changes on the definition altered the prevalence of cognitive impairment; however, these changes did not modify the proportion of progression to dementia. Still, the several definitions were unstable, and each included a group who had improved after 5 years (Davis & Rockwood, 2004). Findings of population-based studies have shown that up to 44% of patients with cognitive impairment, at their first visit, were estimated to return to normal a year later (Ganguli, Dodge, Shen, & DeKosky, 2004; Ritchie, 2004). These epidemiological studies underline the fact that there are many factors affecting cognition performance in elderly populations apart from neurodegeneration, such as: “education, vascular risk factors, psychiatric status, genetic background, hormonal changes, and use of anticholinergic drugs; and that these factors can account for the reversibility of many cognitive impairment cases” (Gauthier et al., 2006).

Mild cognitive impairment

The term mild cognitive impairment (MCI) was first used in association with the stage 3 of the GDS (Reisberg et al., 1982). Subjects at GDS stage 3 have objective evidence of mild deficits in cognition that may manifest in more than one area, which affect complex occupational and social activities.

The currently most widespread use of MCI is the notion proposed by Petersen (1995) and aims to identify the stage where a cognitive impairment is greater than expected, considering subjects’ age and education level, but not sufficiently debilitated to reach

dementia (Petersen et al., 1999). MCI has shown to be clinically useful as it carries a heightened risk of conversion to dementia, particularly AD. It is thought to represent a transitional stage within a cognitive continuum that spans from normal ageing to early dementia (Petersen et al., 1999). Its criteria were defined as: complaint of defective memory (preferably corroborated by an informant), objective memory impairment for age and education (1.5 SD below the mean of their peer group on memory tests), normal general cognitive functioning, preserved ADL, and absence of dementia (Petersen et al., 1999). Many studies have shown increased rates of progression to AD in MCI individuals compared to individuals with no cognitive impairment (Bowen et al., 1997; Geslani, Tierney, Herrmann, & Szalai, 2005; Morris et al., 2001; Tierney et al., 1996).

Some investigators have equated GDS 3 or CDR 0.5 to Petersen's notion of MCI, but Petersen believes that this assumption might not always be correct, stating that "as severity scales, these stages may correspond to MCI or may describe individuals with very mild dementia" (Petersen et al., 1999). As such, Petersen et al. (1999) believe that GDS and CDR are severity rating scales and not diagnostic instruments; consequentially they do not represent MCI's syndrome as described by him.

Although the earlier criteria for MCI were specific to memory deficits, developments have extended so that its definition could include non-memory deficits and impairment in several cognitive domains, and clinical subtypes with multiple aetiologies and many potential causes (Petersen, 2004; Winblad et al., 2004). A consensus conference concluded that while MCI represents a high-risk stage for the development of AD, its heterogeneity requires sub-classifications, such as: "amnestic MCI" (aMCI) which focuses on memory loss and may progress to AD; "multiple domains slightly impaired MCI" that may represent normal aging or may progress to AD or vascular dementia; and "single non-memory domain MCI" that may have a wide variety of outcomes (Petersen et al., 2001). More recently, multi-domain MCI was redefined and divided into amnestic and non-amnestic subtypes (Winblad et al., 2004).

The classification of MCI can be operationalized in a stepwise manner, taking into account each criterion, as following: first, persons should be judged as not normal in spite of not fulfilling diagnostic criteria for dementia; secondly, functional ADL are mainly preserved, or at least with minimal impairment; furthermore, there should be

evidence of cognitive decline, measured either by self and/or informant report in conjunction with deficits on objective cognitive tasks, and/or evidence of decline over time on objective neuropsychological assessment (Winblad et al., 2004).

In order to determine the specific subtype of MCI, comprehensive cognitive assessment through neuropsychological testing is essential. Nevertheless, no generally accepted instruments were recommended and specific domains of episodic memory might be assessed with different paradigms (word list learning procedure or paragraph recall) (Winblad et al., 2004). If the subject's memory is significantly lower than would be expected for their age and educational level, the clinician must determine whether other cognitive domains are also impaired (e.g. language, executive function or visuospatial skills) and when non-memory domains are intact, classifying the person as having aMCI; if there are mild deficits in a number of different domains, multi-domain MCI (with or without a memory component) applies (Petersen et al., 2001; Winblad et al., 2004). Alternatively, when there is cognitive impairment in a single non-memory domain – like an isolated deficit in language or visuospatial skill – single non-memory domain MCI would be the appropriate classification (Petersen et al., 2001; Winblad et al., 2004).

Besides the increased risk of progressing (or "converting") to dementia (AD) among aMCI persons (Petersen, 2000), findings on community-based samples have shown that 11.1 to 21.2% of those with aMCI remained stable MCI, and 33.3 to 55.6% converted to non-MCI, half of them reverting to normal two-years later (Ganguli et al., 2004). These epidemiological studies highlight that many factors affecting cognitive performance in elderly populations can account for the reversibility of many MCI cases (Gauthier et al., 2006).

Although accepting that the rate of progression to AD is increased in MCI, researchers have drawn conflicting hypothesis on why not all individuals identified with MCI appear to progress to AD (Davis & Rockwood, 2004). It has been suggested that MCI may represent an incipient form of AD which would be revealed with a sufficiently long period of follow-up – "early-stage AD" (Morris et al., 2001) or "prodromal AD" (Dubois & Albert, 2004; Dubois, 2000). Alternatively, MCI may represent a heterogeneous group of individuals, among which some are at an increased risk to develop a neurodegenerative dementia, while others have a more non-progressive form of

cognitive impairment (Davis & Rockwood, 2004); supporting the latter view is the previously referred finding of reversibility of many MCI cases (Davis & Rockwood, 2004; Ganguli et al., 2004).

Revising the established criteria

Combining both the interest in capturing the earliest stages of AD and the new available biomarkers of the illness, the International Working Group on AD (IWG-1; Dubois et al., 2007) developed and published new diagnostic criteria for AD. These revised criteria were established in order to overcome the limitations of both the DSM-IV-TR and the NINCDS-ADRDA (1984 version). The IWG-1 core diagnostic criterion includes the evidence of a significant and progressive episodic memory impairment confirmed by objective testing; supportive features include at least one biological footprint of the disease: presence of medial temporal lobe atrophy, abnormal cerebrospinal fluid biomarker, specific pattern on functional neuroimaging with FDG-PET or an autosomal dominant mutation within the immediate family (Dubois et al., 2007). The IWG-1 criteria were the first to introduce biomarkers into the core diagnostic framework in the presence of two requisite features (Dubois et al., 2010). The IWG-1 suggests that AD could be recognised in vivo and independently of dementia, therefore moving AD from a clinicopathological to a clinicobiological entity (Dubois et al., 2010). The great advance in the AD-biomarkers field is also due to the intense research interest in characterising the earliest stages of AD that precede dementia's threshold, defined by functional disability (Dubois et al., 2007). By relying on AD- specific clinical and biological features, the newly proposed criteria enable its diagnosis with a high level of accuracy, even at the stage of earliest clinical manifestations – prodromal stage (Dubois et al., 2007, 2010). The IWG-1 suggested and operationalised the term prodromal AD to define the symptomatic pre-dementia phase of AD that is characterised by symptoms not severe enough to meet diagnostic criteria for AD. This concept refers to clinically affected patients who do not yet have dementia and who are diagnosed to have AD on the basis of their clinical presentation and supportive evidence of Alzheimer's pathology from biomarkers (Dubois et al., 2010).

Prodromal AD must be distinguished from the wide and heterogeneous state of cognitive functioning that falls outside normal ageing (Dubois & Albert, 2004). This state corresponds to the previously reported nosological terms of AAMI, AACD, ARCD, MCD, CIND and MCI. The IWG-1 recognises the subtyping of Petersen's MCI in order to address its assumed clinical and pathological heterogeneity. However, it is known that not all aMCI patients that clinically progress to dementia met neuropathological criteria for AD. Accordingly, the IWG-1 believes that applying clinically AD criteria to aMCI, without objective evidence such as neuroimaging or cerebrospinal fluid (CSF) analyses, will lack specificity for predicting the future development of AD, due to the high presence of non-AD pathology (Dubois et al., 2007). As such, the IWG-1 proposal for a multidimensional identification of AD would advance the heterogeneous state of MCI to the next level of identifying prodromal AD (Dubois et al., 2007).

Despite the IWG-1 great interest in capturing the early stages of AD, this framework aimed also to amend the low specificity of DSM-IV-TR and NINCDS-ADRA criteria against other dementias, by improving both the recognition of non-AD dementias and the identification of AD phenotype (Dubois et al., 2007).

Although the IWG-1 framework raised an innovative way to classify AD, it did not initially address the nosology of AD-related states as "dual clinicobiological entities" that require both a clinical typical phenotype and AD specific neuropathological changes (Dubois et al., 2010). Additionally, it focused only on typical AD with amnestic presentations, and some conditions that were not considered within the new research criteria framework include: clinically asymptomatic individuals who are positive for biomarkers of Alzheimer's pathology; clinically symptomatic individuals without evidence of biomarker findings; and those with atypical features (atypical AD) (Dubois et al., 2010). Atypical presentations of AD include non-amnestic focal cortical syndromes, such as progressive non-fluent aphasia, logopenic aphasia, and posterior cortical atrophy (PCA), which are neuropathologically confirmed as being AD (Dubois et al., 2010, 2014). Therefore, in 2010, the IWG provided a broader diagnostic coverage of the AD clinical spectrum and proposed a common new lexicon to account for the different entities and concepts related to AD. The basis of this lexicon is to consider AD solely as a clinical and symptomatic entity that encompasses both the pre-dementia and the dementia phases (Dubois et al., 2010). Prodromal AD is also called "pre-

dementia stage of AD", in the new lexicon, and is now included in the new definition of AD; AD is distinguished based on its clinical phenotype as "typical" (most common clinical phenotype) and "atypical" (less common and well characterised clinical phenotypes that occur with Alzheimer's pathology); "mixed AD" (diagnostic criteria for typical AD and additional evidence of other comorbid disorders); "preclinical states of AD" (including both "asymptomatic at-risk state for AD" and "pre-symptomatic AD"). MCI remains as a term of exclusion for individuals who are suspected to have but do not meet the proposed new research criteria for AD (meaning that they do not present the clinicobiological phenotype of prodromal AD either because memory symptoms are not characteristic of AD or because they are biomarker negative) (Dubois et al., 2010). The new lexicon specifies that prodromal AD should not be confused with preclinical AD: while the former describes a symptomatic disease phase, no matter how early, the latter refers to the preceding asymptomatic state (Dubois et al., 2010). Importantly, it proposed the conceptual shift between prodromal AD and MCI: subjects previously diagnosed as having MCI should no longer be considered at risk for developing AD dementia, but should instead be recognised as already having AD at a prodromal stage with an inevitable progression to AD dementia over time (Dubois et al., 2010). According to the IWG-1 new criteria, a clinical phenotype combined with biomarker evidence will now no longer be predictive of AD but diagnostic; therefore the diagnosis of prodromal AD is preferred over MCI, considering that an early identification of the disease responsible for the syndrome is more valuable for the patient in terms of prognosis and treatment (Dubois et al., 2010).

The National Institute on Aging–Alzheimer's Association (NIA–AA; Jack et al., 2011) criteria were updated to encompass also the biological footprints that were developed and established ever since. These revised diagnostic guidelines, similarly to IWG, advanced the NINCDS–ADRDA framework to cover the full staging of the disease: the dementia phase (due to AD; McKhann et al., 2011); the symptomatic, pre-dementia phase (MCI due to AD; Albert et al., 2011); and the asymptomatic, preclinical phase of AD (Sperling et al., 2011). Accordingly, the revised NIA-AA framework distinguishes the syndromic labels (that denote different qualitative and quantitative clinical expressions of disease) from the pathophysiological process (that underlies the syndrome) across the three phases. Although the reference to biomarkers is used in the revised

definitions in all three AD-disease phases, the role of biomarkers differs somewhat amongst them. In the preclinical phase, “biomarkers are used to establish the presence of AD pathophysiological processes in research subjects with no or very subtle overt symptoms” (Jack et al., 2011). In both the MCI and AD dementia phases, clinical criteria are dominant and biomarkers are complimentary, i.e., the core clinical diagnostic criteria are completely operational in a setting, regardless of biomarkers’ access. Considering this general rule, in the symptomatic pre-dementia phase (MCI due to AD), biomarkers are used to establish the underlying aetiology and its severity indicates the likelihood of imminent progression to AD dementia (Albert et al., 2011; Jack et al., 2011). In the dementia phase (due to AD), biomarkers are used to adjust the level of certainty that the pathophysiological processes causes the dementia in an individual (Jack et al., 2011; McKhann et al., 2011). The two major classes of biomarkers (amyloid accumulation and neuronal degeneration or injury) are treated as equivalently in both the MCI and dementia criteria. In contrast, in the preclinical criteria, they are ranked in a temporal hierarchy in which amyloid biomarkers become abnormal first and neuronal injury biomarkers become abnormal later (Jack et al., 2011; Sperling et al., 2011). While this temporal ordering concept for biomarkers is central to the staging proposed in the preclinical research criteria, its use is much more conservative in symptomatic subjects, as “it was felt to be a judicious approach pending more definitive outcomes research in this area” (Jack et al., 2011). Another fundamental difference is that the core clinical criteria of the recommendations regarding AD dementia and MCI due to AD are intended to guide diagnosis in clinical settings, while the preclinical AD is intended for research purposes (Jack et al., 2011). Concerning the diagnosis of MCI due to AD, whose definition is very similar to the one previously described by Petersen et al. (1999, 2001), its core clinical criteria include: a concern regarding a change in cognition, an impairment in one or more cognitive domains, preservation of independence in functional abilities, and absence of dementia (Albert et al., 2011). The applicability of criteria for MCI due to AD, as it is proposed by the NIA-AA framework in both the community and clinical trials settings, has already been confirmed (Petersen et al., 2013). These criteria represent an improvement in the previous efforts to define MCI and define an entity of MCI owing to AD

pathophysiological processes, based on the conjunction of the clinical diagnosis and the presence of biomarkers (Jack et al., 2011).

In what respects the criteria for dementia because of AD, and specially the revised criteria for probable AD dementia, it has expanded the scope of the 1984 NINCDS–ADRDA framework and included biomarker enhancements to the diagnosis of AD dementia (Jack et al., 2011). The diagnosis of dementia due to AD is divided into probable AD dementia, possible AD dementia (atypical course and mixed presentation), and probable or possible AD dementia with evidence of the AD pathophysiological process (including biomarker evidence). A two-step diagnostic process of an initial criterion for dementia followed by clinical criteria for probable AD is sustained in this revised version, and it includes the amnestic and non-amnestic (language, visuospatial, and executive dysfunction) presentations, according to the initial and most prominent cognitive deficits (McKhann et al., 2011).

Finally, the preclinical stages of AD aim at reviewing biomarker, epidemiological, and neuropsychological AD-evidence, and to develop recommendations to determine the factors which best predict the risk of progression from “normal” cognition to MCI and AD dementia; these recommendations are solely intended for research purposes and do not have any clinical implications (Sperling et al., 2011).

The NIA-AA framework shared many features with the IWG-1 criteria, including the integration of AD biomarkers in the diagnostic process, and the recognition of an asymptomatic biomarker-positive stage (Dubois et al., 2007, 2014; Jack et al., 2011). However, the NIA–AA criteria differ conceptually from the IWG criteria in several points (Dubois et al., 2014): i) The NIA–AA suggested three different sets of diagnostic criteria, one for each disease stage: dementia phase (due to AD), pre-dementia phase (MCI due to AD), and preclinical phase of AD (Jack et al., 2011), while the IWG criteria characterises a disease (AD) and not a syndrome (MCI or dementia) (Dubois et al., 2014); ii) although both frameworks recognise that the disease starts before the occurrence of clinical symptoms, the NIA–AA criteria support the diagnosis of AD in asymptomatic individuals with biomarker evidence of amyloid accumulation (Sperling et al., 2011), whereas the IWG-1 considers it to be only an at risk of disease state (Dubois et al., 2007); iii) the NIA–AA criteria provides, both for the MCI and dementia stages, different levels of probabilistic likelihood (high, intermediate, or unlikely) that

the syndrome is due to AD based on biomarker information (Albert et al., 2011; Dubois et al., 2014; McKhann et al., 2011); iv) the NIA–AA diagnostic framework has the advantage of being applicable when no supportive biomarkers are available, although at the expense of diagnostic specificity (Dubois et al., 2014). Yet, "the IWG criteria are less complex in their semiology, have the advantage of consistency, and are more readily applicable in clinical trials and in clinical diagnosis when biomarkers are available" (Dubois et al., 2014).

In 2014, advances to improve the diagnostic framework were proposed by the IWG-2 (Dubois et al., 2014). The diagnosis of AD was simplified, requiring the presence of an appropriate clinical AD phenotype (typical or atypical) and a pathophysiological biomarker consistent with the presence of Alzheimer's pathology; and further elaborates on the specific diagnostic criteria for atypical forms of AD, for mixed AD, and for the preclinical states of AD (Dubois et al., 2014). The proposed diagnostic change for typical AD is to include either pathophysiological markers of Alzheimer's amyloid pathology in CSF (Aβ and tau) or evidence of amyloid deposition in [Pittsburgh compound B (PiB-PET)]. The rationale is that they exhibited the highest specificity when correlated to the underlying AD pathology in post-mortem studies, and are the "most specific biomarkers to determine that an individual is within the AD continuum even several years before the clinical onset of disease" (Dubois et al., 2014). This change in the diagnostic algorithm enabled AD diagnosis to be extended into the prodromal stage, where the disease can be identified with supportive biomarkers as markers of Alzheimer's pathology. Thus, the designation of prodromal AD disappears, and the designation of AD encompassing both the pre-dementia and dementia stages uses the same criteria irrespective of the severity of cognitive and functional deficits (Dubois et al., 2014).

Vos et al. (2015) compared the two sets of framework from the IWG (1 and 2) and the NIA-AA criteria on prevalence and outcome of Alzheimer's disease at the MCI stage in a 3-year longitudinal study, based on a large multicentre consortium. Their results support the use of all the framework research criteria to identify AD at the MCI stage. The NIA-AA criteria revealed the most accurate prognosis in clinical settings, whereas for clinical trials, selection of subjects either in the NIA-AA (high AD likelihood) or the IWG-2 (prodromal AD) could be considered (Vos et al., 2015).

Memory impairment

Due to the early and pronounced damage in the hippocampus and its related structures, memory is the leading cognitive impairment in (typical) AD. These brain medial temporal regions are one of the major structures of the Papez circuit involved in the declarative memory and specially in episodic memory, which is critical for the acquisition and retention of new information (Squire & Kandel, 1999; Squire, Stark, & Clark, 2004). The initial symptom of a decline in episodic memory – "forgetfulness" – is often expressed in ADL as an inability to remember recent events, conversations or appointments and forgetting the names of new acquaintances (Salmon, 2000). Because memory problems are also the most frequent complaint in the elderly (Goeman & De Deyn, 2003) and may be the result of normal ageing or of various clinical conditions (such as depression), they should be carefully taken into account as they are also associated to a high risk of AD. Impairment in declarative episodic memory (the fact-oriented memory system that allows the storage and recall of specific information and experiences) is the most prevalent and prominent feature of AD spectrum disorders, and its objective evidence on neuropsychological tests is transversal to all the clinical diagnostic criteria (Albert et al., 2011; American Psychiatric Association, 1994, 2000; Dubois et al., 2007, 2010, 2014; Jack et al., 2011; Mckhann et al., 1984, 2011; Morris et al., 2001; Petersen, 2004; Petersen et al., 1999; World Health Organization, 1993); likewise it is often considered an essential (but not sufficient) feature for a clinical diagnosis. Neuropsychological evaluation of AD patients reveal significant impairments in their ability to learn and retain new verbal or non-verbal information (i.e., anterograde amnesia), as well as deficits in the ability to recollect previously well-known information from the past (i.e., retrograde amnesia) (Salmon, 2000); while the former gets worse with the disease progression, the latter is more present in the more advanced stages of AD. Memory for concepts, the meaning of words, and factual information may also be impaired in patients with AD, even in its early stages; furthermore these memory deficits encompass all aspects of cognition and contribute to impairments in non-memory cognitive domains such as language, conceptualization, and visuospatial functioning (Salmon, 2000).

According to cognitive psychology, memory processing is based in a three-stage information system: encoding (learning), storage and retrieval (Baddeley, 2004). Moreover, three kinds of memory are distinguishable, providing a suitable framework for conceptualizing and understanding dysfunctional memory: sensory memory (or registration), short term (immediate memory), and long term memory (Lezak, 1995). Clinically, measures of the ability to learn and retain new information are quite useful in differentiating between healthy ageing elders and AD patients, and delayed recall trials revealed to be more effective than measures of learning across trials (Salmon, 2000). Nevertheless, "impaired delayed recall is not itself evidence of an AD-related memory disorder", and deficits in encoding and storage processes that are characteristic for AD must be distinguished from non-AD deficits that can also affect delayed recall, such as attentional difficulties or inefficient retrieval strategies that may be present in normal ageing or in other clinical conditions (Dubois et al., 2007).

The nature of the memory defect of AD has been studied through a variety of methods and paradigms, mostly looking at aspects of verbal memory. On tests of free recall, AD patients perform very poorly either on tests with meaningful material (sentences, stories) or on rote learning tasks, displaying the most severe losses in the earliest stimuli presented in a series (primacy effect) (Lezak, 1995). Moreover, AD patients' responses on memory tests tend to include as many or more intrusions or other kinds of errors as correct answers, and they do not benefit either from repetition or cueing (Lezak, 1995). Forgetting further compromises the defective learning process, leading to retrieval and recognition problems where the latter is represented by a deficit in discriminating between target items and distractors or false positive responses, thus comprising a large proportion of the total number of responses (Lezak, 1995).

The contribution of cognitive studies in searching for an early AD-diagnosis revealed that the changes associated to AD can be detected before its effective diagnosis, and people experiencing these impairments can be distinguished from healthy elders through the administration of conventional neuropsychological tests; moreover, the literature supports that it is possible to identify and quantify the cognitive deficits associated with the preclinical stages of AD and MCI using neuropsychological measures (Collie & Maruff, 2000).

Buschke, Sliwinski, Kuslansky, and Lipton (1997) proved that an accurate diagnosis of the episodic memory deficit of AD can be improved through the use of tests that provide encoding specificity. This principle states that memory retrieval is best in conditions that match encoding conditions the closest, enabling superior memory effectiveness when information available at encoding is also present at retrieval (Tulving & Thomson, 1973). Within the encoding specificity paradigm, test materials are encoded along specific cues that are used to control for an effective encoding and are subsequently presented to maximise retrieval (Tulving & Thomson, 1973).

Cognitive decline on tasks that involve episodic learning and recall are consistently reported as being able to discriminate preclinical AD patients both from normal elderly controls and probable AD subjects (Collie & Maruff, 2000). Furthermore, aMCI patients present a memory deficit with normal short-term memory abilities and poor episodic long-term memory when comparable to mild AD patients, thus supporting the hypothesis that "a pure amnesic syndrome characterizes the preclinical phase of AD" (Perri, Carlesimo, Serra, & Caltagirone, 2005). This amnestic profile of AD-related disorders is typically characterized by poor learning and rapid memory decay over relatively short periods, often concurrent with damage to the medial temporal structures (Squire, Stark, & Clark, 2004), and should be confirmed for an accurate diagnosis of (typical) AD spectrum disorders through the use of cued recall measures based on encoding specificity (Dubois et al., 2007, 2014).

Despite the episodic memory deficit, other cognitive changes could be associated to AD, such as impairment in orientation, executive functioning, language, praxis, visuospatial abilities and gnosis (Dubois et al., 2007; Geldmacher, 2009). As previously referred, the presence of a dysfunction in at least another cognitive domain, along with memory, is mandatory on NIA-AA (McKhann et al., 2011) and DSM-IV-TR criteria (American Psychiatric Association, 2000).

Therefore, the neuropsychological evaluation is considered fundamental on the investigation of AD. Together with a comprehensive neuropsychological assessment covering different cognitive functions, the evaluation of functional performance on ADL is of great importance on the diagnosis.

Biomarkers

According to Jack et al. (2011) "biomarkers are parameters (physiological, biochemical, anatomic) that can be measured *in vivo* and that reflect specific features of disease-related pathophysiological processes". The increasing availability of data on biomarkers' performance and operationalization reinforces their robustness and scientific progress on AD research (Dubois et al., 2014). In the most recent frameworks, researchers divided biomarkers' categories according to their relation to AD pathology. The NIA-AA group considered two major categories: biomarkers of Aβ accumulation, and biomarkers of neuronal degeneration or injury (Jack et al., 2011); and the IWG-2 categorised them as pathophysiological or topographical if they identified downstream brain changes indicative of the regional distribution of AD pathology (Dubois et al., 2014).

Cerebrospinal fluid (CSF)

Although AD may be seen as a multifactorial disorder, with "different primary mechanisms resulting in similar patterns of neuronal failure and pathological expression in different individuals" (Geldmacher, 2009), its hallmark pathological features remain, besides neuronal death and synaptic dysfunction, the neuritic plaques (NP) and the neurofibrillary tangles (NFT) (Braak & Braak, 1997) only accessed through brain biopsy/autopsy. NP are extracellular structures with a central core of amyloid beta (Aβ) and cellular elements, namely dystrophic neuritis; NFT consist of intracellular collections of tau protein hyperphosphorylated and deposited as abnormal filaments with a distinctive paired helical structure (Geldmacher, 2009). Along with Aβ aggregation, the tau protein represents hallmarks of AD, and although there are several mechanistic links between both proteins, controversy remains about which one is primary involved in the cascade of events that leads to neuronal death in AD. The hypothesis of the amyloid cascade (Hardy & Higgins, 1992) as well as the identification of mutation in the Aβ precursor protein (APP), as a cause of early genetic cases of AD, place Aβ as a primary pathophysiological target in the majority of disease-models. Despite these evidences, mechanisms leading to Aβ deposition and plaque formation in late-onset cases are much more controversial (Geldmacher, 2009): "either an increased proportion of Aβ is produced, or there is reduced clearance of Aβ,

or there is some combination of the two factors". Moreover there are other factors playing as intermediary mechanisms of cellular death and eventually as triggering factors in the amyloid cascade, namely oxidative stress or bioenergetic failure (Swerdlow & Khan, 2004). Those proteins can be accessed in CSF and their concentrations are expected to reflect brain events, namely sequestration of Aβ42 in NP, conditioning low CSF levels as well as increased levels of tau and of its phosphorylated form (P-tau) as consequence of neuronal death. Back in the old NINCDS–ADRDA guidelines, CSF examination was recommended as an exclusion procedure for non-AD dementia (Mckhann et al., 1984); since that time, the CSF AD-profile, with low Aβ levels and high tau (total or phosphorylated) when compared to healthy controls (Motter et al., 1995; Vandermeeren et al., 1993), was recognized and valued as an important biomarker for AD and was further included in the most recent diagnostic framework criteria (Dubois et al., 2007, 2010, 2014; McKhann et al., 2011). Moreover, since the high diagnostic value of CSF biomarkers in MCI stage has been proved over memory impairment in the diagnostic scheme, its inclusion as a diagnostic criterion provides an incremental value in identifying prodromal AD (Dubois et al., 2007). As referred before, the high specificity of CSF biomarkers, when correlated to the underlying AD pathology in post-mortem studies, enabled the IWG-2 criteria to keep it as a pathophysiological benchmark criterion for typical AD (Dubois et al., 2014). Nevertheless, because CSF proteins are also altered in other neurological disorders, and Aβ elevations in AD are more specific than tau alterations, the NIA-AA divided these proteins into the major categories: low $A\beta_{42}$ as a biomarker of Aβ accumulation, and elevated tau as a marker of neuronal degeneration or injury (Jack et al., 2011).

Neuroimaging

Neuronal death and widespread cortical synaptic loss occur in AD and are the major determinants of cognitive disability, with the deep layers of the temporal cortex and the hippocampus suffering the greatest degree of synaptic loss (Geldmacher, 2009) and leading to significant cortical atrophy. This atrophy of the medial temporal lobe (MTL) structures, assessed through cerebral structural Magnetic Resonance Imaging (MRI), showed to be common in AD, frequent in MCI, but less frequent in healthy ageing (De Leon et al., 1997; Visser, Scheltens, Pelgrim, & Verhey, 2005). As expected,

a strong correlation between MTL volumes and memory performance has been showed in patients with AD (Deweer et al., 1995). Nonetheless, in MCI studies, and despite the fact that qualitative MTL atrophy ratings could identify prodromal AD, its low accuracy limits its usefulness as an early-identification biomarker (Dubois et al., 2007). Because MRI had proved to be important in differential diagnosis, by distinguishing patients with AD from those with non-AD dementia (Wahlund, 2000), the inclusion of MTL atrophy as a supportive diagnostic criterion for AD is justified in order to exclude other causes of MTL structural abnormality (Dubois et al., 2007). Its assumption as a biomarker in the framework of the different diagnostic criteria is more contentious: while the NIA-AA criteria placed structural MRI achievements as a biomarker of neuronal degeneration or injury, within a pattern involving medial, basal, and lateral temporal lobes and medial and lateral parietal cortices atrophy (Jack et al., 2011); the IWG-2 framework positioned it as downstream topographical marker playing the role of an additional investigation to exclude other causes of cognitive disorders or dementia (Dubois et al., 2014).

Molecular neuroimaging methods are gradually more integrated into the clinical routine evaluation of dementia. Those include single-photon emission computed tomography (SPECT), positron emission tomography (PET) as in vivo nuclear radioisotopic scans that can measure blood flow (HMPAO SPECT), glucose metabolism [fluorodeoxyglucose (FDG-PET)], and, more recently, protein aggregates of amyloid (PiB-PET) and tau (tau radiotracers). Within AD diagnosis, both techniques have been successful in distinguishing different forms of dementia and also in discriminating patients from normal subjects (Coleman, 2005; Dougall, Bruggink, & Ebmeier, 2004). The most consistent pattern described in AD is a reduction of glucose metabolism or hypoperfusion in posterior bilateral temporal parietal regions and in the posterior cingulate gyrus (Coleman, 2005). Using this regional pattern, FDG-PET reached sensitivity and specificity of 86% in the discrimination between AD patients from healthy controls (Patwardhan, McCrory, Matchar, Samsa, & Rutschmann, 2004), while SPECT pooled weighted sensitivity and specificity values of 77% and 89%, respectively (Dougall et al., 2004). The relevance of these molecular neuroimaging techniques in the prognosis of clinical deterioration in MCI patients is controversial due to the small samples size and limited follow-ups. The usefulness of FDG-PET reached an overall

diagnostic accuracy of 84% for predicted conversion to AD (Mosconi et al., 2004), whereas SPECT images identified pre-clinical AD with an accuracy of 78% when combined with baseline memory deficits; the hypoperfusion pattern involved the parietal and temporal lobes, precuneus, and posterior cingulate cortex (Borroni et al., 2006). Because the low diagnostic accuracy of SPECT falls below the requisite of 80% accuracy levels, it was not included in any of the criteria (Dubois et al., 2007; Jack et al., 2011). On the other hand, the decreased glucose metabolism on FDG-PET has been included as a supportive feature in the IWG-1 criteria (Dubois et al., 2007), and as a biomarker of neuronal degeneration or injury in the NIA-AA framework (Jack et al., 2011); but the IWG-2 framework positioned it also as a downstream topographical marker, which may "better serve in the measurement and monitoring of the course of disease" (Dubois et al., 2014). More recently, the powerful PET techniques that provide in-vivo visualisation of amyloid and potentially NFT are gaining ground – amyloid PET (or PiB-PET) (Klunk et al., 2004). Both quantitative and qualitative measures of amyloid pathology with PET ligands have strongly correlated with post-mortem senile NP pathology (Wolk et al., 2011) and have shown good predictability for progression to AD dementia in MCI groups (Visser & Knopman, 2009). Therefore, amyloid PET is considered as a valid pathophysiological marker of brain fibrillar amyloid pathology (Dubois et al., 2014). Accordingly, it is included in the more recent framework criteria both as a pathophysiological biomarker (Dubois et al., 2014) and as a biomarker of Aβ accumulation (Jack et al., 2011).

Genetics

AD is a genetically complex and heterogeneous disorder, as it follows an age-related dichotomy in which rare autosomal dominant mutations cause early-onset familial AD, while risk for late-onset AD is probably modulated by genetic variants with relatively low penetrance but high prevalence (Tanzi, 1999). Early-onset (<60 years) AD is caused by defects in any of three different genes: presenilin 1 (PSEN1) on chromosome 14, presenilin 2 (PSEN2) on chromosome 1, and the amyloid β protein precursor (APP) on chromosome 21; yet, late-onset AD is associated with genetic polymorphisms that appear to operate as risk factors and/or genetic modifiers (Tanzi, 1999). The ε4 allele of the apolipoprotein E (ApoE) is the only firmly established genetic susceptibility

factor associated with anticipation and increased risk for sporadic late-onset AD (Tanzi, 1999). However, the contribution of the ApoE to AD pathogenesis is still controversial: whereas some admit its involvement in Aβ circulation serving as an amyloid catalyst or "pathological chaperone" (Wisniewski & Frangione, 1992), others indicate it as an inflammatory and/or acute phase protein that plays an essential role in accelerating the disease progress (Nilsson, Rogers, & Potter, 1998). While ApoE-ε4 has been confirmed as a strong risk factor for AD, it is clearly not necessary for the development of AD: first, it is present in 20-30% of the general population, so its presence in an AD subject does not necessarily mean that it is responsible for the disease; second, even though carriers of the ε4 allele in homozygosity have a great risk (80%), it is not sufficient to cause the disease; finally, the ApoE-ε4 appears to act primarily as a modifier of age at onset of AD (Tanzi, 1999). For these reasons, none of the diagnostic frameworks considers the carriage of the ε4 allele as a positive AD biomarker (Dubois et al., 2007, 2014; McKhann et al., 2011). On the other hand, the autosomal dominant mutations (PSEN1, PSEN2, or APP) are fully penetrant which means that a proband with genetic-testing evidence of one of those mutations can be considered as "strongly supportive for the diagnosis of AD for affected individuals within the immediate family who did not themselves have a genetic test for this mutation" (Dubois et al., 2007). For the IWG-1 and IWG-2 diagnostic frameworks, the presence of an autosomal dominant genetic mutation is a diagnostic marker of the disease that, together with an amnestic deficit, meets criteria for AD (Dubois et al., 2007, 2014). The NIA-AA criteria considers the evidence of a causative genetic mutation, in one of the referred genes, as increasing the certainty of an AD pathology condition (McKhann et al., 2011).

Looking for new biomarkers

As previously reported, apart from the objective episodic memory deficit, additional brain systems may be altered in the AD spectrum leading to impairment in other cognitive changes such as orientation, executive functioning, language, praxis, visuospatial abilities and gnosis (Dubois et al., 2007; Geldmacher, 2009). Besides, structural imaging in AD reveals a pattern of atrophy that surpasses the medial temporal lobes and involves the medial and lateral parietal cortices (Jack et al., 2011).

This pattern is corroborated by molecular neuroimaging that demonstrates both hypometabolism and hypoperfusion in bilateral temporal parietal regions and in the posterior cingulate gyrus (Coleman, 2005). Moreover, recent evidence indicates that sensory and motor changes may precede these well-known AD cognitive alterations, focusing on age-related and neuropathological changes in the olfactory, visual, auditory, and motor systems (Albers et al., 2015).

Vision is a well-studied cortical function that encompasses not only occipital but also temporal and parietal brain areas. Accordingly, the visuospatial processing is supported by two main pathways: the ventral stream – consisting of occipitotemporal regions that enable the recognition of object shape properties (Milner & Goodale, 2008) - and the dorsal pathway that is involved in spatial vision and motion perception, including structure-from-motion (SFM) integration, which comprises extracting three-dimensional shapes from depth and motion cues (Farivar, 2009; Konen & Kastner, 2008). For this reason, visual function studies associated with these two pathways allow to infer about the performance of the temporal and parietal lobes. In the specific case of AD, studies focusing on vision are important because ventral and dorsal regions may be important for predicting AD and understanding its pathophysiology (Jacobs et al., 2015; Rizzo, Anderson, & Nawrot, 2000; Villain et al., 2010). Moreover, AD neuropathological findings (NFT and NP) are also present in the visual cortical areas, especially in the visual association areas (Valenti, 2004), leading to impaired visual function in this condition.

Visual impairments have been extensively reported in AD, ranging from contrast sensitivity and colour perception deficits to impairments in higher-order visual functions, including: SFM perception, object and face perception and visual attention, visual memory and learning (Duffy, Tetewsky, & O'Brien, 2000; Rizzo et al., 2000). These visual perceptual impairments, apart from deficits in topographical memory, may explain why AD patients get lost in familiar surroundings, providing evidence for the clinically important symptom of visuospatial disorientation present in this condition (Tetewsky & Duffy, 1999). Furthermore, posterior cortical atrophy (PCA) or AD's visuospatial presentation (McKhann et al., 2011) is now accepted amongst the atypical forms of AD (Dubois et al., 2010, 2014). This condition is characterized by an insidiously progressive cognitive disorder where patients present early visual

complaints due to deficits in complex visual processing (Mendez, 2004), and is associated with atrophy of the occipital and occipitoparietal regions of the cerebral cortex.

There is a lack of visual function studies in MCI, especially when compared to the amount of research in AD. Nevertheless, some studies report deficits in high-level visual functions, showing visual search and attentional impairment in MCI (Mapstone, Steffenella, & Duffy, 2003; Tales, Snowden, Haworth, & Wilcock, 2005). It seems that MCI subjects are impaired in some functions early on, but other functions seem to be preserved, at least in the initial stages. It would be interesting to investigate comprehensible visual function through the spectrum of AD, using MCI as a target and compare it to AD and healthy ageing subjects. Another important assessment-goal is the potential value of the visual function status as a predictor of MCI-conversion to dementia, either through the use of psychophysical techniques (like the majority of behavioural studies) or through the support of both structural and functional neuroimaging techniques. This topic will be addressed in the second chapter of this thesis through the investigation of the visuospatial processing in MCI and AD patients.

General outline of the thesis

The present thesis is divided in two chapters. In *Chapter I* we focus on the impairment of episodic memory and revise the interest of the cued recall measures, based on encoding specificity, for the assessment of AD spectrum disorders. In *Chapter II* we investigate the visuospatial processing of these conditions as a potential new biomarker.

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CHAPTER I

"Hay que haber empezado a perder la memoria, aunque sea solo a retazos, para darse cuenta de que esta memoria es lo que constituye toda nuestra vida. (…) Nuestra memoria es nuestra coherencia, nuestra razón, nuestra acción, nuestro sentimiento. Sin ella, no somos nada."

In *Mi último suspiro*, LUIS BUÑUEL

In this chapter, we focus on the impairment of episodic memory of AD spectrum disorders and specifically address the use of cued recall measures based on encoding specificity, such as the Free and Cued Selective Reminding Test (FCSRT), as suggested by the IWG-1 (Dubois et al., 2007) and the IWG-2 (Dubois et al., 2014) criteria.

Background

Memory impairment is essential for the diagnosis of both aMCI (Petersen et al., 1999, 2001) and AD (American Psychiatric Association, 2000; Dubois et al., 2007, 2014; McKhann et al., 2011), and also a strong predictor of dementia's development (Dubois et al., 2007, 2014; Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999). A compromise of the long-term episodic memory is the characteristic profile of mild AD (Perri, Serra, Carlesimo, Caltagirone, & Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's Disease, 2007), as it reflects the early involvement of the hippocampus and its related structures. Moreover, these brain structures are critical in memory consolidation and tasks of delayed recall are particularly sensitive to hippocampal dysfunction. Standard criteria for the diagnosis of both aMCI and AD require an objective validation of a significant impairment in episodic memory on neuropsychological testing (Albert et al., 2011; Dubois et al., 2007, 2014; McKhann et al., 2011; Petersen et al., 1999, 2001). Therefore, the test used to identify this memory impairment should be highly accurate (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994), and individual deviations must be concretely specified along with its cut-off values (Petersen, 2004). In AD clinical practice, verbal memory impairment is assessed using different neuropsychological test paradigms (Burrell & Piguet, 2015; Lezak, Howieson, Bigler, & Tranel, 2012; Salmon, 2000). In addition to story passages (e.g., Wechsler Memory Scale – Logical Memory; WMS LM), common tasks include pairs (e.g., WMS Paired-Associate Learning), arrays (the Rey Auditory Verbal Learning Test - RAVLT, the Buschke Selective Reminding Test - SRT), or lists of words with variable semantic relations (the California Verbal Learning Test – CVLT, the Free and Cued Selective Reminding Test – FCSRT). Most of these tasks include immediate and delayed (i.e., after 20 – 30 min) recalls (free and/or cued) components, as well as recognition (Burrell & Piguet, 2015).

Considering the framework criteria for both AD and aMCI, there is no particular suggestion of a memory test for the diagnosis of aMCI (Petersen et al., 1999, 2001) or NIA-AA (Albert et al., 2011; McKhann et al., 2011). On the other hand, the IWG-1 (Dubois et al., 2007) and the IWG-2 (Dubois et al., 2014) proposals suggested the use of cued recall measures for the early diagnosis of AD, based on encoding specificity to assess the memory impairment of AD spectrum disorders, such as the FCSRT (Buschke, 1984; Grober & Buschke, 1987).

The memory impairment in AD spectrum disorders

Episodic memory deficits can be achieved either by tests that control for encoding at the time of study and provide retrieval cues at the time of testing or by traditional free-recall procedures in which encoding is typically not controlled and cues are not provided at retrieval (Carlesimo, Perri, & Caltagirone, 2011). Nevertheless, in the specific case of AD, the former type of declarative memory test is expected to be more effective than the latter in differentiating AD patients (preclinical or clinical phase) either from healthy controls or from patients with memory deficits caused by other pathological conditions (Carlesimo et al., 2011). In fact, an impairment on tasks of delayed recall as sensitive measures to hippocampal dysfunction is not itself evidence of an AD-related memory disorder, and the effectiveness of delayed recall trials (Salmon, 2000) in differentiating between patients with AD and healthy ageing subjects or other conditions is dependent on the paradigm for encoding the information. Accordingly, performance in delayed recall and consolidation reflect the quality of learning, and because of that, paradigms that control and superimpose reinforcement to the encoding process may increase test acuity (Belleville, Sylvain-Roy, de Boysson, & Ménard, 2008; Buschke, Sliwinski, Kuslansky, & Lipton, 1997; Moulin, James, Freeman, & Jones, 2004; Wang & Zhou, 2002). Therefore, deficits in encoding and storage processes that are characteristic of AD must be distinguished from non-AD deficits that can also affect delayed recall, such as attentional difficulties or inefficient retrieval strategies that may be present in normal ageing or in other clinical conditions (Dubois et al., 2007). Thus, if the experimental conditions ensure support for elaborative encoding and provide valuable cues at the time of retrieval, healthy

subjects and non-AD patients may have normal or quasi-normal retrieval accuracy (Carlesimo et al., 2011). It is predicted that the memory deficit in AD can be differentiated from deficits in the other conditions due to the presence of the qualitative features of mesio-temporal amnesia in the former and, conversely, the presence of memory impairment with qualitative features similar to frontal lobe amnesia in the latter (Carlesimo et al., 2011).

The involvement of the hippocampal formation and entorhinal region in the AD spectrum is reflected as early as in aMCI, whose main cognitive characteristic is a deficit of declarative memory (Petersen et al., 2001). Therefore, the memory tests used in the assessment should be able to identifiy aMCI deficits that are more likely due to a severe failure of learning than to long-term processes of defective storage mechanisms (Carlesimo et al., 2011) and to define a pattern of memory dysfunction between MCI and AD. Highly accurate tests should indicate a similar profile of impairment among MCI patients with a higher risk of conversion to AD, therefore confirming its great predicitive value for conversion to AD.

In this context, a memory test is undoubtly valid for the early detection of AD if its paradigm is correlated with supportive AD features, such as neuroimaging measures, showing the characteristic involvement of medial temporal lobe structures, and neurochemical (CSF) biomarkers.

All these reasons reinforce the recommendation of the FCSRT (Buschke, 1984; Grober & Buschke, 1987) to assess the memory impairment of AD spectrum disorders by the IWG-1 (Dubois et al., 2007) and the IWG-2 (Dubois et al., 2014) criteria.

The Free and Cued Selective Reminding Test (FCSRT)

The FCSRT was designed to improve the original Buschke SRT (Buschke, 1973) for a more complete and accurate assessment of verbal learning and memory, and for the detection of its impairment (Buschke, 1984). The FCSRT method relies on cued recall, which allows the “control of processing by manipulation of encoding as well as retrieval through specified concurrent processing of cues and to-be-remembered target items during learning” (Buschke, 1984).

The paradigm that underlies the FCSRT is based on encoding specificity. This principle states that "specific encoding operations performed on what is perceived determine what is stored, and what is stored determines what retrieval cues are effective in providing access to what is stored", i.e., memory retrieval is best in situations that match encoding conditions the closest, enabling superior memory effectiveness when the information available at encoding is also present at retrieval (Figure I) (Tulving & Thomson, 1973). This procedure has shown to promote deeper engagement with attention and semantic processing in the encoding phase of memory, and it also controls the conditions of retrieval through the use of the same cues to direct learning and produce effective cued recall (Tulving & Thomson, 1973). Tulving and Thomson (1973) argued that cueing aids recall if the cue information has been encoded with the target word at presentation and thus forms part of the same encoded unit. Moreover, in terms of cueing, a semantically orienting task leads to a higher retention than structural tasks in which the non-semantic aspects of the words are attended to (Craik & Tulving, 1975). Additionally, attention to the word's meaning is a necessary prerequisite of good retention (Craik & Tulving, 1975). Moreover, it is suggested that at encoding "the stimulus is interpreted in terms of the system's structured record of past learning, that is, knowledge of the world or semantic memory", whereas at retrieval the information provided as a cue utilizes the same structure of semantic memory in order to reconstruct the initial encoding (Craik & Tulving, 1975).

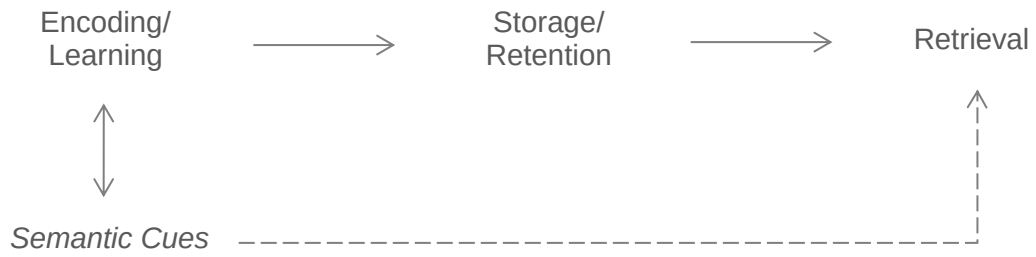

Figure I - The Encoding Specificity Principle (based on Tulving & Thomson, 1973)

Concerning the type of stimulus, there is the suggestion that pictures allow a better retention due to a concomitant verbal and image code stimulation, whereas written words are confined to verbal coding (Paivio, 1995). Yet, turning individuals' attention to semantic aspects of the to-be recalled pictures and words during encoding was found to eliminate the picture superiority effects (Paivio, 1975).

The FCSRT (Buschke, 1984; Grober & Buschke, 1987) is a memory test that controls attention and cognitive processing, requiring subjects to search for items in response to their category cues in the learning process. This multi-trial test uses a "selective reminding" paradigm by presenting only the words not recalled, instead of all the to-be-remembered words. This paradigm is intended to facilitate learning by directing the subject's attention to the words not recalled in the previous trial. Furthermore, the category cues are given later to participants in order to elicit the recall of the items not retrieved on the free recall trial, thus controlling acquisition and retrieval. Performance on the cued recall trial provides an estimate of the items that the subject has stored, and it has been shown that this estimate is minimally affected by guessing (Grober, Gitlin, Bang, & Buschke, 1992).

There are two versions of the FCSRT: the Busckhe's FCSRT (Buschke, 1984; Buschke's FCSRT. Copyright, 2002), that includes words to be identified and remembered, and the Grober-Busckhe modified version (Grober & Buschke, 1987), that includes pictures and comprises an immediate cued recall during the learning phase after the identification of a group of four items. The picture and word versions of the FCSRT showed to be moderately associated (free recall – 0.56; total recall – 0.46) in a sample of cognitively normal older adults, but should not be considered equivalent; still, formulas of conversion between the two versions are provided for nondemented older adults (Zimmerman et al., 2015). Nevertheless, the FCSRT (words' version) present "printed words to avoid perceptual errors, ensure that all subjects use the same verbal encoding to learn the same items, and avoid dual perceptual and verbal encoding" (Buschke's FCSRT. Copyright, 2002).

This paradigm has been used in several normative studies in the aging population, providing normative data to be available for different language/cultural populations (Dion et al., 2015; Frasson et al., 2011; Girtler et al., 2015; Ivnik et al., 1997; Hind Mokri, Avila-Funes, Meillon, Gutiérrez Robledo, & Amieva, 2013; O'Connell & Tuokko, 2002; Palomo et al., 2013; Peña-Casanova et al., 2009) and proving its interest as a valid neuropsychological instrument for the assessment of episodic memory. This test was also used in healthy ageing (Castro-Lionard et al., 2011; Vercambre et al., 2010) and confirmed that cognitive complaints of the elderly can either reflect objective memory impairment independently of affective disorders (Rouch et al., 2015), or be

associated with depressive symptoms rather than objective cognitive performance (Minett, Da Silva, Ortiz, & Bertolucci, 2008); furthermore, a poor performance on the FCSRT was associated with smaller hippocampal volumes and lower levels of hippocampal N-acetyl aspartate/creatine ratio metabolites among nondemented older adults (Zimmerman et al., 2008).

This test was also used to assess memory deficits in other conditions, such as diabetes (Grober, Hall, Hahn, & Lipton, 2011), endogenous hormones (Zimmerman et al., 2011), blood pressure levels (Beauchet et al., 2010; Sacktor et al., 1999), chronic obstructive pulmonary disease (Crews et al., 2001), alcoholism (Chanraud et al., 2009), sleep behaviour disorders (Uguccioni et al., 2013; Uguccioni, Pallanca, Golmard, Leu-Semenescu, & Arnulf, 2015), neurodegenerative Langerhans cell histiocytosis (Le Guennec et al., 2014), CADASIL (Epelbaum et al., 2011).

Information concerning the psychometric properties of the FCSRT is scarce in the literature and limited to the modified Grober-Buschke procedure (Grober, Ocepek-Welikson, & Teresi, 2009). When comparing the three available English test equivalent forms, the factor analysis indicate a single construct or dimension which the authors presumed to be memory ability. The three forms show good concurrent criterion validity, good internal consistencies and similar values of accuracy in the diagnosis of mild dementia (Grober et al., 2009). Moreover, the study of Zimmerman et al. (2015) reported good values of test-retest reliability for the Busckhe's FCSRT word version (free recall – 0.80; total recall – 0.83), and modest association (r=0.36) between the FCSRT free recall and the WMS LM I subtest among healthy elders.

The version of the test used throughout the present work is the Busckhe's FCSRT. This version starts by asking subjects to identify words in response to a unique category cue. The 16 items to be learned are presented four at a time on a card, distributed by one word per quadrant. The subject is asked to search each card and point to and name aloud each item after its semantic cue was aurally presented. During this procedure, the subject is instructed to learn the 16 words. After this, there are three recall trials, each preceded by 20 seconds of counting backward to prevent recall from short-term memory. Each recall trial consists of two parts. First, each subject has up to two minutes to freely recall as many items as possible. Next, aurally presented category cues are provided for items not retrieved by free immediate recall (IR) - cued

IR. If subjects fail to retrieve the item within the category cue, they are reminded by presenting the cue and the item together. The sum of free and cued recalls gives a measure of total IR - TR. After a 30-minute interval, while subjects are required to perform non-verbal tasks, the same procedure of recalling (freely and cued) is done (delayed recall – DR) allowing the measure of free DR, cued DR, and total DR.

The FCSRT in AD-related memory assessment

The rationale underneath the use of the FCSRT in clinical neuropsychology is that its controlled search procedure during learning results in apparently normal cued recall by some amnesic patients with impaired free recall learning, suggesting that their ability to encode and retrieve may be relatively intact when they are induced to carry out effective processing during learning (Buschke, 1984). Consequently, the cued recall should be useful for the evaluation of residual learning and memory capacity.

In the case of AD spectrum disorders, testing memory by controlling the learning conditions proved to be more sensitive to AD early signs (Buschke et al., 1997), and was able to distinguish its genuine deficits in encoding and storage from the memory deficits associated with normal ageing (Grober & Buschke, 1987). The memory impairment associated with healthy ageing was likely to be secondary to impaired attention, inefficient information processing, or ineffective retrieval operations (Grober & Buschke, 1987; Petersen, Smith, Kokmen, Ivnik, & Tangalos, 1992). Retrieval deficits that occur in healthy elders showed to improve with controlled learning procedures (Buschke, Sliwinski, Kuslansky, & Lipton, 1995; Grober, Merling, Heimlich, & Lipton, 1997). On the contrary, in patients with dementia of the AD-type these procedures have very limited benefits, and these patients are often not helped by semantic cueing (Buschke et al., 1997). As a consequence, controlled learning measures should expand the differences produced by normal ageing and dementia, thus improving discriminative validity (Grober, Sanders, Hall, & Lipton, 2010; Oltra-Cucarella, Pérez-Elvira, & Duque, 2014), and allow the identification of the earliest stages of AD (Dubois et al., 2007, 2014). The utility of this cued selective reminding paradigm has been widely reported in the memory dysfunction characterization of AD (review studies, as following: (Carlesimo et al., 2011; de Souza, Sarazin, Goetz, &

Dubois, 2009; Lin, O'Connor, Rossom, Perdue, & Eckstrom, 2013; Lin, O'Connor, Rossom, Perdue, Burda, et al., 2013; Peña-Casanova, Sánchez-Benavides, de Sola, Manero-Borrás, & Casals-Coll, 2012).

The first reported studies incorporated samples of AD, vascular dementia (VaD), and mixed dementia in their analysis. The total recall score was found to enable a higher sensitivity in identifying individuals with dementia compared to the free recall procedure (Grober, Buschke, Crystal, Bang, & Dresner, 1988; Grober & Buschke, 1987). Regarding specificity in identifying healthy matches, higher results were also achieved for total recall score rather than for free recall (Grober et al., 1988; Grober & Buschke, 1987). In the same context, Buschke et al. (1997) proved that encoding specificity tests had substantially higher sensitivity (93%) and specificity (99%) for the diagnosis of early dementia than paradigms with category cues only used for retrieval (53%, 94%), the WMS Paired Associates (68%, 91%), and the WMS Logical Memory (48%, 92%). The FCSRT free recall showed a good sensitivity (86%) and a medium specificity (73%), at optimal cut-off values, for identifying dementia in primary care settings (Grober, Hall, Mcginn, et al., 2008). High values of sensitivity (100%) and specificity (87.2%) were also reported for the diagnosis of dementia in a Spanish elderly population sample (del Ser, Sánchez-Sánchez, García de Yébenes, Otero, & Munoz, 2006). In study specific populations, such as Spanish speaking Latino patients, the FCSRT proved also to be an effective tool for dementia screening, since its impairment were 10 times more likely to predict dementia than an intact recall, whereas an impaired Mini-Mental State Examination (MMSE) were 4.5 times more likely to predict dementia than intact scores in educationally diverse primary care populations (Grober, Ehrlich, Troche, Hahn, & Lipton, 2014); Mokri et al. (2012) suggested that participants with reading abilities exhibit more efficient learning processes with potentially better spontaneous encoding strategies, in the FCSRT, but not necessarily better memory capacity. Aging subjects with higher cognitive reserve revealed a greater protective effect of executive function (digit symbol substitution test) and episodic memory (FCSRT) against gait speed decline (Holtzer, Wang, Lipton, & Verghese, 2012). This paradigm was also used to assess the effect of drugs with anticholinergic properties on verbal episodic memory function, but while some proved no direct impairment on explicit memory (Grober et al., 1992),

others revealed a significant unfavourable effect of these drugs on episodic verbal memory (Fortin et al., 2011).

Other studies using the FCSRT and analyzing the relationship between biological risk factors for dementia reported: a higher adherence to a Mediterranean-type diet was not associated with risk for incident dementia (Féart et al., 2009); the cholesteryl ester transfer protein was associated with slower memory decline, lower incident dementia, and AD risk (Sanders et al., 2010); stable memory scores after one year of deep brain stimulation in mild AD patients (Fontaine et al., 2013).

The importance of studying AD as an independent diagnostic entity led subsequent studies to specifically include AD patients on their pathological samples. Consequently, the validity of the cued selective reminding paradigm for AD was found to effectively discriminate between mildly AD and controls (sensitivity of 88% with specificity set at 95%), but little more effective in detecting very mild AD (sensitivity of 62% with specificity of 95%) than the WMS Logical Memory subtest (sensitivity of 58% with 95% of specificity) (Brown & Storandt, 2000). The authors attribute this discrimination difficulty to the presence of outliers in the very mildly demented group that did not fall below the level of memory performance of people at the low end of “normal” ability represented by the control group (Brown & Storandt, 2000). Vogel, Mortensen, Gade, & Waldemar (2007) found also equivalent discriminative validities (sensitivity >88%, and specificity >89%) for very mild AD, between a category cued recall paradigm and the 10-word memory list from the ADAS-cog (as a measure of free recall). Carcaillon, Amieva, Auriacombe, Helmer, and Dartigues (2009) found that the MMSE subscores for orientation to time and the 3-word recall task were well correlated with FCSRT scores; additionally, the summation of these two MMSE subscores was more strongly associated with dementia and AD than the FCSRT scores and the total MMSE score. Drolet et al. (2014) compared the performance of healthy elders and AD’s on the FCSRT and the RAVLT and found that: the RAVLT demonstrated a slightly better sensitivity (100%) and specificity (100%) than the FCSRT (90% and 100%, respectively) in classifying subjects; the FCSRT showed ceiling effects and a decline in performance on free recall throughout trials in AD patients, but was less sensitive to recency effects than the RAVLT, possibly providing a more realistic view of the long-term memory performance of these patients; the semantic cues provided in the FCSRT appeared to

increase intrusions in AD whereas the interference list in the RAVLT was the first source of false recognitions in both healthy elderly and AD. The FCSRT was included as memory test in neuropsychological batteries for AD assessment (Millet et al., 2008; Mormont, Jamart, & Robaye, 2012).

Furthermore, the FCSRT was able to differentiate AD patients from other forms of dementia in general (Grober, Hall, Mcginn, et al., 2008), since the latter benefited more from controlled learning procedures, and specifically from VaD (Grober, Hall, Sanders, & Lipton, 2008; Grober et al., 2010; Traykov et al., 2005) and FTD (Basely, Ceccaldi, Boyer, Mundler, & Guedj, 2013; Bertoux et al., 2014; Pasquier, Grymonprez, Lebert, & Van der Linden, 2001), supporting the presence of an amnestic syndrome of the hippocampal type as representative of typical-AD spectrum disorders.

A poor performance on the FCSRT has also shown a high correlation with the medial temporal lobe, by means of atrophy (Diamond et al., 2007; Sánchez-Benavides et al., 2010, 2014; Sarazin et al., 2010; Wenger, Negash, Petsersen, & Petersen, 2011), hypoperfusion (Habert et al., 2011) and hypometabolism (Van Der Gucht et al., 2014), and was also significantly associated with CSF profile of AD (Rami et al., 2011; Wagner et al., 2012; Xie et al., 2014); thus, when combined with an AD-biomarker, the FCSRT improves the diagnostic accuracy in the early detection of AD. Functional imaging showed correlations between the FCSRT and the inferior parietal lobule, the precuneus, the hippocampus and the parahippocampal gyrus in mild AD dementia over 6 months (McLaren et al., 2012), and evidenced the involvement of the posterior cingulate cortex as a potential risk for AD in the elderly (Bernard et al., 2015).

Genetic susceptibility factor, through the presence of the ApoE-ε4 allele, presented conversely results: while some found it to be correlated with an impaired FCSRT (Caselli et al., 2004; Hall, Lipton, Katz, & Wang, 2015; Petersen, 1995), others found no relation (Amariglio et al., 2015).

In early stages of decline, such as MCI or prodromal AD, the observed deficits are usually only psychometrically defined, i.e., the subject performs the cognitive task with a lower performance than what is expected for their reference population (Peña-Casanova et al., 2012). As such, transitional states of amnestic impairment between normal ageing and dementia are expected to have a detectable episodic memory

deficit on cognitive tests, but with an intermediate pattern of severity between healthy ageing and AD. The FCSRT has evidenced this gradual pattern of impairment among normal ageing, MCI, and AD (Boeve et al., 2003; Petersen, 2004; Petersen et al., 1999). This result was also supported by Saka, Mihci, Topcuoglu, and Balkan (2006) that found enhanced cued recall paradigms to highly and moderately discriminate AD and MCI from controls, respectively. The FCSRT, as a measure of low verbal memory performance, was also included in neuropsychological batteries for MCI assessment (Barbeau et al., 2004; Onen, Henry-Feugeas, Roy, Baron, & Ravaud, 2008; Poissonnet et al., 2012; Traykov et al., 2007). FCSRT results enabled to show a higher degree of memory impairment in MCI patients with apathy (Robert et al., 2006).

Costa et al. (2014) documented that, in subjects with aMCI associated to Parkinson's disease, episodic memory impairment is related to retrieval rather than to consolidation failure, as these patients had an impaired free recall but normal cued recall and a better performance than regular aMCI; moreover, memory deficits might be due to altered frontal-related executive functioning in this population.

Due to the increased risk of progression to dementia among people with memory complaints – mainly MCI subjects – an intra-subject longitudinal comparison would be of more interest to predict the progression of cognitive decline, rather than comparisons to general population norms (Peña-Casanova et al., 2012). Cued recall paradigms were also analysed for the purpose of predicting AD. Ivanoiu et al. (2005) showed that this memory test correctly classified 88% of the MCI and subjective memory complaints participants, being the best predictor of the status of MCI and mild AD as well as of the outcome of the MCI patients, when compared to other verbal (Ten Word-List Recall from CERAD) and visual ("Doors" and the "Shapes" tests from "The Doors and People Test Battery") memory tests. Dickerson, Sperling, Hyman, Albert, and Blacker (2007) revealed that the presence of both higher CDR-sum of boxes (OR=1.65) and lower verbal memory and executive function at baseline predicted greater likelihood of probable AD in patients with MCI, with similar odds (OR) between the FCSRT (OR=0.78) and the CVLT (OR=1.2). Mura et al. (2014) investigated the sensitivity of a large set of neuropsychological tests to detect cognitive changes due to prodromal AD, and the results showed that the most sensitive tests in detecting cognitive changes due to prodromal AD were the FCSRT (free, total, and delayed free

recalls), followed by the semantic verbal fluency and the Deno100 (both language tets). Moreover, while the two free recalls of the FCSRT were better at detecting cognitive changes at high levels of cognition, the total recall score was better for low levels of cognition. The total recall of ther FCSRT was also the most sensitive (>79%) and specific (>89%) test for conversion diagnosis of prodromal AD, among other neuropsychological tests (the Benton Visual Retention Test for visual memory; the Deno 100 and verbal fluency for language; a serial digit learning test and the double task of Baddeley for working memory; WAIS similarities for conceptual elaboration; and the Stroop test, the TMT, and the WAIS digit symbol test for executive functions) (Sarazin et al., 2007). Rabin et al. (2012) also showed that the free recall of the FCSRT was the neuropsychological measure most strongly associated with incident AD when compared to WMS LM, Trail Making Test, Digit Symbol and Digit Span, Letter Fluency Test, and the short form of the Boston Naming Test; nevertheless, the risk of developing AD was associated both with the FCSRT, the WMS LM and the informant reports, showing the incremental effect of informant reports in addition to the neuropsychological test scores. In an imaging study, Koric et al. (2013) enhanced that cued recall deficits are associated with a progression of atrophy that closely parallels the spatiotemporal distribution of neurofibrillary degeneration in early AD, which is indicative of possible AD pathological changes.

While the previous paragraph has shown the usefulness of the FCSRT in the assessment of aMCI patients (prodromal AD), we will now focus on studies of prediction of AD among healthy ageing – preclinical AD. These studies aim at defining the nature and timing of cognitive changes in order to understand AD's natural history and therefore define prediction models and preventive interventions. Grober and Kawas (1997) found that learning that controls cognitive processing, and not retention, was superior in the detection of preclinical and very early AD. Grober, Hall, Lipton, et al. (2008) showed that while a decline in episodic memory (FCSRT) accelerated 7 years before diagnosis in subjects with incident AD that were followed for up to 15 years, deficits in executive function accelerated 2–3 years before diagnosis, and in verbal intelligence close to diagnosis. This profile supports pathologic data suggesting that structures which mediate memory are affected earlier than frontal structures during the preclinical onset of AD, and that VIQ does not decline during the preclinical onset

of AD. Grober, Lipton, Hall, and Crystal (2000) proved that poor performance on free recall from FCSRT predicts future dementia, supporting the existence of a preclinical phase present for at least 5 years before diagnosis. Nevertheless, Auriacombe et al. (2010) stated that the FCSRT had reasonable sensitivity (>60%) and specificity (>77%), and excellent negative predictive values (>98%), but low positive predictive values (<16%) for AD, i.e., many subjects with low scores on the FCSRT remained free of dementia at 5 years. These results indicate that low FCSRT scores must be interpreted with caution, as subjects who often do not have memory complaints may have unrecognized poor memory status. The FCSRT was also included in neuropsychological batteries for the early detection of patients in the pre-demented stage of AD, proving its utility as a measure of low verbal memory performance (Amariglio et al., 2015; Mahieux et al., 2009). Derby et al. (2013) reported that the free recall of the FCSRT had better operating characteristics than the immediate recall of the WMS LM for identifying those with memory complaints who will develop incident AD dementia over 2-4 years, with the former presenting sensitivities >81%, and specificities >70%, and the latter sensitivities of >67%, and specificities of >68%. Papp et al. (2015) showed that the sensitivity of free versus cued memory paradigms may be dependent on the biomarker-defined stage of preclinical AD among clinically normal older adults, as following: a reduced free recall seems to be associated with amyloidosis alone, while a decline in cued recall may represent a progression to amyloidosis and neurodegeneration. Holtzer, Verghese, Wang, Hall, and Lipton (2008) claimed to be the first proving that within-person across-neuropsychological test variability was associated with development of incident dementia independent of neuropsychological test performance (FCSRT was included).

General outline and aims of Chapter I

The main purpose of the first chapter aimed at adapting the FCSRT for the portuguese population and validating its usefulness, on a memory clinic basis, to the AD spectrum early diagnosis, hence contributing to the IWG-1 and IWG-2 criteria by means of finding that: 1) AD patients do not improve with cueing or, at the very least, improve significantly less than patients with other dementing and non-dementing conditions; 2)

aMCI patients display an intermediate pattern of severity between healthy ageing and AD; 3) this paradigm is more accurate at identifying people affected by AD than other declarative memory tests with no support for encoding or cue for retrieval – free recall procedures; 4) a great predicitive value for conversion to AD is detectable among MCI patients that exhibit a similar profile of impairment to AD.

Study 1, *Adaptation of the Free and Cued Selective Reminding Test to the Portuguese population*, describes the transcultural adaptation of the FCSRT to Portuguese, taking into account linguistic and cultural adequacy criteria. Materials and instruction of the FCSRT were provided to our team by the original author (Buschke's FCSRT. Copyright, 2002. Albert Einstein College of Medicine of Yeshiva University, New York). The selection of the 16 stimulus words followed the same principles of the English version – intermediate frequency words were selected within a semantic category (frequencies in Portuguese from the CORLEX database) (Nascimento et al., 2003).

Results from the validation of the FCSRT for MCI and AD through the analysis of the diagnostic accuracy and the suggestion of cut-off scores are provided in Study 2, *Validation of the Free and Cued Selective Reminding Test for Mild Cognitive Impairment and Alzheimer's disease*. Moreover, the results from this study enabled to illustrate the heterogeneity of MCI at baseline.

In Study 3, *Construct and diagnostic validities of the Free and Cued Selective Reminding Test in the Alzheimer's disease spectrum*, we assessed the construct related and diagnostic validities of the FCSRT in AD spectrum disorders. The factorial structure of two models, and respective construct and diagnostic validities were analysed. The appropriated convergent validity and the lack of discriminant validity support the two-factors as measuring the same construct, i.e. memory ability. High classification accuracy and diagnostic validity were present for both aMCI and AD groups.

Study 4, *The Free and Cued Selective Reminding Test for predicting progression to Alzheimer's disease in patients with Mild Cognitive Impairment*, aims to investigate whether the performance on the FCSRT would enhance the ability to predict conversion to AD in an aMCI group. A longitudinal study was conducted and neuropsychological tests were analysed on the relative risk of conversion to AD. The FCSRT demonstrated utility for detecting AD at its prodromal stage, thus supporting its use as a valid clinical marker.

Chapters 5 and 6 compared the performance of MCI and AD patients on the FCSRT and on other memory tests.

In Study 5, *Selective Reminding and Free and Cued Selective Reminding in Mild Cognitive Impairment and Alzheimer´s disease*, we compared the psychometric properties and accuracies of the SRT and the FCSRT in discriminating aMCI from AD. Like FCSRT, SRT also comprises a "selective reminding" paradigm that presents only the missing words from the previous recall trial. But, while in the FCSRT semantic cues are provided to elicit recall, in the SRT subjects are merely reminded of the missing items by repeating them. Both tests are widely used in dementia neuropsychological assessments. Our results revealed a benefit of category cueing (FCSRT) on both groups, and a higher accuracy in discriminating aMCI from AD patients on the FCSRT.

In Study 6, *The Free and Cued Selective Reminding Test and the Wechsler Memory Scale in discriminating Mild Cognitive Impairment from Alzheimer's disease*, we compared the Wechsler Memory Scale [Logical Memory (LM) and Verbal Paired Associative Learning subtests] and the FCSRT in terms of psychometric properties of accuracy in classifying aMCI and AD. All instruments revealed good results, whilst the FCSRT was able to classify more patients as having memory impairment in the aMCI group rather than the WMS subtests. The FCSRT proved to be good in discriminating the two groups in both lower and higher educational levels, whereas the LM was more useful in higher educated patients.

In order to confirm the ability of the FCSRT in assessing the genuine deficits in encoding and storage processes characteristic of typical-AD spectrum disorders, as a result of an amnestic syndrome of the hippocampal type, we examined in Study 7 – *The Free and Cued Selective Reminding Test distinguishes Alzheimer's disease from Frontotemporal Dementia*, the usefulness of the FCSRT in the distinction between behavioural frontotemporal dementia (FTD) and AD. Results proved that while AD patients exhibited an overall impairment in FCSRT, FTD subjects showed to benefit more from the controlled learning through category cues. AD patients were significantly more likely to have an impaired FCSRT. The FCSRT has shown its utility in the distinction between FTD and AD, therefore increasing the diagnostic accuracy.

To conclude this chapter, we present a discussion covering all the results achieved throughout this work plan, reflecting on the main limitations of our studies, and emphasizing the main conclusions and implications for the neuropsychological contribution to the clinical practice and the scientific research on AD spectrum disorders.

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STUDY 1

Adaptation of the *Free and Cued Selective Reminding Test* to the Portuguese population

Adapted from: **Lemos, R**., Martins, C., Simões, M., & Santana, I. (2012). Estudo de adaptação do Teste de Recordação Selectiva Livre e Guiada para a população portuguesa [Adaptation study of the Free and Cued Selective Reminding Test to the Portuguese population]. *Avaliação Psicológica*, 11(1), 49–61.

Abstract

The *Free and Cued Selective Reminding Test* (FCSRT) involves a new paradigm of memory assessment, using selective reminding with semantic cueing. This allows for an assessment of memory that is independent of normal age-related changes in cognition. Therefore, the FCSRT has shown to be useful for memory characterization in Alzheimer's disease (AD).

The International Working Group on Alzheimer's disease (2007) has suggested new diagnostic criteria for AD. The main criterion is evidence for a significant and progressive episodic memory impairment confirmed by objective testing. The authors suggest the FCSRT to assess memory, since it showed high sensitivity and specificity in the differentiation of AD patients from healthy controls and from other dementias.

The goal of this paper is to describe the adaptation of the FCSRT for the Portuguese population, taking into account linguistic and cultural adequacy criteria.

Introduction

A memória no envelhecimento normal e patológico

O estudo da memória constitui uma etapa fundamental da avaliação neuropsicológica de populações geriátricas, não só porque "o esquecimento" é uma das queixas mais comuns dos doentes idosos (Goeman & De Deyn, 2003), sendo motivo frequente de encaminhamento para consultas da especialidade (Lezak, Howieson, & Loring, 2004), mas também porque a memória é a capacidade cognitiva mais afectada no contexto das doenças neurológicas e psiquiátricas do envelhecimento (Delis & Kramer, 2000).

As queixas de memória mais frequentes referem-se à dificuldade em aprender e/ou recordar informação, objectos e/ou eventos (Lezak et al., 2004). Este tipo de memória é habitualmente designado por "memória declarativa" (memória de longo-prazo), e representa a "informação que pode ser convertida em recordações conscientes sob a forma de proposição verbal ou de imagem visual" (Squire & Kandel, 2002, p.23). A memória declarativa pode ainda dividir-se em dois subtipos: *memória episódica* – recordação de acontecimentos específicos ("episódios"), delimitados no tempo e no espaço e com um carácter contextual, e a *memória semântica* – recordação de acontecimentos gerais, inerentes a uma determinada cultura e aprendidos como "conhecimento" (por exemplo, o alfabeto) (Lezak et al., 2004). A memória episódica, também designada comummente por "memória recente", é a mais sensível ao dano neurológico e ao envelhecimento pelo que constituirá o principal alvo do nosso interesse.

A memória é uma função cognitiva central e complexa a partir da qual a informação nova é codificada, guardada e recuperada no cérebro e estes processos desenvolvem-se em determinadas estruturas cerebrais, com localização no lobo frontal e no lobo temporal. Do lobo temporal destacam-se as estruturas mesiais (hipocampo e amígdala) e neocorticais (córtices perirrinal, entorrinal e parahipocampal) (Squire & Kandel, 2002b). O processamento mnésico inicia-se na fase de "codificação" ou aprendizagem, i.e., a capacidade de o indivíduo processar e adquirir uma nova informação. A aprendizagem implica consolidação (o que é aprendido é consolidado) e a "consolidação refere-se ao processo hipotético de reorganização dentro das representações da informação armazenada, que se mantém durante o esquecimento da informação" (Squire, 1986, citado por Lezak et al., 2004). O processo de

consolidação resulta na fase de "armazenamento" ou retenção – que representa a conservação das informações adquiridas. Por fim, a "recuperação" da informação engloba o conjunto de mecanismos que permite aceder à informação adquirida.

Uma vez que a memória representa um processo dividido em diversas fases, as alterações mnésicas podem assumir perfis distintos resultantes do envolvimento diferenciado dos processos já citados. O mesmo se passa com o designado "envelhecimento fisiológico". No decorrer do envelhecimento normal verifica-se, genericamente, um decréscimo na capacidade mnésica, embora nem todos os tipos de memória evidenciem declínio (Goeman & De Deyn, 2003). Vários estudos têm sugerido que a memória a curto prazo e, também, a memória semântica são relativamente resistentes ao envelhecimento, enquanto outras funções, tais como a memória episódica a longo prazo, apresentam alterações relevantes (Goeman & De Deyn, 2003). Num estudo em que se pretendeu avaliar o funcionamento mnésico em sujeitos idosos cognitivamente normais utilizando diversas provas de memória, Petersen, Smith, Kokmen, Ivnik, e Tangalos (1992) evidenciaram que a aprendizagem ou aquisição declinava significativamente com o aumento de idade. Por outro lado, a evocação diferida ou o esquecimento mantinham-se relativamente estáveis ao longo da idade, quando ajustados em função da quantidade de material inicialmente aprendido. Os resultados descritos são importantes na caracterização do funcionamento mnésico normal mas têm implicações ainda mais relevantes no diagnóstico das alterações patológicas do envelhecimento e, em particular, na investigação de alterações precoces da memória na demência. De acordo com a investigação de Petersen et al. (1992), deverá suspeitar-se de uma alteração patológica do processamento mnésico quando se verifica um declínio mais acentuado do que o esperado para a idade na fase da aprendizagem; um prejuízo na aquisição que não melhora com técnicas de ajuda/pistas; ou uma alteração significativa na evocação diferida.

A avaliação neuropsicológica da memória pressupõe a utilização de diferentes tipos de tarefas com o objectivo de "identificar os componentes mnésicos (registo, retenção, recuperação) que se encontram comprometidos ou preservados" (Simões, Lopes, & Pinho, 2003, p.247). A memória episódica é habitualmente avaliada com recurso a tarefas de memorização de listas de palavras, com uma posterior restituição das mesmas usando a recordação livre ou o índice de reconhecimento (Amieva et al.,

2007). Uma crítica habitualmente apontada a este tipo de provas remete para o facto de não permitirem controlar as estratégias efectivamente utilizadas pelo sujeito, sobretudo nas fases de codificação e de recuperação (Amieva et al., 2007), o que poderá comprometer o rigor da avaliação da memória.

A doença de Alzheimer

O envelhecimento da população em países desenvolvidos, resultante do incremento da esperança média de vida, é acompanhado de uma elevação da prevalência das doenças degenerativas associadas à idade. De entre as patologias típicas do envelhecimento, a demência é a mais significativa, ao afectar cerca de 5% dos indivíduos com mais de 60 anos e ao registar uma incidência e prevalência que duplicam a cada 5 anos de idade (Jorm, 1990). A doença de Alzheimer (DA) é a forma de demência mais comum, compreendendo cerca de 50 a 80% entre todos os tipos de demência (Lobo et al., 2000). Em Portugal, a Alzheimer Europe (2009, Projecto European Collaboration on Dementia – Eurocode – conduzido pela Alzheimer Europe e financiado pela Comissão Europeia, *www.alzheimerportugal.org)* prevê que existam cerca de 153.000 pessoas com demência e 90.000 com DA.

A identificação precoce da DA é crucial para uma intervenção e tratamento eficazes, assim como para o estabelecimento de um plano assistencial para estes doentes. Como é típico das doenças degenerativas, o défice cognitivo manifesta-se gradualmente, o que implica, pelo menos conceptualmente, que exista um estado intermediário ou transitório entre o envelhecimento saudável e a demência do tipo Alzheimer (Petersen, 2000; Petersen, 2004; Petersen et al., 2001; Santana, 2003). O conceito de Défice Cognitivo Ligeiro - DCL (*Mild Cognitive Impairment- MCI,* na terminologia anglo-saxónica) sugerido por Petersen et al. (1999), corresponde a este estadio transicional e aplica-se aos sujeitos que apresentam um declínio cognitivo superior ao esperado para a idade, mas que mantêm a sua autonomia funcional. Não são normais, mas também não poderão ser classificados de dementes de acordo com os critérios internacionais vigentes (DSM-IV-TR: American Psychiatric Association, 2000; NINCDS-ADRDA: Mckhann et al., 1984). Este vazio classificativo é aliás uma das limitações mais sérias apontadas aos sistemas de classificação e de diagnóstico referidos. Outras opiniões críticas salientam uma deficiente operacionalização dos

critérios clínicos, a não utilização de instrumentos de avaliação neuropsicológica recomendados e a sua desactualização no que respeita aos biomarcadores entretanto identificados (Blennow, de Leon, & Zetterberg, 2006).

O *International Working Group on Alzheimer's Disease* (IWG; Dubois et al., 2007) desenvolveu e publicou uma proposta de novos critérios de diagnóstico para DA, tentando colmatar as limitações dos ainda vigentes de forma a englobar todo o espectro da doença (incluindo as fases mais precoces de declínio cognitivo - DCL) e valorizar os biomarcadores laboratoriais e de imagem. Nesta nova proposta, o critério de diagnóstico principal considera a evidência objectiva de uma alteração significativa e progressiva da memória episódica, desde que associada a, pelo menos, um marcador biológico da doença (Dubois et al., 2007). Os autores sugerem que o défice mnésico seja comprovado com a utilização de metodologias que controlem a aprendizagem do material a reter, para que seja possível obter uma medida de memória não confundível com o declínio cognitivo associado ao envelhecimento normal. Nesta linha, propõem que a avaliação deva desenvolver-se com base num paradigma de *codificação específica*, visto este ter revelado sensibilidade e especificidade elevadas na diferenciação entre doentes com Alzheimer e controlos saudáveis ou outras formas de demência (Buschke, Sliwinski, Kuslansky, & Lipton, 1997) e sugerem, explicitamente, o *Teste de Recordação Selectiva Livre e Guiada* (*Free and Cued Selective Reminding Test,* Buschke, 1984). Desde a publicação de Dubois et al. (2007), tem havido a preocupação de avaliar a validade destes critérios, ou seja testar a sua sensibilidade e especificidade. A questão da especificidade é obviamente a mais complexa porque implica a confirmação de que os doentes que apresentam um defeito progressivo de memória (demonstrado pelo paradigma TRSLG) evoluem efectivamente para DA. Estes resultados começaram a emergir muito recentemente na literatura científica (Bouwman et al., 2010; Ewers et al., 2012).

O *Teste de Recordação Selectiva Livre e Guiada* (TRSLG)

O paradigma de *recordação selectiva* foi originalmente proposto por Buschke (Buschke & Fuld, 1974; Buschke, 1973) na prova *Selective Reminding Test* (SRT). Este paradigma baseia-se numa medida de aprendizagem forçada, uma vez que o indivíduo é selectivamente recordado das palavras não evocadas. Mais tarde, Buschke (1984)

adicionou uma componente de evocação com ajuda a este teste. Esta versão é conhecida como *Teste de Recordação Selectiva Livre e Guiada* (TRSLG).

O TRSLG (Buschke, 1984) é uma prova de aprendizagem e memória verbal que permite controlar as condições de codificação e de recuperação através da utilização de pistas semânticas no controlo da aprendizagem e na evocação. A aprendizagem é controlada ao impor aos sujeitos a codificação dos itens em resposta à sua categorização semântica; estas mesmas pistas são posteriormente utilizadas para facilitar a evocação dos itens não reproduzidos na evocação livre. Este paradigma fomenta a especificidade da codificação, revelando-se mais eficaz ao permitir uma recordação através de pistas e ao garantir uma atenção selectiva e de enquadramento semântico de todos os itens (Buschke, 1984). Desta forma, asseguram-se os pressupostos defendidos pelo Princípio de Codificação Específica (Tulving & Thomson, 1973) que defende que o modo como a informação é codificada determina o modo como é retida e armazenada, bem como o tipo de indicadores/pistas que facilitam o acesso à informação retida. Por outro lado, é de salientar que no TRSLG são utilizadas as mesmas pistas semânticas na fase de aprendizagem e na fase de evocação, seguindo os princípios definidos de que uma pista só é eficaz na recuperação de informação se tiver sido utilizada na codificação dos itens (Tulving & Thomson, 1973) e que a presença de pistas na fase de codificação e na fase de evocação facilita a recordação dos itens (Tulving & Osler, 1968).

O TRSLG (Buschke, 1984) é composto por 16 itens/palavras categorizados semanticamente e não relacionados entre si. As 16 palavras são apresentadas, 4 de cada vez, em 4 cartões separados, cada um dos quais divididos em 4 quadrantes. Os cartões são apresentados na mesma ordem a todos os indivíduos. O examinador pede aos indivíduos para apontar e ler em voz alta cada palavra do cartão (por exemplo, "figo") em resposta à sua categoria semântica ("fruto") – Aprendizagem Controlada. Após uma tarefa distractora de contagem decrescente, durante 20 segundos – para evitar repetição – a memória é avaliada através da Evocação Livre. Para os itens não recordados espontaneamente na Evocação Livre, são fornecidas as mesmas pistas semânticas usadas na codificação, na tentativa de que eles sejam evocados (Evocação com Ajuda). Se esta ajuda falhar, o sujeito é, então, recordado do item-alvo (recordação selectiva). O teste é constituído por 3 ensaios de Evocação Livre e de

Evocação com Ajuda e cada ensaio é precedido de uma tarefa de interferência de 20 segundos. Um ensaio de Evocação Diferida é efectuado 30 minutos depois.

A memória e a aprendizagem em cada ensaio são medidas através da Evocação Livre e da Evocação Total (somatório da Evocação Livre e com Ajuda). A Evocação com Ajuda é uma medida de recuperação "auto-organizada", enquanto a Evocação Total representa a medida da recuperação máxima, fornecendo uma estimativa da codificação e da retenção.

Em 1987, Grober e Buschke apresentaram uma versão alternativa deste instrumento - o *Teste de Recordação Selectiva Livre e Guiada - Evocação Imediata* (TRSLG-EI). Esta versão obedece aos mesmos princípios conceptuais do TRSLG: utiliza uma medida de aprendizagem controlada de 16 itens não relacionados, a mesma codificação por pistas, e a recordação selectiva com a utilização das mesmas pistas. Como aspecto diferenciador, no TRSLG-EI substituíram-se as palavras por desenhos de objectos impressos em cartões, facilmente reconhecíveis e codificados a partir de categorias semânticas (uma para cada figura). Para além disto, no TRSLG-EI é realizada uma tarefa de evocação imediatamente após a identificação dos itens. Este procedimento é feito para cada cartão, num total de quatro e denomina-se *fase de estudo* (*study phase*). Segue-se uma *fase de teste* (*test phase*) constituída por três ensaios de evocação, análogos ao do TRSLG. Nesta versão, não existe uma tarefa de evocação diferida.

Comparando as duas versões, Buschke (2002) indica a sua preferência pela utilização de palavras escritas (em detrimento do recurso a desenhos) no sentido de evitar erros perceptuais, assegurar que todos os sujeitos utilizam a mesma codificação verbal na aprendizagem dos itens, e impedir uma codificação dupla – perceptual e verbal. Buschke (2002) explica também que foi propositado não incluir no TRSLG a Evocação Imediata com Ajuda (recordação do item-alvo), quando a evocação imediata falha durante a fase de aprendizagem. Neste contexto, são vários os elementos de enquadramento referidos por Tounsi et al. (1999, citado por Buschke, 2002). Em primeiro lugar, a aprendizagem adicional, quando a evocação imediata falha, deteriora a medida de aprendizagem através da evocação. O TRSLG mede a aprendizagem através do número de itens evocados quando a mesma apresentação (estandardizada) de cada item prevê uma oportunidade idêntica de aprender cada item – Aprendizagem Controlada. O número de itens aprendidos pode ser medido através do número de

itens evocados apenas quando todos os itens foram apresentados com igual frequência para aprender. A evocação de diferentes sujeitos pode apenas comparar-se quando foi dada a cada um a mesma oportunidade de aprender os itens; se dois sujeitos evocam o mesmo número de itens, mas um recebeu aprendizagem adicional para alguns itens e o outro não, os seus níveis de evocação não indicam a mesma "quantidade" de aprendizagem. Em segundo lugar, quando a evocação imediata falha, a aprendizagem adicional possibilita maior facilidade na aprendizagem em sujeitos com alterações de memória, uma vez que estes têm mais falhas na evocação imediata e porque o número de omissões na evocação imediata aumenta ao longo do desenvolvimento da patologia (Tounsi et al., 1999, citado por Buschke, 2002). Em casos patológicos, a aprendizagem adicional pode favorecer a evocação e tornar mais difícil a detecção da alteração na aprendizagem e/ou na memória. Quando a memória é avaliada longitudinalmente em sujeitos com deterioração progressiva observa-se que a aprendizagem adicional dificulta a detecção e quantificação do aumento do défice. Por outro lado, a evocação imediata durante a aprendizagem, com aprendizagem adicional quando a evocação imediata falha, ainda não demonstrou mais rigor quer na avaliação da memória, quer na discriminação do défice mnésico. Finalmente, a evocação imediata durante a aprendizagem, com aprendizagem adicional quando a evocação imediata falha, demora mais tempo e prolonga a sessão de avaliação.

Não são conhecidos estudos acerca das propriedades psicométricas do TRSLG. Grober, Ocepek-Welikson, e Teresi (2009) descreveram algumas das propriedades psicométricas das três formas (A, B e C) do TRSLG-EI, aplicadas a uma população geriátrica. A análise factorial sugere a presença de um modelo unidimensional que os autores consideram tratar-se da capacidade de memória. As três formas revelaram uma boa validade concorrente, bons indicadores de consistência interna (α = 0,85; 0,86 e 0,88, respectivamente) e valores semelhantes de sensibilidade (≥75%) e especificidade (≥82%) na detecção de demência ligeira, traduzindo uma acuidade adequada de classificação.

Grober, Merling, Heimlich, e Lipton (1997) compararam a *performance* entre a versão original (SRT) e o TRSLG-EI num grupo de sujeitos idosos sem patologia, comparando o número de palavras evocadas nas duas versões. Verificaram que o paradigma de ajuda semântica do TRSLG-EI permitiu a evocação do dobro de palavras, comparativamente

ao SRT. Os autores concluíram que o procedimento e o método de recordação subjacente ao TRSLG-EI facilitam a evocação livre.

Estudos Internacionais

A versão original (inglês) do TRSLG (*Free and Cued Selective Reminding Test*) foi desenvolvida por Buschke (1984). Os dados normativos para esta prova fazem parte do projecto MOANS (*Mayo's Older Americans Normative Studies,* Ivnik et al., 1997). A amostra é constituída por 734 sujeitos, com idades compreendidas entre os 56 e os 98 anos. Os resultados são apresentados por intervalos de idade, uma vez que a escolaridade e o género evidenciaram uma influência mínima.

A versão espanhola do TRSLG (*Test de Recuerdo Libre y Selectivamente Facilitado*) foi criada como parte dos Estudos Normativos Multicentros Espanhóis (Projecto NEURONORMA) (Peña-Casanova, Gramunt-Fombuena, et al., 2009). A amostra normativa é constituída por 340 participantes, de idades entre os 50 e os 94 anos. Os resultados brutos foram transformados em resultados ajustados à idade e, posteriormente, convertidos em resultados ajustados à escolaridade. O estudo confirma uma influência da idade e da escolaridade no desempenho no TRSLG, enquanto o género teve um efeito sem significado. Constatou-se um declínio em todas as medidas da prova com o aumento da idade e um efeito discreto da escolaridade (cerca de 11% na evocação total) (Peña-Casanova, Blesa, et al., 2009).

A versão TRSLG-EI (*Test de rappel libré/rappel indicé à 16 items*) foi adaptada para o Francês por Amieva et al. (2007). Este estudo normativo, conhecido como "L'étude des 3 Cités" envolve uma amostra de 1458 sujeitos, com idade igual ou superior a 65 anos. Os dados normativos foram calculados de acordo com a idade (65 – 70 anos, 70 – 74 anos, 74 – 78 anos, 78 – 90 anos), nível de escolaridade (ensino primário ou curso técnico *versus* ensino secundário e superior) e género. A avaliação longitudinal (intervalos de 2 e 5 anos) dos participantes do estudo de normalização (Amieva et al., 2007) permitiu analisar a validade do TRSLG-EI na predição de demência (Auriacombe et al., 2010). Os índices de Evocação Livre e Evocação Total (livre e com ajuda) mostraram uma boa sensibilidade e razoável especificidade na predição de DA, ainda que o valor preditivo positivo tenha sido baixo. Por outro lado, o valor preditivo

negativo mostrou resultados excelentes, indicando que os indivíduos com pontuações acima do valor médio têm um risco mínimo de desenvolver DA em 5 anos.

O paradigma subjacente ao TRSLG e ao TRSLG-EI tem sido utilizado em faixas etárias mais avançadas, quer no plano do estudo do envelhecimento normal, quer na investigação clínica de doenças associadas ao envelhecimento.

Assim, esta prova tem sido utilizada como medida de avaliação da memória verbal em estudos recentes de populações de idosos saudáveis (de Souza, Sarazin, Goetz, & Dubois, 2009; Vercambre et al., 2010), ou em estudos prospectivos associados ao risco de desenvolver demência (Féart et al., 2009; Grober, Lipton, Katz, & Sliwinski, 1998; Grober, Lipton, Hall, & Crystal, 2000; Holtzer, Verghese, Wang, Hall, & Lipton, 2008). Comparativamente a outras provas, os resultados no TRSLG mostraram correlações significativas com os subtestes de orientação temporal e a tarefa de evocação no *Mini-Mental State Examination* (MMSE; Carcaillon, Amieva, Auriacombe, Helmer, & Dartigues, 2009; Folstein, Folstein, & McHugh, 1975; Guerreiro, 1998). Por sua vez, Rouch et al. (2008) comprovaram que a alteração mnésica, no envelhecimento normal, está relacionada com queixas cognitivas mas não com perturbações afectivas. Já Minett, Da Silva, Ortiz, e Bertolucci (2008) demonstraram que queixas subjectivas de memória estão mais associadas a sintomatologia depressiva do que a uma alteração cognitiva objectiva. Adicionalmente, Zimmerman et al. (2008) verificaram que uma baixa *performance* no TRSLG, no envelhecimento normal, estava relacionada com alterações neuroquímicas e volumétricas (atrofia) do hipocampo.

A maior parte dos estudos realizados em contexto clínico (demência) tem-se debruçado especificamente sobre a DA: na confirmação do envolvimento precoce da memória na DA pré-clínica (Grober et al., 1997; Grober et al., 2008; Mahieux et al., 2009) e na DA (Grober, Hall, Lipton, et al., 2008). Millet et al. (2008) utilizaram uma adaptação desta prova para mostrar que a memória implícita (*priming*) em doentes com DA está preservada. Outros estudos procuraram relacionar estruturas anatómicas cerebrais associadas à memória na DA e desempenhos no teste. Neste contexto, Sarazin et al. (2010) observaram uma relação entre baixa *performance* no TRSLG e atrofia do hipocampo esquerdo ao nível da região CA1, e Diamond et al. (2007) apontaram para a existência de uma relação entre o desempenho nesta prova e uma

activação nos córtices temporal esquerdo superior e pré-frontal esquerdo, numa experiência de Ressonância Magnética Funcional.

Alguns estudos têm comprovado a utilidade desta prova na avaliação do défice mnésico no DCL: isolado (Traykov et al., 2007; Wenger, Negash, Petersen, & Petersen, 2010), ou em associação a outras alterações, especificamente, memória visual (Barbeau et al., 2004) e apatia (Robert et al., 2006).

O perfil de alteração mnésica semelhante entre o DCL e a DA tem sido descrito em estudos de comparação nos dois grupos clínicos (Onen, Henry-Feugeas, Roy, Baron, & Ravaud, 2008; Petersen et al., 1999) ou de progressão do primeiro para o segundo (Petersen, 1995; Sarazin et al., 2007). Comparativamente a outros meios de diagnóstico, esta prova de memória tem mostrado uma elevada especificidade, na detecção da DA precoce, quando associada a medidas de Tomografia Computadorizada por Emissão de Fotão Único (SPECT) (Habert et al., 2011) e de Ressonância Magnética (Sánchez-Benavides et al., 2010).

Ainda em contexto clínico, este teste foi utilizado na caracterização do perfil mnésico em diferentes condições: demência vascular subcortical (Epelbaum et al., 2011; Traykov et al., 2005), na presença de factores de risco vascular (Beauchet et al., 2010; Sacktor et al., 1999; Sanders et al., 2010), dependência alcoólica (Chanraud et al., 2009), no impacto do consumo de escopolamina (fármaco anticolinérgico) na memória, no envelhecimento normal e na demência (Grober, Gitlin, Bang, & Buschke, 1992).

A utilização deste paradigma de avaliação da memória (e do TRSLG) tem comprovado a sua sensibilidade aos diversos contextos clínicos e facilitado a caracterização do défice mnésico no envelhecimento normal.

O presente trabalho tem por objectivo central descrever o processo de adaptação transcultural do TRSLG para a população portuguesa. Desta forma, torna-se possível a avaliação da validade deste instrumento no contexto dos novos critérios para DA propostos pelo IWG (Dubois et al., 2007).

Methods

Fase 1: Autorização

A autorização para a realização de estudos de adaptação e validação do TRSLG para a população portuguesa foi solicitada e concedida em 2010 (Buschke, 2002; Buschke's FCSRT, Copyright, 1996-2000. Albert Einstein College of Medicine of Yeshiva University, New York; devido à necessidade de salvaguardar direitos de autor, os itens não são aqui apresentados). A adaptação da prova e a tradução para português do respectivo manual de instruções de administração e de cotação foram realizadas nesse mesmo ano.

Fase 2:

- Criação da lista de palavras

A adaptação para o português da prova original em inglês foi realizada por uma especialista em Linguística, fluente na língua inglesa e com experiência em tarefas de adaptação de provas de avaliação cognitiva (co-autora C.M.).

Deu-se preferência a itens mais facilmente passíveis de representação pictórica, uma vez que a versão original do TRSLG contempla a utilização de imagens em alternativa às palavras (Buschke, 2002). Deste modo, a possibilidade de uma opção por esta metodologia de apresentação dos estímulos fica ressalvada. Decorrente deste cuidado, foram seleccionados apenas nomes.

A lista final de palavras é constituída por 16 itens que respeitam os critérios considerados pelos autores na selecção das palavras da língua inglesa:

a) De acordo com o manual do FCSRT, os itens devem apresentar frequência moderada (Buschke, 2002). Assim sendo, procedeu-se à verificação da frequência dos itens que constam da prova adaptada para português na base de frequências lexicais CORLEX (Nascimento et al., 2003). Todos apresentam frequência média na língua portuguesa, com um valor, na CORLEX, que se situa no intervalo de 28-161;

b) Cada item representa uma categoria semântica distinta. Seleccionaram-se 16 categorias semânticas entre as 48 distribuídas pelas três formas originais (A, B e C). Outras categorias possíveis e constantes das listas originais foram preteridas por: i) dificuldades em encontrar nomes correspondentes com frequência média na CORLEX; ii) não corresponderem a nomes, mas a adjectivos; iii) corresponderem a nomes

próprios, cuja frequência não é apresentada na CORLEX; iv) apresentarem designações que, em português, serão pouco transparentes.

Para além de salvaguardar os pressupostos da versão original, outros critérios foram tidos em conta, nomeadamente: a) exclusão de nomes polissémicos, homógrafos, homófonos e estrangeirismos; b) salvaguarda, no conjunto dos itens, da existência de alguma diversidade quanto à letra e som (sempre consonânticos) iniciais, sobretudo nos itens pertencentes a categorias semânticas mais próximas; c) selecção de nomes bi-, tri- e tetrassilábicos.

Para a ordenação final dos itens, foram colocados itens/categorias semânticas com maior grau de afinidade em diferentes cartões de apresentação.

- Tradução do manual

O manual do TRSLG contempla as instruções para a administração da prova e os critérios para a cotação dos diferentes índices. O manual foi traduzido da versão original (Buschke, 2002).

Results and Discussion

A escassez de instrumentos rigorosos e sensíveis, na detecção de défices nas áreas cognitivas mais vulneráveis ao processo de envelhecimento e doença, constitui uma limitação na área da avaliação psicológica, com consequências limitativas em diferentes domínios/circunstâncias: no diagnóstico e detecção precoce do défice cognitivo, na reavaliação do défice num contexto de acompanhamento clínico e na elaboração de planos de intervenção. Por este motivo, em países onde faltam instrumentos de avaliação sólidos, é fundamental a criação de novos testes ou a adaptação e validação de testes cujos resultados já demonstraram sensibilidade e especificidade noutros países e/ou contextos (Guerreiro, 2005).

Frequentemente recorre-se à adaptação de instrumentos já disponíveis noutras línguas e experimentados em populações clínicas. Esta metodologia apresenta a vantagem de serem já conhecidos os resultados da sua aplicabilidade clínica permitindo, assim, antever a sua validade e utilidade no estudo de determinada função cognitiva. A adaptação é uma forma de maximizar a conformidade cultural dum instrumento e, dessa forma, minimizar o enviesamento resultante da simples tradução

da versão original. Como referem Malda, van de Vijver, Srinivasan, Transler, Sukumar, & Rao (2008) mais do que traduzir um instrumento, a sua adaptação respeita idiossincrasias linguísticas e culturais.

No que se refere especificamente à tradução e adaptação de testes, a Comissão Internacional de Testes (2010) contempla a possibilidade de tradução das provas a partir da sua versão original. No entanto, a mera tradução dos itens linguísticos originais não será, para todos os casos, a solução mais recomendável. Frequentemente, é preferível o recurso ao processo de adaptação das provas, através do qual se melhor se controla o grau de adequação dos itens às características da língua materna da população-alvo. No processo de adaptação de um instrumento para outra língua, o essencial é que sejam utilizados procedimentos metodológicos rigorosos e que se respeitem os pressupostos da versão original da prova (International Test Commission, 2010). A utilização de um instrumento, numa determinada população, sem uma adaptação prévia criteriosa compromete a validade, a precisão e a posterior interpretação dos resultados.

O processo de adaptação do TRSLG para a população Portuguesa foi norteado pelas linhas orientadoras propostas na literatura (Giusti & Befi-Lopes, 2008; Hambleton, 2005; International Test Commission, 2010). Assim, procurou-se alcançar o grau máximo possível de paridade relativamente à versão original, de forma a evitar distorções ao nível da equivalência de construto (Giusti & Befi-Lopes, 2008; Hambleton, 2005; International Test Commission, 2010; Malda et al., 2008). Herdman, Fox-Rushby, & Badia (1998) alertam para o facto da tradução *ipsis verbis* de um item poder adulterar o seu verdadeiro significado. Desta forma, sugerem uma abordagem universalista de adaptação transcultural de instrumentos, que considere uma avaliação da equivalência entre a versão original e a nova versão. Estes autores defendem que a equivalência entre as duas versões deve ser avaliada a seis níveis: conceptual, de item, semântica, operacional, de mensuração e funcional.

A versão portuguesa do TRSLG procurou respeitar, sempre que aplicável, a equivalência com a sua versão original, de acordo com o modelo de Herdman et al. (1998). Neste processo de adaptação não se verifica uma "tradução" dos itens, mas sim uma selecção de palavras de frequência média para determinadas categorias semânticas, tal como sugerido no original (Buschke, 1984, 2002). As categorias

semânticas foram seleccionadas de um total de 48 disponíveis na versão original. Os restantes critérios utilizados na escolha dos itens levaram em consideração particularidades linguísticas da Língua Portuguesa.

Conclusion

A versão Portuguesa do TRSLG resulta de um processo de adaptação que procurou respeitar as orientações existentes na literatura sobre esta problemática. Neste processo, foram tidos em conta os pressupostos da versão original, bem como a adequação à realidade portuguesa (linguística e cultural).

O enfoque deste trabalho foi dado aos procedimentos *a priori* do processo de adaptação de testes. No entanto, este estudo deve ser complementado com investigações *a posteriori* (através da recolha e análise de dados) de forma a validar a adaptação.

Pretendemos, com este trabalho de adaptação, aumentar o leque de alternativas nos testes de avaliação da memória episódica verbal. O TRSLG constitui uma mais-valia, não só por apresentar um paradigma de avaliação diferente dos testes mais usuais, como por ser o teste recentemente proposto pelo IWG (Dubois et al., 2007) para a avaliação objectiva das alterações de memória em doentes com DA.

O TRSLG é objecto de estudo de um programa de trabalhos que permitirá completar o processo de adaptação aqui descrito. Deste programa de trabalhos destacamos: i) a avaliação das qualidades psicométricas do TRSLG, nomeadamente validade concorrente, e ii) estudos de validação clínica e exploração da capacidade diagnóstica no DCL, na DA e na Demência Frontotemporal.

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STUDY 2

Validation of the *Free and Cued Selective Reminding Test* for Mild Cognitive Impairment and Alzheimer's disease

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Abstract

The International Working Group on Alzheimer's disease (AD) suggested the Free and Cued Selective Reminding Test (FCSRT) to assess memory, since it showed high sensitivity and specificity in the differentiation of AD from healthy controls and other dementias. The FCSRT involves the use of selective reminding with semantic cueing in memory assessment. This study aims to validate the FCSRT for Mild Cognitive Impairment (MCI) and AD through the analysis of the diagnostic accuracy and the suggestion of cut-off scores. Patients were classified in two groups according to standard criteria: MCI (n=100) and AD (n=70). A matched control group (n=101) of cognitively healthy subjects was included.

The reliability and the validity of the FCSRT were analysed on the Immediate (IR) and Delayed (DR) recalls. The Cronbach's alpha was 0.915 for the IR and 0.879 for the DR. The total recall measures revealed good Areas Under the Curve for MCI (IR: .818; DR: .828) and excellent for AD (IR: .987; DR: .991). Furthermore, the MCI group was subdivided with respect to a non-similar/similar AD pattern of impairment, with almost half of the subjects showing an AD-like decline. This analysis represents a novel contribution regarding the properties of the FCSRT in illustrating the heterogeneity of MCI at baseline. The FCSRT has proved to be a very useful tool in the characterization of the memory impairment of the AD spectrum.

Introduction

The International Working Group proposal for early diagnosis of Alzheimer's disease (AD) (Dubois et al., 2007) considers the evidence of significant and progressive episodic memory deficit as the core diagnostic criterion. This impairment should be confirmed by objective testing and corroborated by the presence of at least one supportive neuroradiological, neurometabolic, or neurochemical abnormal biomarker of AD. This memory-criterion applies to cases of amnestic Mild Cognitive Impairment (aMCI), a clinical entity characterized by an isolated deficit of declarative memory in the absence of dementia (Petersen et al., 2001; Petersen et al., 1999). By providing a diagnostic set of tools that is able to capture the earliest stages of the disease (AD), the new criteria aim to consider MCI as a preclinical phase of AD or prodromal AD (Albert et al., 2011; Dubois et al., 2007, 2010). The authors recommend the use of the Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984) to assess memory, since it showed high sensitivity and specificity in differentiating AD patients from healthy controls (Grober, Sanders, Hall, & Lipton, 2010) and from other types of dementia (Buschke, Sliwinski, Kuslansky, & Lipton, 1997). In fact, the performance in FCSRT has been associated with preclinical and early dementia in several longitudinal epidemiological studies (Ivnik et al., 1997; Peña-Casanova et al., 2009; Sarazin et al., 2007). This test provides a measure of memory under conditions that control attention and cognitive processing in order to obtain an assessment of memory without the effect of the normal age-related changes in cognition (Dubois et al., 2007, 2010).

The FCSRT was designed to coordinate acquisition and retrieval by using the same semantic cues to control learning and elicit effective cued recall, enabling encoding specificity (Buschke et al., 1997). Encoding specificity is a technique that produces efficient learning and memory in normal ageing, (Ivnik et al., 1997). However, in conditions such as AD, brain regions that are essential for these cognitive processes (i.e., medial temporal structures) are usually impaired. Thus, tasks that maximize encoding specificity, such as the FCSRT, might be particularly sensitive to early AD (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994).

The relevance of this selective reminding paradigm has been widely reported in the memory dysfunction characterization of AD (Brown & Storandt, 2000; Buschke et al.,

1997; Grober, Buschke, Crystal, Bang, & Dresner, 1988; Grober & Buschke, 1987; Grober & Kawas, 1997; Grober et al., 2008; Ivanoiu et al., 2005; Mahieux et al., 2009; Saka, Mihci, Topcuoglu, & Balkan, 2006; Sánchez-Benavides et al., 2010; Vogel, Mortensen, Gade, & Waldemar, 2007) and of MCI (Ivanoiu et al., 2005; Saka et al., 2006). The comparable profiles of memory dysfunction of MCI and of AD have also been described (Petersen et al., 1999). Further, this similar profile has been described for MCI patients with a higher risk of conversion to AD (Sarazin et al., 2007). Nevertheless, results pointing to the superiority of this paradigm for differentiating AD or MCI patients from healthy elderly are controversial (Carlesimo, Perri, & Caltagirone, 2011). A poor performance on the FCSRT has also shown a high correlation with atrophy in the medial temporal lobe (Sánchez-Benavides et al., 2010; Sarazin et al., 2010) and was significantly associated with cerebrospinal fluid (CSF) AD-biomarkers (Wagner et al., 2012), increasing the validity of this paradigm in the early detection of AD. Despite the amount of literature describing the utility of the FCSRT in the characterization of the memory deficit of AD and MCI patients, to our knowledge no study has yet explored the heterogeneity of MCI patients, at baseline, with respect to a non-similar/similar AD pattern of impairment on the FCSRT.

The FCSRT allows several scores which can be investigated as measures of diagnostic accuracy in AD and also in the characterization of the memory impairment that is typical of this pathology. Studies on the validity of the properties of the FCSRT paradigm (for a review see Carlesimo et al., 2011) have been reported using the modified Grober-Buschke (Grober & Buschke, 1987) procedure. The Grober-Busckhe modified version differs from the Busckhe FCSRT as it includes an immediate cued recall during the learning phase after the identification of a group of four items. The immediate total recall, i.e., the sum of the free and the cued recall, revealed better sensitivity and specificity in identifying individuals with AD (Grober et al., 1988; Grober & Buschke, 1987) and MCI (Saka et al., 2006) than the free recall alone. Information concerning the psychometric properties of the FCSRT paradigm is scarce in the literature and limited to the modified Grober-Buschke procedure (Grober, Ocepek-Welikson, & Teresi, 2009). When comparing the three available test forms, the factor analyses indicate a single construct or dimension which the authors presume to be memory ability. The three forms show good concurrent criterion validity, good internal

consistencies and similar values of accuracy in the diagnosis of mild dementia (Grober et al., 2009).

The main objective of the present study is to validate the FCSRT in the assessment and characterization of the memory dysfunction of MCI and AD patients. This was carried out through the analyses of the FCSRT diagnostic accuracy and with the proposal of the optimal cut-off scores for MCI and AD detection. Additionally, we compared the performance of MCI and AD patients in order to divide the MCI group with respect to a non-similar/similar AD pattern of impairment. We believe that this approach represents a novel contribution in terms of analysing the heterogeneity of MCI patients, regarding the FCSRT, at baseline.

Methods

Participants

The clinical study sample included 100 MCI patients and 70 AD patients, recruited at the Neurology Department of Coimbra University Hospital where they have periodic medical examination and are enrolled in controlled prospective evaluation. Diagnostic investigation included a standard clinical evaluation, an extensive cognitive and staging assessment, laboratory tests, imaging studies and Apolipoprotein E allele genotyping. Standard laboratory tests essential to exclude a reversible form of dementia (including chemistry profile, CBC count, thyroid function tests, vitamin B12 and folic acid level, syphilis and Lyme serology), imaging studies (CT or MRI) and SPECT were always performed; while Positron Emission Tomography and Cerebrospinal Fluid analysis, and genetic studies were more restricted, although considered in younger patients. A comprehensive evaluation battery was administered, including: 1) Cognitive instruments as the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro, 1998), the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog; Guerreiro, Fonseca, Barreto, & Garcia, 2008; Mohs, Rosen, & Davis, 1983) and a comprehensive neuropsychological battery with normative data for the Portuguese population (Battery of Lisbon for the Assessment of Dementia - BLAD; Guerreiro, 1998) exploring memory and other cognitive domains (attention, language, verbal and non-verbal reasoning, visuospatial ability, calculation, right-left orientation,

and praxis) – data not shown; 2) The Clinical Dementia Rating (CDR; Garrett et al., 2008; Morris, 1993) was used for global staging.

Altogether, these auxiliary exams supported the diagnosis which was established by a multidisciplinary team headed by a board certified neurologist based on international consensus diagnostic criteria. The MCI group included patients classified as "amnestic" (single or multi-domain) (Petersen, 2007) and was selected according to Petersen's criteria (Albert et al., 2011; Petersen, 2004, 2007) operationalized as this: 1) A subjective complaint of memory decline (reported by the subject or an informant); 2) An objective memory impairment (considered when scores on standard memory tests were >1.5 SDs below age/education adjusted norms) with or without deficits in other cognitive domains; 3) Normal general cognition suggested by normal scores in the MMSE and ADAS-Cog; 4) Largely normal daily life activities; 5) Absence of dementia, indicated by a CDR rating of 0.5. The standard criteria for the diagnosis of AD were the Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM-IV-TR; American Psychiatric Association, 2000); and the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders (NINCDS-ADRDA; McKhann et al., 1984). The AD group only included patients with mild severity (CDR = 1). Moreover, to be eligible for this particular study, we considered that patients had to be in a stable condition, without acute significant events or recent/undergoing changes in medication, and we defined as exclusion criteria neurological or psychiatric conditions other than MCI or AD; CT or MRI demonstration of significant vascular burden (Román et al., 1993) (large cortico-subcortical infarct; extension superior to 25% of subcortical white matter lesions; uni- or bilateral thalamic lacune; lacune in head of caudate nucleus; more than 2 lacunes).

The control group is composed by 101 cognitively healthy adults belonging to the local community (recruited among the patients' spouses, hospital or university staff, or their relatives), that were age and education matched to the patients. They had no history of neurological or psychiatric relevant condition, including abuse of alcohol or drugs or head trauma; neither significant motor, visual or auditory deficits which could influence the neuropsychological performance. All control subjects were assessed using the following instruments for a global assessment: a complete socio-demographic questionnaire; an inventory of current clinical health status, and past

habits and medical history; the MMSE; the CDR; and the Geriatric Depression Scale (GDS-30; (Barreto, Leuschner, Santos, & Sobral, 2008; Yesavage et al., 1982). All subjects had normal MMSE scores (mean 28.95), were fully autonomous in daily life activities (CDR) with information supplemented with information obtained through a general practitioner, and/or an informant. The depressive complaints were measured through clinical interview and GDS-30, excluding subjects with a score of 20 or more points in this instrument.

All subjects from the 3 groups were submitted to the same experimental research protocol. Informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of our local ethics committee.

Demographic and clinical characteristics of the population are shown in Table 2.1.

Procedure

Subjects were assessed using the Portuguese version of the FCSRT (Lemos, Martins, Simões, & Santana, 2012). Materials and instruction of the FCSRT were provided by the original author (Buschke's FCSRT. Copyright, 2002. Albert Einstein College of Medicine of Yeshiva University, New York). The FCSRT (Buschke, 1984; Grober & Buschke, 1987) is a multi-trial memory test that use a "selective reminding" paradigm by presenting only the words not recalled, instead of all the to-be-remembered words. This paradigm is intended to facilitate learning by directing the subject's attention to the words not recalled on the previous trial.

The test starts by asking subjects to identify words in response to a unique category cue. The 16 items to be learned are presented four at a time on a card, distributed by one word per quadrant. The subject is asked to search each card and point to and name aloud each item after its semantic cue was aurally presented. During this procedure, the subject is informed to learn the 16 words. There are three recall trials, each preceded by 20 seconds of counting backward to prevent recall from short-term memory. Each recall trial consisted of two parts. First, each subject had up to two minutes to freely recall as many items as possible. Next, aurally presented category cues were provided for items not retrieved by free immediate recall (free IR). If subjects failed to retrieve the item with the category cue, they were reminded by

presenting the cue and the item together - cued immediate recall (cued IR). The sum of free and cued recalls gives a measure of total immediate recall (total IR). The same procedure of recalling (freely and cued) is done after a 30 minute interval (Delayed Recall – DR), while subjects are required to perform non-verbal tasks, allowing the measure of the free DR, cued DR, total DR.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 19.0) (IBM SPSS, Inc., Chicago, IL). When data significantly deviated from normal distributions (verified using the Kolmogorov-Smirnov normality check and Levene homogeneity tests), we did therefore choose to apply non-parametric statistical methods. Results with $p<.05$ were considered statistically significant. Descriptive statistics were used for sample's characterization, comparisons between variables were performed with the use of the general linear model [one-way analysis of variance (ANOVA)] with post-hoc Tukey for multiple comparisons where appropriate; or the Kruskal-Wallis one-way ANOVA for k samples with pairwise comparisons with adjusted *p* value; the χ^2 test was used for comparisons between categorical variables. Cronbach's alpha reliability coefficient was considered as an index of internal consistency, and analysed separately for the immediate and delayed recalls.

A series of binary logistic regressions, using the Backward (conditional) method, were performed to assess the effect of the demographic characteristics (age, education and gender) and the measure of the FCSRT (cued and total IR; cued and total DR) on the likelihood of having MCI or AD. The variance inflation factor (VIF) was used to check for the problem of multicollinearity among the predictor variables, considering a VIF < 5 as no evidence of multicollinearity; a 5 ≤ VIF ≤ 10 as moderate multicollinearity; and a VIF > 10 as serious multicollinearity problem with the variables. The fit of the logistic regression model was assessed through the receiver operating characteristics (ROC) curve analysis. In this analysis, the areas under the curve (AUC) can vary between 0.5 and 1, with larger AUC indicating better diagnostic accuracy. The optimal cut-off points for each measure of the FCSRT that generated the highest Youden index were selected, with higher Younden index indicating maximization of the sensitivity and

specificity. For the analysis of the predictive value of the measures of the FCSRT we calculated, for each cut-off point, the sensitivity (the probability for subjects with cognitive impairment to have a positive test), specificity (the probability for subjects without cognitive impairment to have a negative test), the positive predictive value (PPV, the probability of disease in subjects who have a positive test), the negative predictive value (NPV, the probability of the classification "lack of disease" in subjects who have a negative test), and the classification accuracy (the probability of correct classification of subjects with or without cognitive impairment).

The classification of the MCI group with respect to a similar/non-similar AD pattern of impairment was done using a hierarchical cluster analysis for a range of two to three solutions using the furthest neighbour method with squared Euclidian distance measure, complemented with a dispersion diagram.

Results

Sample characterization

Demographical and clinical characteristics of the population are shown in Table 2.1. No statistically differences were found on age [$F_{(2,268)}$=1.868, p =.157], educational level ($\chi^2_{KW(2)}$=.611, p =.737), or gender [$\chi^2_{(2)}$=4.554, p=.103] between the three groups.

As expected, a significant effect was found for MMSE performance ($\chi^2_{KW(2)}$=146.860, p<.001) among the three groups. Therefore, multiple comparisons revealed that both MCI (p<.001) and AD (p<.001) performed poorly on the MMSE, when compared to control subjects; and AD patients had a worse performance, when compared to MCI subjects (p<.001).

Significant differences were found between ApoE-ε4 carriers and non-carriers among the clinical groups [$\chi^2_{(1)}$=4.390, p=.036].

Psychometric properties – internal consistency reliability

Internal consistency reliability of the FCSRT was estimated using Cronbach's alpha. Within this analysis the Cronbach's alpha of the FCSRT as an index of internal consistency was 0.915 for the immediate recall and 0.879 for the delayed recall on the total study sample, confirming an overall good reliability of the test when used to examine Portuguese participants.

Table 2.1 Population demographical characteristics and performance on the FCSRT

	Control subjects (n=101)	MCI (n=100)	AD (n=70)
Gender (m:f)	48:53	39:61	22:48
Age (years), mean (SEM)	70.22 (0.76)	71.08 (0.83)	72.63 (0.98)
Education Level (years), median [IQR]	4 [4, 11]	4 [4, 9]	4 [4, 11]
MMSE (score), median [IQR]	29 [28, 30]	28 [25, 29]*	21 [19, 25]*/†
ApoE ε4 carrier, n (%)	----	44 (44)	42 (61)¥

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; MMSE – Mini-Mental State Examination.
Note:
Comparisons between Controls-MCI, Controls-AD and MCI-AD patients were carried out by a one-way ANOVA with post-hoc Tukey tests, Kruskal-Wallis 1-way ANOVA for k samples with pairwise comparisons, or χ^2 test, where:
* Controls vs. MCI: p <.001; Controls vs. AD: p <.001
† MCI vs. AD: p <.001.
¥ MCI vs. AD: p <.05.

Group differences

When analysing the performance on all the FCSRT selected measures, both the MCI and the AD groups were impaired relative to controls (p<.001), and there was also a significant difference between the AD and MCI patients (p<.001) (Table 2.2). The overall profile on the FCSRT was Controls>MCI>AD.

Table 2.2 Performance on the FCSRT

	Control subjects (n=101)	MCI (n=100)	AD (n=70)	χ^2_{KW}	Between-group comparisons
FCSRT Free IR	22 [18.5, 27]	11.5 [6, 20.75]	3 [1, 7]	148.949	p < .001*
FCSRT Cued IR	18 [14, 20]	14 [11, 18]	9 [4, 12.25]	79.120	p < .001*
FCSRT Total IR	40 [37, 44]	28 [19.25, 36.75]	11 [6, 19]	152.164	p < .001*
FCSRT Free DR	9 [7, 10.5]	4 [0, 7]	0 [0, 0]	144.851	p < .001*
FCSRT Cued DR	5 [4, 7]	4 [3, 6]	2 [1, 3.25]	64.423	p < .001*
FCSRT Total DR	15 [13, 15]	9 [5, 12]	3 [1, 4]	155.897	p < .001*

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall.
Note: Data are expressed as median [IQR].
Comparisons between Controls-MCI, Controls-AD and MCI-AD patients were carried out by the Kruskal-Wallis 1-way ANOVA for k samples with pairwise comparisons, where:
* Controls vs. MCI: p <.001; Controls vs. AD: p <.001; MCI vs. AD: p <.001.

Cut-off points and accuracy of the FCSRT

In order to assess the measure of the FCSRT (free, cued and total IR; free, cued and total DR) on the likelihood of having MCI or AD, a series of binary logistic regressions, using the Backward (conditional) method, were performed.

Table 2.3 presents the significant logistic regression models for predicting MCI and AD using FCSRT measures. In this analysis age, education and gender were included as covariates. The two free recall measures (IR and DR) were automatically excluded from the collinearity statistics, and therefore not included on the logistic regression computation. The VIFs showed that there was no evidence of a problem among all the predictor variables (all VIFs < 5, and on average: 1< VIF <2).

For the MCI group, significant effects were found for both total recall measures (IR and DR) (p<.001) on the logit modelling the probability of being MCI. The FCSRT cued recall did not reach significance on both IR and DR. Neither age, nor education, nor gender reached significance on the likelihood of having MCI.

For the AD patients, similar results were found. The analysis showed that the two total measures (IR and DR) were significantly associated with the dementia status (p<.001). However, the FCSRT cued IR (p=.007) and age (p=.036), on the DR analysis, showed also significant effects. The other demographic characteristics were not statistically significant (Table 2.3).

Table 2.3 Significant logistic regression models for predicting MCI and AD using the FCSRT (IR and DR)

	B	S.E.	X^2_{wald}	df	*p*-value	Exp(B)	95% C.I. for EXP(B)
MCI							
Total IR	-.165	.025	44.397	1	.000	.848	]0.808; 0.890[
Total DR	-.463	.071	42.976	1	.000	.629	]0.548; 0.723[
AD							
Cued IR	.459	.170	7.252	1	.007	1.582	]1.113; 2.208[
Total IR	-.704	.182	14.899	1	.000	.495	]0.346; 0.707[
Age	-.166	.079	4.395	1	.036	.847	]0.725; 0.989[
Total DR	-1.163	.269	18.669	1	.000	.312	]0.184; 0.530[

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall.

In order to evaluate the fit of the logistic regression models in the diagnostic accuracy of the FCSRT measures (total IR and total DR) in discriminating MCI and AD patients from cognitively healthy controls, the receiver operating characteristic (ROC) curve and the corresponding predictive values were implemented (Figure 2.1).

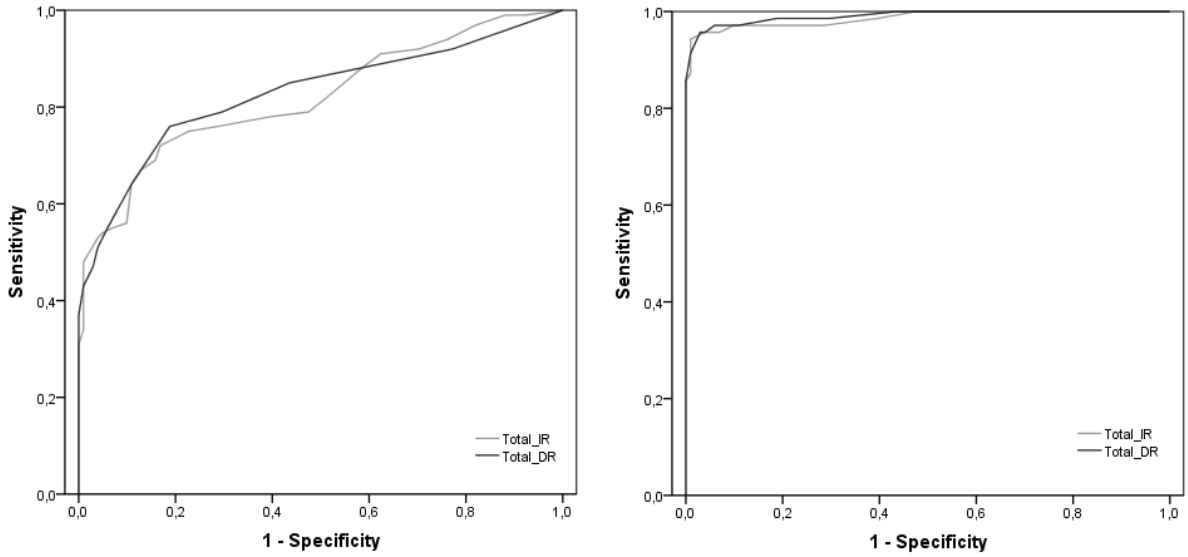

Figure 2.1 ROC curve analyses of the FCSRT total recall measures (IR –light grey; DR – dark grey) to detect MCI (left) and AD (right).

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall.

The ROC curves revealed that the total recall measures had good AUC's for MCI [IR: .818 (95% IC = .759 - .878); DR: .828 (95% IC = .769 - .887)] and excellent AUC's for AD [IR: .987 (95% IC = .971 - 1.000); DR: .991 (95% IC = .979 - 1.000)].

The optimal cut-off scores for maximum accuracy (Youden index), of each total recall measure, and its respective values of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and classification accuracy are described in Table 2.4.

For MCI patients, the cut-off scores were set at ≤35 (out of 48) for total IR and ≤12 (out of 16) for total DR, since they produced the greatest Youden index. For AD subjects, the cut-off scores were set at ≤27 (out of 48) for total IR and ≤8 (out of 16) for total DR as it fixed excellent values of diagnosis accuracy.

Table 2.4 Diagnostic classification accuracy of the FCSRT

	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	Classification accuracy
MCI							
Total IR	≤35	.818	72	83	81	75	78
Total DR	≤12	.828	76	81	80	77	79
AD							
Total IR	≤27	.987	94	99	99	95	97
Total DR	≤8	.991	96	97	97	96	96
MCI vs AD							
Total IR	≤21	.844	84	71	74	82	78

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall (maximum score =48); DR – Delayed Recall (maximum score =16); AUC – area under the operating characteristics curve; PPV - positive predictive value; NPV - negative predictive value.
Note1: Sensitivity, Specificity, PPV, NPV and Classification Accuracy values are expressed in percentage.
Note2: Cut-off values indicate the minimum score required for absence of signal.

Distinguishing MCI from AD

In order to better discriminate MCI patients from the dementia stage of AD we performed a similar array of statistical analysis within the FCSRT performance between the two clinical samples. The demographical variables were again included as covariates.

A new binary logistic regression was performed within the total IR and total DR recalls, in order to know which of these two measures was better in discriminating MCI from AD. A significant effect was found for the immediate total recall ($B_{total\,IR} = -.074$; $X^2_{wald}(1) = 4.017$; $p = .045$; $OR = .928$) on the logit modelling the probability of being AD, when compared to MCI. Once more, the ROC curve analyses was implemented in order to evaluate the fit of the logistic regression models in the diagnostic accuracy of the FCSRT total IR in discriminating between MCI from AD patients. The ROC curves revealed that the total IR had a good AUC of .844 (95% IC = .786 - .902) (Figure 2.2). Respective values of sensitivity, specificity, PPV, NPV, and classification accuracy are described in Table 2.4.

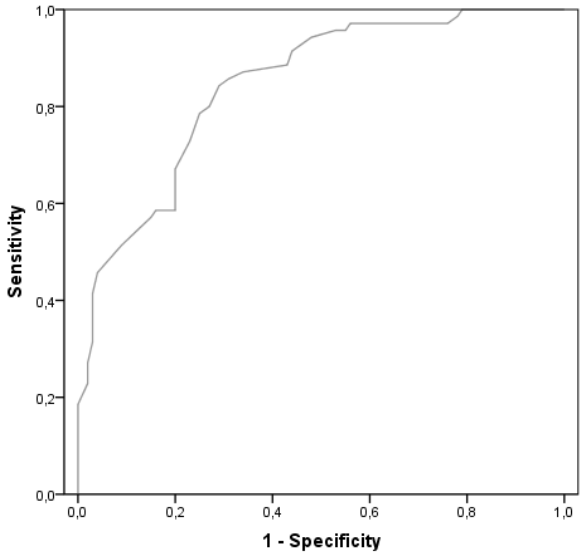

Figure 2.2 ROC curve analyses of the FCSRT total IR measure to discriminate MCI from AD.
Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall.

Distinguishing MCI sub-groups

The new AD criteria aim to consider some cases of aMCI as a pre-dementia symptomatic stage of AD, the so-called prodromal AD (Albert et al., 2011; Dubois et al., 2007; 2010). The pattern of cognitive performance in prodromal AD is characterized by the AD specific episodic memory deficit suggested by the new AD criteria (Dubois et al., 2007; 2010).

With the purpose of analysing the accuracy of the distinction between MCI and AD patients, and taking into consideration the assumption that some cases of aMCI may be considered as a pre-dementia symptomatic stage of AD (prodromal AD), we decided to divide the MCI group with respect to a similar/non-similar AD pattern of impairment. For that, we used the cut-off score of ≤27 for AD (out of 48) of the FCSRT total IR (see Table 2.4), as it revealed to be the best measure in discriminating MCI from AD. We have considered that all the subjects with a FCSRT total IR ≤27 would be MCI-AD, and the subjects with a performance above this cut-off score would be MCI-MCI. After this new subdivision, 54 MCI patients out of 100 revealed a MCI-MCI pattern, whereas 46 subjects had a similar pattern of impairment as AD and were considered MCI-AD. Therefore, we compared the performance of the three groups on the MMSE and on the FCSRT total DR (in order to be a different measure of the FCSRT from the one used to divide the MCI group). Demographical characteristics and

performance of the pathological subgroups, on the MMSE and on the FCSRT total DR, are shown in Table 2.5.

Table 2.5 Demographical characteristics and performance of the pathological subgroups on the FCSRT

	MCI-MCI (n=54/100)	MCI-AD (n=46/100)	AD (n=70)
Age (years), mean (SEM)	69.04 (1.17)	73.48 (1.08)*	72.63 (0.98)*
Education Level (years), median [IQR]	4 [4, 9]	4 [4, 9.5]	4 [4, 11]
MMSE (score), median [IQR]	29 [27, 30]	26 [24, 28]**	21 [19, 25]**/†
FCSRT Total DR, median [IQR]	12 [11, 15]	4.5 [2, 7]**	3 [1, 4]**
ApoE ε4 carrier, n (%)	13 (24)	31 (69)**	42 (61)**

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; MMSE – Mini-Mental State Examination; FCSRT – Free and Cued Selective Reminding Test; DR – Delayed Recall.
Note:
Comparisons between MCI-MCI, MCI-AD and AD patients were carried out by a one-way ANOVA with post-hoc Tukey tests, Kruskal-Wallis 1-way ANOVA for k samples with pairwise comparisons, or χ^2 test, where:
* MCI-MCI vs. MCI-AD: p <.05; MCI-MCI vs. AD: p <.05;
** MCI-MCI vs. MCI-AD: p <.001; MCI-MCI vs. AD: p <.001;
† MCI-AD vs. AD: p <.001.

In terms of demographical characteristics, a significant effect for age was found between the three groups [$F_{(2,167)}$=4.484, p=.013], where post-hoc analysis revealed significant differences between MCI-MCI and MCI-AD (p=.019); MCI-MCI and AD: (p= .041); but with no differences when comparing MCI-AD and AD (p=.845). No statistically differences were found on educational level ($\chi^2_{KW(2)}$=1.510, p=.470), between the three groups.

A significant effect was found for MMSE performance ($\chi^2_{KW(2)}$=94.244, p<.001) among the three groups, with multiple comparisons revealing significant differences among the three groups (p<.001). A significant effect was also found for the FCSRT total DR ($\chi^2_{KW(2)}$=100.121, p<.001) with an overall profile of MCI-MCI>MCI-AD=AD.

Significant differences were found between ApoE-ε4 carriers and non-carriers among the three groups [$\chi^2_{(2)}$=24.120, p<.001], with differences between MCI-MCI and MCI-AD subgroups [$\chi^2_{(1)}$=19.965, p<.001]; MCI-MCI and AD patients [$\chi^2_{(1)}$=16.591, p<.001]; but not between MCI-AD and ADs [$\chi^2_{(1)}$=.761, p=.383).

A dispersion diagram (Figure 2.3), complemented by a hierarchical cluster analysis, was performed to classify the neuropsychological profiles on the MMSE and FCSRT Total DR according to their similarity based on the three groups (MCI-MCI, MCI-AD and AD).

Misclassifications were used to identify the optimal number of clusters, resulting in a two cluster solution (Table 2.6).

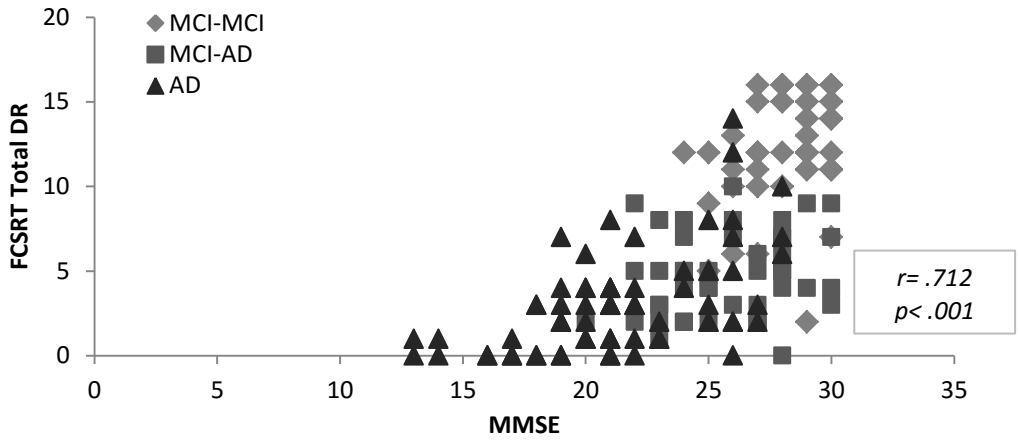

Figure 2.3 Recall FCSRT Total DR dispersion against performance on the MMSE for MCI-MCI, MCI-AD and AD.

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; MMSE – Mini-Mental State Examination; FCSRT –Free and Cued Selective Reminding Test; DR – Immediate Recall.
Spearman correlation ($r^2 = .712$, $p < .001$) was performed between the two measures.

Table 2.6 Crosstabulation of cluster membership on the groups' subdivision, for the two cluster solution

			Complete Linkage		Total
			1	2	
MCI subgroups and AD	MCI-MCI	Count (%)	49 (90.7)	5 (9.3)	54 (100.0)
	MCI-AD	Count (%)	7 (15.2)	39 (84.8)	46 (100.0)
	AD	Count (%)	4 (5.7)	66 (94.3)	70 (100.0)
Total		Count (%)	60 (35.3)	110 (64.7)	170 (100.0)

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease

Discussion

The main purpose of this study is to validate the FCSRT for MCI and AD because it is the memory test suggested by the International Working Group on AD (Dubois et al., 2007). According to these criteria (Dubois et al., 2007), objective testing using the FCSRT must confirm the presence of significant and progressive episodic memory impairment. Thus, a low free recall and total recall performance on FCSRT constitutes the core neuropsychological marker of prodromal AD as recommended in the newly proposed diagnostic criteria (Dubois et al., 2007).

Overall, in our analyses, none of the demographic characteristics showed a significant effect on the results, namely the education level. As most of the screening and cognitive tests are sensitive to education (Jefferson et al., 2011; Muniz-Terrera, Matthews, Dening, Huppert, & Brayne, 2009), they require different cut-offs depending on the educational level. However, the absence of any significant effect by education on the FCSRT for predicting MCI and AD suggests that the FCSRT measures can be used to classify subjects in different pathological groups without the need of adjustment for different educational levels. This is a very important issue since socio-demographic diversity is common, especially in countries where levels of education are generally low such as Portugal.

The FCSRT revealed an overall good reliability (internal consistency) when used to examine Portuguese subjects.

A great advantage of the FCSRT's paradigm is that it allows the distinction between the three different components of episodic memory: *registration* (by ensuring that all items have been truly registered), *storage* (by providing the semantic cues for facilitating the access to stored information), and *retrieval* (by the spontaneous recall of items after delay) (Sarazin et al., 2010). Like in other studies (Grober et al., 2010; Sarazin et al., 2010), the total recall item (the sum of the spontaneous and the cued recalls) revealed to be the most important measure in the distinction between patients and controls. This result is interesting as the total recall reflects the amount of information that is stored by the subject and it is the most important marker of long term episodic memory (Sarazin et al., 2010).

The analysis of group differences indicated that the FCSRT was able not only to distinguish the clinical groups from the control group, but also to separate the degree of impairment between MCI and AD. The two pathological groups showed impairment on the three measures of the test: free, cued and total. This proves that MCI and AD have a similar pattern of impairment. In neither case did the patients seem to show to benefit from category cues, as the impairment occurred also on the cued recall. Nevertheless, the AD group was significantly worse on all these measures.

When analysing the impact of the FCSRT two recalls, on the likelihood of having MCI or AD, significant effects were found for the two total recall measures. Total recall, which is the sum of the free and the cued recalls, is an interesting parameter to consider as it

reflects the amount of information that is stored spontaneously and facilitated by the subject. Accordingly, we analysed the diagnostic accuracy and the corresponding cut-off scores for the FCSRT on MCI and AD patients. The ROC curves revealed that the total recall measures had good AUCs for MCI (IR: .818; DR: .828) and excellent AUCs for AD (IR: .987; DR: .991). For MCI patients, the cut-off scores were set at ≤35 for total IR and ≤12 for total DR with good values of accuracy. For AD subjects, the cut-off scores were set at ≤27 for total IR and ≤8 for total DR with fixed excellent values of diagnosis accuracy.

Studies on the validity of the properties of the FCSRT paradigm were reported using the modified Grober-Buschke (Grober & Buschke, 1987) procedure (Grober et al., 2009). The immediate total recall, i.e., the sum of the free and the cued recall, revealed better sensitivity and specificity in identifying individuals with AD (Grober et al., 1988; Grober & Buschke, 1987) and MCI (Saka et al., 2006) than the free recall. Nevertheless, Saka et al. (2006) proved the superiority of the immediate total recall in terms of sensitivity, but showed that it is less specific when compared to the free recall in discriminating AD patients from healthy elders. Vogel et al. (2007) analysed the delayed recall and revealed that it increased the sensitivity of the total recall in AD identification when compared to the immediate recall. Another study assessed the validity of this test for predicting dementia two and five years after the initial evaluation and reported good sensitivity, fair specificity and high negative predictive values for the diagnosis of dementia on the subtests of free and total immediate recall. However, positive predictive values were low as many subjects with low scores for free and total recall remained free of dementia after 5 years (Auriacombe et al., 2010). Nevertheless, in our study both the immediate and the delay recalls showed a significant impairment in the two clinical groups. This result is in line with the hypothesis of a memory deficit, mainly in encoding, in AD patients (Grober & Kawas, 1997). Moreover, the delayed recall measure showed to be more sensitive, although the immediate recall presented a higher value of specificity. This proves the importance of having a delayed recall to account for the milder forms of cognitive decline (Ivanoiu et al., 2005) such as MCI, and avoid the inclusion of false negatives that can occur when the immediate recall is the only memory measure tested.

As the new criteria (Dubois et al., 2007) aim to capture the earliest stages of the disease (AD) and some cases of aMCI that may be considered as a preclinical phase of AD or prodromal AD (Albert et al., 2011; Dubois et al., 2007, 2010), we decided to analyse and compare the performance of the two pathological groups. The immediate total recall revealed to be the best measure of the FCSRT in discriminating MCI patients from AD, with a good AUC of .844. This result is interesting, considering the great impairment of AD patients in encoding and storing new information (Tounsi et al., 1999). To better understand an AD-like profile of impairment among MCI patients, we subdivided the MCI group into MCI-MCI and MCI-AD sub-groups. This split was done according to a FCSRT total IR ≤27, since it proved to be the best measure to discriminate the two clinical groups. The MCI patients with a performance above this cut-off point were allocated to the MCI-MCI sub-group, and the remaining patients, with a performance on FCSRT total IR below 27, were allocated to the MCI-AD sub-group. After this new subdivision, almost half of the subjects (46%) showed an AD-like pattern of impairment. Among the three pathological groups, a pattern of impairment was observed for the FCSRT with an overall profile of MCI-MCI>MCI-AD=AD. Furthermore, the MCI-AD group showed an increased distribution of the ApoE-ε4 allele, which is a major risk factor for sporadic AD (Fleisher et al., 2007). The frequency of ε4 allele carriers in the MCI-AD group was similar to that observed in the AD group, while the MCI-MCI group had a significantly lower percentage of ε4 allele carriers. Therefore, we performed a cluster analysis based on the cognitive performance, which produced a two cluster solution. The first cluster was made up predominantly of MCI-MCI subjects, and the second cluster was essentially a combination of the MCI-AD and AD patients. With this approach we believe that the heterogeneity of the MCI group may be subdivided according to an AD-similar pattern of performance with respect to the FCSRT profile. The diagnostic properties of the FCSRT were reported in the literature. However, we believe that our study brings a novel contribution to the attempt to differentiate MCI patients in terms of an AD-like pattern of impairment at baseline. This approach facilitates the aim of capturing the earliest stages of AD (Dubois et al., 2007) by exploring the performance on the FCSRT in a hierarchical manner (subdividing the MCI group with respect to a non-similar/similar AD pattern of impairment). Although the most important objective is to capture the earliest stages of

AD, we have examined the pattern of performance in a memory test, which alone should not be enough to characterize the patients as prodromal AD. Therefore, these results should be corroborated in the future with studies relating to AD biomarkers.

In sum, our study demonstrated that the FCSRT is a useful tool in the memory dysfunction characterization of the AD spectrum. The FCSRT proved to be helpful in the differentiation of ADs and MCIs from controls. It also showed that MCI is a heterogeneous group that certainly includes cases of patients at a higher risk of being prodromal ADs (Albert et al., 2011; Dubois et al., 2007, 2010). The importance of the underlying paradigm of this test in discriminating the possible prodromal ADs, should be confirmed by research that correlates the performance on the FCSRT with AD biomarkers. Thus, studies comparing memory tests that use different paradigms, and longitudinal studies with follow-ups of MCI subjects should be carried out in order to achieve accuracy for predicting dementia.

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STUDY 3

Construct and diagnostic validities of the Free and Cued Selective Reminding Test in the Alzheimer's disease spectrum

Adapted from: **Lemos, R.**, Marôco, J., Simões, M., & Santana, I. Construct and Diagnostic Validities of the Free and Cued Selective Reminding Test in the Alzheimer's disease spectrum. (*submitted to publication*)

Abstract

The Free and Cued Selective Reminding Test (FCSRT) is a memory test that controls attention and acquisition, by providing category cues in the learning process. Because it enables an assessment of memory unconfounded by normal age-related changes in cognition and a high accuracy on Alzheimer's disease (AD) evaluation, it has been suggested by the International Working Group on AD. Our aim was to assess the construct related validity of the FCSRT in the AD spectrum disorders.

Patients were classified in two groups according to standard criteria: amnestic Mild Cognitive Impairment (n=100) and AD (n=70). A matched control group (n=101) of cognitively healthy subjects was included. The factorial structure of two models, and respective construct and diagnostic validities were analyzed.

Both models revealed adequate fit values. The appropriated convergent validity and the lack of discriminant validity support the two-factors as measuring the same construct (memory ability). The unidimensionality of the FCSRT enabled us to add a global score for the FCSRT. All recalls of the FCSRT enabled high classification accuracy and diagnostic validity for both pathological groups.

This study represents a novel contribution regarding the adequacy of the FCSRT in terms of construct and diagnostic validities, and shows the interest of including both immediate (learning) and delayed (retention) recalls. It gives also new possibilities regarding the use of the FCSRT in the memory assessment of AD spectrum disorders.

Introduction

The Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984) provides a measure of memory under conditions that control attention and cognitive processing, in order to obtain an assessment of memory unconfounded by normal age-related changes in cognition. Testing memory by controlling learning conditions was suggested to distinguish the genuine AD deficits in encoding and storage, from the memory deficits associated with normal aging that are likely to be secondary to impaired attention, inefficient information processing, or ineffective retrieval operations (Grober & Buschke, 1987). Retrieval deficits that occur in healthy elderly subjects showed to improve with controlled learning procedures (Buschke, Sliwinski, Kuslansky, & Lipton, 1995; Grober, Merling, Heimlich, & Lipton, 1997). On the contrary, in patients of the AD clinical spectrum these procedures have very limited benefits (Boeve et al., 2003; Buschke, 1984; Saka, Mihci, Topcuoglu, & Balkan, 2006). As a consequence, controlled learning procedures should expand the differences produced by normal aging and dementia and thus improving discriminative validity (Grober, Sanders, Hall, & Lipton, 2010). As such, the International Working Group (IWG-1; Dubois et al., 2007, 2010) proposal for the early diagnosis of Alzheimer's disease (AD) suggested the use of the FCSRT to assess memory. By providing a diagnostic set of tools that is able to capture the earliest stages of the disease (AD), the new criteria aims to consider some cases of amnestic Mild Cognitive Impairment (aMCI) as symptomatic prodromal AD (Albert et al., 2011; Dubois et al., 2007, 2010). According to the IWG-1 criteria, subjects were classified in the prodromal AD group if they had memory impairment and at least one abnormal AD biomarker: presence of medial temporal lobe atrophy, abnormal CSF biomarkers, specific pattern on functional neuroimaging with FDG-PET or an autosomal dominant mutation within the immediate family (Dubois et al., 2007). More recently, the IWG-2 criteria reinforced the choice of the FCSRT, along with abnormal CSF biomarkers, as valid clinical markers for typical prodromal AD (aMCI and abnormal biomarkers) (Dubois et al., 2014).

It is expected that different levels of impairment discriminate between normal aging and early dementia, as AD patients would have limited benefit from controlled

learning; thus, it may allow identifying the earliest stages of AD (Albert et al., 2011; Dubois et al., 2007, 2010; 2014).

The utility of this cued selective reminding paradigm has been widely reported in the memory dysfunction characterization of AD (Brown & Storandt, 2000; Carlesimo, Perri, & Caltagirone, 2011; Grober & Kawas, 1997; Grober et al., 2008b; Mahieux et al., 2009; Sarazin et al., 2010; Vogel, Mortensen, Gade, & Waldemar, 2007) and aMCI (Ivanoiu et al., 2005; Saka et al., 2006; Wagner et al., 2012). The comparable profiles of memory dysfunction of MCI and of AD have also been described (Petersen, 2004a; Petersen et al., 1999; Sánchez-Benavides et al., 2014). Further, this similar profile has been described for MCI patients with a higher risk of conversion to AD (Petersen, 2007; Sarazin et al., 2010). The FCSRT also showed its capability to differentiate a group of aMCI patients according to their similarity with AD impaired performance (Lemos, Simões, Santiago, & Santana, 2015). Normative studies of the FCSRT provided reference data for a reliable use of the test (Ivnik et al., 1997; Peña-Casanova et al., 2009).

Studies on the psychometric properties of the FCSRT paradigm's validity (for a review on the Buschke's different controlled learning procedures see Carlesimo et al., 2011) have been reported using the modified Grober-Buschke procedure (FCSRT-IR; Grober & Buschke, 1987). The FCSRT-IR version differs from the FCSRT as it includes an immediate cued recall during the learning phase after the identification of a group of four items. The total recall, i.e., the sum of free and cued recalls, delivered better sensitivity and specificity in identifying individuals with AD (Grober & Buschke, 1987; Lemos et al., 2015) and with aMCI (Lemos et al., 2015; Saka et al., 2006) than the free recall alone. Information on the psychometric properties of the FCSRT paradigm is scarce in the literature and limited to the FCSRT-IR procedure (Grober, Ocepek-Welikson, & Teresi, 2009). In that study, when comparing the three available test forms, the factor analyses indicated a single construct or dimension which the authors presume to be memory ability. The three forms showed good concurrent criterion validity, good internal consistencies and similar values of accuracy in the diagnosis of mild dementia (Grober et al., 2009).

In the FCSRT category cues are provided for items not retrieved by free recall. If subjects fail to retrieve the item with the category cue, they are reminded by

presenting the cue and the item together. The sum of free and cued recall gives a measure of total recall (Immediate Total Recall - ITR). The same procedure of recalling (freely and cued) is done after a 30 minute interval (Delayed Total Recall - DTR).

Standard criteria for the diagnosis of both aMCI and AD require an objective confirmation of the memory dysfunction (American Psychiatric Association, 2000; Dubois et al., 2007; McKhann et al., 2011; Petersen, Doody, et al., 2001). Therefore, the test used to identify the memory impairment should be highly accurate (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994) and individual deviations must be concretely specified along with its cut-off values (Petersen, 2004a).

Valid and accurate neuropsychological tests must have good diagnostic classification properties. In terms of memory, a significant impairment in neuropsychological testing is essential to the diagnosis of both aMCI and AD (Dubois et al., 2007; 2014; Portet et al., 2006).

Apart from the study on the FCSRT-IR (Grober et al., 2009), and as far as we are aware of, there are no available studies on the factorial structure of the Buschke's FCSRT in clinical (AD spectrum) populations nor in community samples, representing an important gap in the construct related validity of this test.

Construct validity is an important concept that relates to the importance of validating a psychometric test for use in a particular clinical population (American Educational Research Association, American Psychological Association, & National Council on Measurement in Education, 1999). Basically, the goal is to guarantee that the psychological instrument is accurately evaluating the underlying dimension(s), rather than something different, in the clinical population in which it is being used (Maroof, 2012).

The main objectives of the present study are to analyze the FCSRT factorial structure and to establish its respective construct and diagnostic validities in the AD spectrum disorders.

Methods

Participants and Procedures

The total sample was composed of 271 participants distributed between two main sub-groups (Lemos et al., 2015).

The healthy group is composed by 101 cognitively healthy adults belonging to the local community (recruited among the patients' spouses, hospital or university staff, or their relatives) that were age and education matched to the patients. They had no history of neurological or psychiatric relevant condition, including abuse of alcohol or drugs or head trauma; neither significant motor, visual or auditory deficits which could influence the neuropsychological performance. All control subjects were assessed using the following instruments for a global assessment: a complete sociodemographic questionnaire; an inventory of current clinical health status, and past habits and medical history; the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro, 1998); the Clinical Dementia Rating (CDR; Garrett et al., 2008; Morris et al., 2001); and the Geriatric Depression Scale (GDS-30; Barreto, Leuschner, Santos, & Sobral, 2008; Yesavage et al., 1983). All subjects had normal MMSE scores (mean 28.95), were fully autonomous in daily life activities (CDR=0) and their information was provided by a general practitioner and/or an informant. The depressive complaints were measured through clinical interview and GDS-30, excluding subjects with a score of 20 or more points in this instrument.

The clinical study sample included 100 aMCI patients and 70 AD patients, recruited at the Neurology Department of Coimbra University Hospital where they have periodic medical examination and are enrolled in controlled prospective evaluation. Diagnostic investigation included a standard clinical evaluation, an extensive cognitive and staging assessment, laboratory tests, imaging studies and Apolipoprotein E allele genotyping. Standard laboratory tests essential to exclude a reversible form of dementia (including chemistry profile, CBC count, thyroid function tests, vitamin B12 and folic acid level, syphilis and Lyme serology), imaging studies (CT or MRI) and SPECT were always performed; Positron Emission Tomography and Cerebrospinal Fluid analysis and genetic studies were more restricted although applied to younger patients. A comprehensive evaluation battery was administered, including: 1) Cognitive instruments such as the MMSE, the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog; Guerreiro, Fonseca, Barreto, & Garcia, 2008; Mohs, Rosen, & Davis, 1983) and a comprehensive neuropsychological battery with normative data for the

Portuguese population (Battery of Lisbon for the Assessment of Dementia; Guerreiro, 1998) exploring memory (Logical memory and Verbal Paired-Associate Learning from the Wechsler Memory Scale) and other cognitive domains (attention, language, verbal and non-verbal reasoning, visuospatial ability, calculation, right-left orientation, and praxis) – data not shown; 2) the CDR which was used for global staging. Altogether, these auxiliary exams supported the diagnosis which was established by a multidisciplinary team headed by a board certified neurologist, based on international consensus diagnostic criteria. The aMCI group included single or multi-domain amnestic patients (Petersen, 2007) and was selected according to Petersen's criteria (Albert et al., 2011; Petersen, 2007; Petersen, 2004b) operationalized in the following terms: 1) A subjective complaint of memory decline (reported by the subject or an informant); 2) An objective memory impairment (considered when scores on standard memory tests were >1.5 SDs below age/education adjusted norms) or without deficits in other cognitive domains; 3) Normal general cognition suggested by normal scores in the MMSE (Guerreiro, 1998) and ADAS-Cog (Guerreiro et al., 2008); 4) Largely normal daily life activities; 5) Absence of dementia, indicated by a CDR rating of 0.5. The standard criteria for the diagnosis of AD were the Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM-IV-TR; American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 2011; McKhann et al., 1984). The AD group only included patients with mild severity (CDR = 1). Moreover, to be eligible to this particular study, we considered that patients had to be in a stable condition, without acute significant events or recent/undergoing changes in medication, and we defined as exclusion criteria neurological or psychiatric conditions other than aMCI or AD; CT or MRI demonstration of significant vascular burden (Román et al., 1993) (large cortico-subcortical infarct; extensive subcortical white matter lesions superior to 25%; uni- or bilateral thalamic lacune; lacune in head of the caudate nucleus; more than 2 lacunes).

In the present study, the FCSRT was not used in the diagnostic process.

All participants were submitted to the same experimental research protocol. Informed consent was obtained from all participants, and the study was conducted in

accordance with the tenets of the Declaration of Helsinki, with the approval of our local ethics committee.

Measure: Free and Cued Selective Reminding Test (FCSRT)

Subjects were assessed using the Portuguese version of the Buschke's FCSRT (Lemos, Martins, Simões, & Santana, 2012). Materials and instruction of the FCSRT were provided by the original author (Buschke's FCSRT. Copyright, 2002. Albert Einstein College of Medicine of Yeshiva University, New York). The selection of the 16 stimulus words followed the same principles as the English version – intermediate frequency words were selected within a semantic category (frequencies in Portuguese in the CORLEX database (Nascimento et al., 2003). The FCSRT (Buschke, 1984) is a multi-trial memory test that use a "selective reminding" paradigm by presenting only the words not recalled, instead of all the to-be-remembered words. This paradigm is intended to facilitate learning by directing the subject's attention to the words not recalled in the previous trial. It controls attention and cognitive processing, requiring subjects to search for items in response to their category cues, in the learning process; moreover, these same category cues are later used to elicit recall of the items not retrieved on free recall, coordinating acquisition and retrieval.

The test starts by asking subjects to identify words in response to a unique category cue. The 16 items to be learned are presented four at a time on a card, distributed by one word per quadrant. The subject is asked to search each card and point to and name aloud each item after its semantic cue was aurally presented. During this procedure, the subject is informed to learn the 16 words. There are three recall trials, each preceded by 20 seconds of counting backward to prevent rehearsal and obtain retrieval from long-term memory. Each recall trial consisted of two parts. First, each subject had up to two minutes to freely recall as many items as possible. Next, aurally presented category cues were provided for items not retrieved by free recall. If subjects failed to retrieve the item with the category cue, they were reminded by presenting the cue and the item together. The sum of free and cued recalls gives a measure of total recall (ITR). The same procedure of recalling (freely and cued) is done after a 30 minute interval (Delayed Total Recall – DTR), while subjects are required to perform non-verbal tasks.

The FCSRT version used in this study differs from the modified FCSRT-IR version included in the study of Grober et al. (2009), as it includes words rather than pictures and does not include immediate cued recall in the learning phase.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 19.0) (IBM SPSS, Inc., Chicago, IL). When data significantly deviated from normal distributions (verified using the Kolmogorov-Smirnov normality check and Levene homogeneity tests), we did therefore choose to apply non-parametric statistical methods. Results with $p<.05$ were considered statistically significant. Descriptive statistics were used for sample's characterization, comparisons between variables were performed with the use of the general linear model [one-way analysis of variance (ANOVA)] with Tukey's post-hoc test for multiple comparisons where appropriate; or the Kruskal-Wallis one-way ANOVA with Dunn's post-hoc comparisons with adjusted p value; the χ^2 test was used for comparisons between categorical variables.

Confirmatory Factor Analysis (CFA) was conducted to provide further evidence to FCSRT's construct validity. Two separate models were tested in this analysis. The model estimation was done with polychoric correlations and the weighted least squares mean and variance adjusted estimation procedure implemented in Mplus6 (Muthén & Muthén, Los Angeles, CA). To evaluate the goodness of fit of the tested factorial structures we considered the indices CFI (Comparative Fit Index), TLI (Tucker-Lewis Index), and RMSEA (Root Mean Square Error of Approximation), according to the suggestion of Schermelleh-Engel, Moosbrugger, and Müller (2003). The cut-off criteria proposed by Schermelleh-Engel et al. (2003) were considered as indicative of goodness of fit, as following: CFI and TLI good fit ~.97, acceptable fit >.0.95; RMSEA: good fit ≤.05, adequate fit].05, .08[. Convergent and discriminant validities were also examined as outcomes of the CFA.

A Linear Discriminant Analysis (LDA) classificatory model, with an enter method, was performed to determine whether the FCSRT would distinguish the three experimental groups. Equal a priori classification probabilities were used for LDA to avoid biases from the data sets.

Receiver operating characteristic (ROC) curves were plotted for the FCSRT recall measures to assess their diagnostic validity for aMCI and AD patients. This analysis was implemented in MedCalc (version 12.7; MedCalc Software, Ostend, Belgium). The areas under the curve (AUC) can vary between 0 and 1, with larger AUC indicating better accuracy. The optimal cutoff points were calculated for each group according to the highest Youden index, which indicates the cutting score that maximizes of the sensitivity and specificity of the classification process.

Results

Sample characterization

Demographical and clinical characteristics of the population are shown in Table 3.1. No statistically differences were found on age [$F_{(2,268)}$=1.868, p=.157], educational level ($\chi^2_{KW(2)}$=.611, p=.737), or gender [$\chi^2_{(2)}$=4.554, p=.103] between the three groups.

As expected, a significant effect was found for MMSE performance ($\chi^2_{KW(2)}$=146.860, p<.001) among the three groups. Therefore, multiple Dunn's post-hoc comparisons revealed that both aMCI (p<.001) and AD (p<.001) performed poorly on the MMSE, when compared to control subjects; and AD patients had a worst performance, when compared to aMCI subjects (p<.001).

When analyzing the performance on all the FCSRT measures, both the aMCI (p=.001) and the AD groups were impaired relative to controls, and there was also a significant difference between the AD and aMCI patients (p<.001) (Table 3.1). The overall profile on the FCSRT was Controls>aMCI>AD.

Table 3.1 Population demographical characteristics and performance on the FCSRT

	Total (N=271)	Control subjects (n=101)	aMCI (n=100)	AD (n=70)
Gender (male), n (%)	162 (59.8)	53 (52.5)	61 (61.0)	48 (68.6)
Age (years)	71.16 (0.49)	70.22 (0.76)	71.08 (0.83)	72.63 (0.98)
Education Level (years)	4 [4, 11]	4 [4, 11]	4 [4, 9]	4 [4, 11]
MMSE (score)	29 [24, 29]	29 [28, 30]	28 [25, 29]*	21 [19, 25]*/†
FCSRT ITR (score)	32 [17, 40]	40 [37, 44]	28 [19.25, 36.75]*	11 [6, 19]*/†
FCSRT DTR (score)	11 [4, 15]	15 [13, 15]	9 [5, 12]*	3 [1, 4]*/†
FCSRT TR (score)	43 [21, 54]	54 [50, 59]	36.5 [24, 50]*	13 [8, 24]*/†

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; MMSE – Mini-Mental State Examination; FCSRT – Free and Cued Selective Reminding Test (Buschke's word version); ITR – immediate total tecall; DTR – delayed total recall; TR – total recall (ITR+DTR).
Note: Results are expressed as median [IQR] for all variables except for age: mean (SEM) and gender.
Comparisons between Controls-aMCI, Controls-AD and aMCI-AD patients were carried out by a one-way ANOVA with post-hoc Tukey tests, Kruskal-Wallis 1-way ANOVA for k samples with pairwise comparisons, or χ^2 Pearson Chi-Square test, where:
* Controls vs. aMCI: $p<.001$; Controls vs. AD: $p<.001$
† aMCI vs. AD: $p<.001$.

Construct Validity

- Confirmatory Factor Analysis

The CFA was performed to provide further evidence of the FCSRT's construct validity. Two models were contemplated: the first model was based on the model proposed by Grober et al. (2009), accounting for the unidimensionality that underlies the FCSRT, which is memory ability. Accordingly, Grober et al. (2009) studied the immediate free recall during the 3 trials on their analysis, while we included both the ITR and the DTR in our first model. Nevertheless, we also fitted a two-factor model in our sample in order to evaluate both learning (ITR) and retention (DTR).

Both models have similar acceptable goodness of fit to the data matrix (Table 3.2).

Table 3.2 Fit indices of the Confirmatory Factor Analysis models

Models	χ^2	*df*	*p*	χ^2/df	CFI	TLI	RMSEA
One-factor model	1311.526	464	<.001	2.83	.964	.962	.082
Two-factor model	1250.043	463	<.001	2.69	.967	.964	.079

Abbreviations: χ^2 – Chi-square test statistic; *df* – degrees of freedom; χ^2/df – relative Chi-square; CFI – comparative fit index; TLI – Tucker-Lewis index; RMSEA – root mean square error of approximation.

The unidimensionality of the FCSRT enabled us to add a global score for the two recalls of the FCSRT on the subsequent analysis.

Given the fit results for the two-factor model, we also examined the convergent validity estimated from the averaged variance extracted (AVE; Fornell & Larcker, 1981) which denotes the proportion of variance in the items explained by the underlying factors, therefore measuring how the items converge in a given factor. The respective results were AVE_{ITR}=.64 and AVE_{DTR}=.717, which is suggestive of appropriated convergent validity, according the criterion AVE >.5 (Fornell & Larcker, 1981). Discriminant validity of the two factors was not observed since the squared correlations between the factors (r^2=1) was larger than the AVE for each of the two factors (Fornell & Larcker, 1981). Thus, this result corroborates the unidimensionality underlining the FCSRT - assumed to be memory ability.

Diagnostic Validity

- Discriminant analysis

The FCSRT recalls were analyzed independently, as predictor variables, to highlight their relative contribution in the discriminating the three groups, through a Linear Discriminant Analysis (LDA). All Wilks' lambdas were significant at p<.05. The FCSRT ITR (λ Wilks =.411; $\chi^2(2) = 238.324$; p<.001; RCanonical =.767) had an accuracy of 67.9% in classifying the subjects; while the FCSRT DTR (λ Wilks =.395; $\chi^2(2) = 248.859$; p<.001; RCanonical =.778) revealed an accuracy of 65.7% in the classification among the three groups. The summation of the two recalls FCSRT TR (λ Wilks =.393; $\chi^2(2) = 250.389$; p<.001; RCanonical =.779) was the predictor with higher accuracy (68.3%) in the subjects classification (Table 3.3).

Table 3.3 Classification results of the FCSRT

		Predicted Group Membership	Control (n=101)	aMCI (n=100)	AD (n=70)
FCSRT ITR	Count (%)	Control	88 (87.1)	13 (12.9)	0 (0)
		aMCI	33 (33)	45 (45)	22 (22)
		AD	2 (2.9)	17 (24.3)	51 (72.9)
FCSRT DTR	Count (%)	Control	89 (88.1)	12 (11.9)	0 (0)
		aMCI	36 (36)	31 (31)	33 (33)
		AD	2 (2.9)	10 (14.3)	58 (82.9)
FCSRT TR	Count (%)	Control	90 (89.1)	11 (10.9)	0 (0)
		aMCI	33 (33)	43 (43)	24 (24)
		AD	2 (2.9)	16 (22.9)	52 (74.3)

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test (Buschke's word version); ITR – immediate total recall; DTR – delayed total recall; TR – total recall (ITR+DTR).

Comparison of ROC curves between the FCSRT scores

The ROC curve analysis was conducted to evaluate the diagnostic accuracy of the FCSRT to discriminate aMCI and AD patients from cognitively healthy adults. The ROC curves revealed that the two recall measures had good AUC's for aMCI both independently [ITR: .818 (95% CI = .757 - .869); DTR: .824 (95% CI = .764 - .874)] and summed (TR: .828 (95% CI = .769 - .878) and excellent AUC's for AD [ITR: .986 (95% CI = .956 -.998); DTR: .990 (95% CI = .962 -.999); TR: .990 (95% CI = .960 - .999)].

Similar analyses were done in order to know which measure was better in discriminating aMCI from AD. The ROC curves revealed that all FCSRT recall measures had good AUC's ITR: .846 (95% CI = .783 - .897); DTR: .838 (95% CI = .774 - .890); TR: .852 (95% CI = .789 - .901).

The optimal cut-off scores for maximum accuracy (Youden index), of each measure, and its respective values of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and classification accuracy are described in Table 3.4.

Table 3.4 Diagnostic classification accuracy of the FCSRT

		Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	Classification accuracy
MCI	Total ITR	≤35	.818	72	83	81	75	78
	Total DTR	≤12	.824	76	80	80	77	78
	Total TR	≤45	.828	67	89	78	73	75
AD	Total ITR	≤27	.986	94	99	99	95	97
	Total DTR	≤8	.990	96	97	97	96	96
	Total TR	≤36	.990	97	98	98	97	98
MCI vs. AD	Total ITR	≤21	.846	86	72	75	84	79
	Total DTR	≤4	.838	77	76	76	77	77
	Total TR	≤28	.852	87	70	74	84	79

Abbreviations: MCI – Mild Cognitive Impairment; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test; ITR – immediate total recall (maximum score =48); DTR – delayed total recall (maximum score =16); TR – total recall (ITR+DTR, maximum score =64); AUC – area under the operating characteristics curve; PPV - positive predictive value; NPV - negative predictive value.
Note1: Sensitivity, Specificity, PPV, NPV and Classification Accuracy values are expressed in percentage.
Note2: Cut-off values indicate the minimum score required for absence of signal.

Discussion

This study aimed to evaluate the factorial structure of the Buschke's FCSRT (Buschke's FCSRT. Copyright, 2002) and analyze its validity in cognitively healthy subjects, as well as in aMCI and AD patients.

The three groups were matched for all the demographic variables, despite the low educational level among them.

The analysis of group differences indicated that the FCSRT was able to distinguish the clinical groups from the control group, but also to separate the degree of impairment between aMCI and AD. In fact, the usefulness of the FCSRT in assessing memory in aMCI and AD patients has been extensively reported (Brown & Storandt, 2000; Carlesimo et al., 2011; Grober & Kawas, 1997; Grober et al., 2008; Ivanoiu et al., 2005; Lemos et al., 2015; Mahieux et al., 2009; Saka et al., 2006; Sarazin et al., 2010; Vogel et al., 2007; Wagner et al., 2012).

To provide further evidence to FCSRT's construct related validity, two models were tested using CFA: a one-factor structure adapted from the model proposed by Grober et al. (2009) that accounts for the unidimensionality of memory ability; and a two-

factor model, considering the two factors as learning (total recall) and retention (delayed recall). In the study of Grober et al. (2009) the factor analysis indicated a single construct, but it comprised the FCSRT-IR (Grober & Buschke, 1987) procedure that only includes free recall from the test (learning) phase and uses pictures rather than words. Furthermore, Grober et al. (2009) included data from patients at a geriatric primary care center with cases of mild dementia with no specified type. In our study, we included both recalls in our first model, and the ITR (learning) and DTR (retention) independently in the two-factor model. Moreover, the presence of appropriated convergent validity and the lack of discriminant validity can be explained by the fact that both factors are evaluating memory ability, and therefore measuring the same construct. The unidimensionality of the FCSRT enabled us to add a global score for the FCSRT, which was further analyzed in terms of accuracy for the AD spectrum disorders.

Another major finding of the present study was the high classification accuracy of the FCSRT recalls. Overall, the FCSRT showed a good accuracy in classifying the subjects among the groups (67.9% on the ITR, 65.7% on the DTR, and 68.3% on the TR). All measures enabled good accuracies in classifying either the control (normal aging) or the AD (memory impairment) groups. Results for the aMCI group are less clear, with different classifications among the three recalls. The aMCI is a very heterogeneous condition that comprises different levels of memory impairment. For a subject to be classified as an aMCI patient, it is necessary to have a subjective memory complaint corroborated by an objective impairment, in the absence of dementia (Petersen et al., 1999, 2001). For this reason, aMCI is recognized as a very heterogeneous condition with an unclear distinction from early AD. Another important argument is that aMCI patients are at a higher risk of conversion to AD (Petersen et al., 1999, 2001). Consequently, the new AD criteria aim to consider some cases of aMCI patients as symptomatic prodromal AD, in the presence of impaired FCSRT in addition to AD-biomarker evidence (Albert et al., 2011; Dubois et al., 2007, 2010; 2014). In fact, (Lemos et al., 2015) confirmed the usefulness of the FCSRT in the characterization of the memory impairment of the AD spectrum, and showed that half of the aMCI patients included had an AD-alike pattern of impairment.

The ROC analysis supported the classification results by comparing the accuracy of the FCSRT measures in the discrimination among the three groups. The results revealed that, all the recalls enabled better accuracies in discriminating AD patients, than MCI subjects. When comparing the two pathological groups, the three recalls revealed similar results. Nonetheless the similar results in accuracy among the recalls, we believe that the outcomes from the two-factor model construct validity of the FCSRT allow to additionally support the importance of including both total (learning) and delayed (retention) recalls. The immediate recall provides qualitative and quantitative information regarding learning, while the delayed recall report memory consolidation/retention that is particularly sensitive to the hippocampal dysfunction present in AD spectrum disorders. In fact, both learning and retention correspond to the process of memory functioning. This shows the significance of a delayed recall to comprise the milder forms of cognitive decline (Albert et al., 2011; Grober & Kawas, 1997; Ivanoiu et al., 2005; Sánchez-Benavides et al., 2014) such as aMCI, and avoid the inclusion of false negatives that can happen when learning is the only memory measure tested. Furthermore, Saka et al. (2006) proved the superiority of the total recall in terms of sensitivity, but showed that it is less specific when compared to the free recall in discriminating AD patients from healthy elders. Vogel et al. (2007) analyzed the delayed recall and revealed that it increased the sensitivity of the total recall in AD identification. According to Salmon (2000), clinically, measures of the ability to learn and retain new information are quite useful in differentiating between healthy aging elders and AD patients, and delayed recall trials revealed to be more effective than measures of learning across trials. Nevertheless, the IWG-1 criteria for AD stated that “impaired delayed recall is not itself evidence of an AD-related memory disorder”, and deficits in encoding and storage processes that are characteristic for AD must be distinguished from non-AD deficits that can also affect delayed recall, such as attentional difficulties or inefficient retrieval strategies that may be present in normal aging or in other clinical conditions (Dubois et al., 2007). With this approach, we believe that we have given a new possibility in terms of using the FCSRT in AD spectrum disorders; psychometrically the FCSRT showed that its factor structure can be regarded either unidimensionally (memory), or as a two-factor model (learning and retention). Thus, it is our understanding that the motivation for deciding which recall

to use should be driven either by differences in study setting, research purposes or clinician preference. According to our results, the FCSRT recalls may be used and reported: i) independently (for a qualitative approach of the retained material), ii) as a composed result/global value (for a more simple way of reporting the result), or iii) as a single unit (in order to reduce patients' fatigue, or on follow-up evaluations). The motivation for the latter version of a single unit is based on the finding that the learning trials of the FCSRT provided similar information as the delayed recall; thus it may have the advantage of reducing patient fatigue and could be used mainly AD (both at baseline or follow-up evaluations). In fact, regarding the FCSRT-IR version, the majority of studies do not apply a delayed recall condition (Zimmerman et al., 2015).

The paradigm that underlies the FCSRT is based on the encoding specificity. This procedure has shown to promote deeper engagement with attentional and semantic processing in the encoding phase of memory, and it also controls the conditions of retrieval through the use of the same cues to direct learning and produce effective cued recall (Tulving & Thomson, 1973). Concerning the type of stimulus used, despite the suggestion that pictures might enable a better retention due to a concomitant verbal and image code stimulation, whereas written words are confined to verbal coding (Paivio, 1995); turning individuals' attention to semantic aspects of the to-be recalled pictures and words during encoding was found to eliminate the picture superiority effects (Paivio, 1975). Accordingly, the FCSRT (words version) present "printed words to avoid perceptual errors, ensure that all subjects use the same verbal encoding to learn the same items, and avoid dual perceptual and verbal encoding" (Buschke's FCSRT. Copyright, 2002).

Concerning dementia studies, memory tests that require the ability to control acquisition and retrieval are known to optimize encoding specificity and thus may be more sensitive to the early signs of AD (Buschke, 1987) than tests that use different paradigms.

We believe that our work brings an original contribution by studying the construct and diagnostic validities of the FCSRT, the memory test specifically recommended to objectively assess the memory impairment of AD spectrum disorders by the IWG-1 and IWG-2 (Dubois et al., 2007, 2014). By comprising both the immediate and the delayed recall of the test, we were able to measure learning and retention on the process of

memory ability, which are very important cognitive constructs and give vital information on memory processing. Additionally, our version includes words and not pictures. To date, and as far as we know, there have been no studies on the factorial structure of this version of the FCSRT in general, nor in AD spectrum disorders in particular. Thus, this study contributes to overcome a significant gap in the evaluation of the construct related validity of the FCSRT.

In sum, in this study we confirmed the usefulness of the FCSRT in analyzing aMCI and AD patients' memory impairments and proved its effectiveness in their classification. Moreover, the factorial structure of the FCSRT revealed robust results.

The possibility of a complete analysis, in terms of the properties of an instrument, is a valuable advantage that results in an important contribution to outline a more systematic and comprehensive neuropsychological evaluation.

The present results may be limited by the relatively small sample size. The factor analyses resulted in acceptable properties, although larger samples would be more appropriate. Another limitation of the present study is the low educational level of our samples, even though the three groups were matched for this variable. A low education level, along with a high socio-demographic diversity, is representative of the geriatric population in Portugal. For these reasons, some future considerations should be taken into account when analyzing the present results, namely the need for more studies conducted in different cultural contexts other than the Portuguese. Moreover, as we aimed to study the construct and diagnostic validities of the FCSRT in AD spectrum disorders, we have exclusively included MCI subjects of the amnestic type and AD patients. Consequently one must be advised against generalizing the obtained results to other clinical populations. We also believe that longitudinal studies with follow-ups of aMCI subjects should be carried on to confirm the utility of the FCSRT at baseline.

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STUDY 4

The Free and Cued Selective Reminding Test for predicting progression to Alzheimer's disease in patients with Mild Cognitive Impairment

Adapted from: **Lemos, R.**, Marôco, J., Simões, M. R., Santiago, B., Tomás, J., & Santana, I. (2015). The free and cued selective reminding test for predicting progression to Alzheimer's disease in patients with mild cognitive impairment: A prospective longitudinal study. *Journal of Neuropsychology*. doi:10.1111/jnp.12075 [Epub ahead of print]

Abstract

Amnestic mild cognitive impairment (aMCI) patients carry a greater risk of conversion to Alzheimer's disease (AD). Therefore, the International Working Group (IWG) on AD aims to consider some cases of aMCI as symptomatic prodromal AD. The core diagnostic marker of AD is a significant and progressive memory deficit, and the Free and Cued Selective Reminding Test (FCSRT) was recommended by the IWG to test memory in cases of possible prodromal AD. This study aims to investigate whether the performance on the FCSRT would enhance the ability to predict conversion to AD in an aMCI group. A longitudinal study was conducted on 88 aMCI patients, and neuropsychological tests were analyzed on the relative risk of conversion to AD. During follow-up (23.82 months), 33% of the aMCI population converted to AD. An impaired FCSRT TR was significantly associated with the risk of conversion to dementia, with a mean time to conversion of 25 months. The FCSRT demonstrates utility for detecting AD at its prodromal stage, thus supporting its use as a valid clinical marker.

Introduction

Among all types of dementia, Alzheimer's disease (AD) is the most common, comprising about 50% to 80% of all the dementia cases. It is an area of significant health concern in the elderly, and has become one of the leading causes of death in modern society (Corey-Bloom, 2004; Ferri et al., 2005). AD diagnosis is generally supported by clinical history, neurological examination, and neuropsychological evidence of cognitive dysfunction, especially in the memory domain (American Psychiatric Association, 2000; McKhann et al., 1984; 2011).

The clinical interest in establishing an early diagnosis has led to the concept of a transitional state between normal aging and dementia (i.e., prodromal AD). This stage is widely known as amnestic Mild Cognitive Impairment (aMCI; Petersen et al., 1999), and aims to identify individuals with memory impairment greater than what is expected for their age and education level, but who are not sufficiently debilitated in their activities of daily living to be considered as demented (Petersen et al., 1999). Thus, the confirmation of a deficit in memory through a reliable instrument is essential for the diagnosis of aMCI (Petersen et al., 1999, 2001). aMCI diagnosis has proven to be clinically useful, as these patients carry a greater risk of conversion to dementia/AD (approximately 12% per year) (Albert et al., 2011; Petersen et al., 1999, 2001), while others may stay in a stable form of selective memory impairment (Dawe, Procter, & Philpot, 1992). In the early stages of AD, neuropathologic changes are already present in medial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex), areas which are critical for long-term episodic memory (Blennow, de Leon, & Zetterberg, 2006; Morris et al., 2001; Sarazin et al., 2010). Consequently, this early involvement of medial temporal structures leads to a deficit in episodic memory, rendering it a reliable neuropsychological marker of AD (Heister et al., 2011; Richard, Schmand, Eikelenboom, & Van Gool, 2013). Along with the baseline diagnostic criteria, severity of the memory deficit is also a dominant predictor of progression to dementia (Dubois et al., 2007; Fleisher et al., 2007; Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999; Morris et al., 2001). Early identification of patients with increased risk is crucial, as disease-modifying treatments may have the greatest potential in the earliest disease stages (DeKosky & Marek, 2003). Moreover, the lack of reliable tools to

detect and follow preclinical AD has been pointed out as one of the main obstacles for the development of new treatments (Lansbury, 2004).

The International Working Group (IWG-1) developed and published revised diagnostic criteria for AD (Dubois et al., 2007, 2010), in an attempt to address the limitations of the Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM-IV-TR; American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders (NINCDS-ADRDA; McKhann et al., 1984). The IWG-1 criteria apply to both the early stages and the full spectrum of the illness, and include biomarkers of AD pathology to increase the confidence that subjects with aMCI have AD as the underlying cause (Dubois et al., 2007, 2010). The core clinical criterion is the evidence of a significant and progressive episodic memory impairment confirmed by objective testing (Dubois et al., 2007, 2010). Dubois et al. (2007, 2010) recommend a cued recall test to define memory impairment, such as the Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984; Grober & Buschke, 1987), as it demonstrated high sensitivity and specificity in differentiating AD patients from both healthy controls (Grober, Sanders, Hall, & Lipton, 2010) and those with other forms of dementia (Grober, Hall, Sanders, & Lipton, 2008; Lemos, Duro, Simões, & Santana, 2014; Pasquier, Grymonprez, Lebert, & Linden, 2001). More recently, the IWG-2 criteria reinforced the choice of the FCSRT as a valid clinical marker for typical prodromal AD (aMCI) (Dubois et al., 2014).

In patients with AD, the amnestic profile is typically characterized by poor learning and rapid memory decay over relatively short periods, often concurrent with damage to the mesial temporal structures, such as the hippocampus (Squire, Stark, & Clark, 2004). It is of clinical importance that deficits in encoding and storage processes that are characteristic of AD can be distinguished from non-AD memory deficits that may have a different etiology. Therefore, the accurate diagnosis of an episodic memory deficit, so often observed in AD patients, may be improved upon by the use of test paradigms that provide information on encoding specificity (Buschke, Sliwinski, Kuslansky, & Lipton, 1997). Memory tests that require the ability to control acquisition and retrieval may optimize encoding specificity and thus may be more sensitive to the early signs of dementia (Buschke, 1984) than tests that use different paradigms.

The FCSRT is based on a selective reminding paradigm where acquisition and retrieval are reinforced by using the same cues to control learning and elicit effective cued recall. The utility of this paradigm has been widely reported in the memory dysfunction characterization of AD (Brown & Storandt, 2000; Carlesimo, Perri, & Caltagirone, 2011; Grober & Kawas, 1997; Grober, Hall, Lipton, et al., 2008; Mahieux et al., 2009; Sarazin et al., 2010; Vogel, Mortensen, Gade, & Waldemar, 2007) and aMCI (Ivanoiu et al., 2005; Saka, Mihci, Topcuoglu, & Balkan, 2006; Wagner et al., 2012). The comparable profiles of memory dysfunction of MCI and AD have also been described (Petersen, 2004b; Petersen et al., 1999). Further, this similar profile has been described for aMCI patients with a higher risk of conversion to AD (Auriacombe et al., 2010; Grober, Lipton, Hall, & Crystal, 2000; Petersen, 2007; Sarazin et al., 2010). In a recent study, the FCSRT showed its capability to differentiate aMCI patients based on a non-similar/similar AD pattern of impairment, and to infer that those AD-alike patients could possibly have prodromal AD (Lemos, Simões, Santiago, & Santana, 2015). Thus, it is imperative to examine how the memory tests suggested in diagnostic criteria show predictive value of the MCI diagnosis for conversion to dementia. In fact, Sarazin et al. (2007) have demonstrated that the FCSRT is able to distinguish patients at an early stage of AD from MCI non-converters, using the modified Grober-Buschke procedure (Grober & Buschke, 1987).

The current study aimed to investigate whether performance on the FCSRT would enhance the ability to predict incident AD in a group of aMCI patients. Positive findings would support its interest as a valid clinical marker for typical AD.

Methods

Participants

The clinical study sample included 100 aMCI patients recruited at the Neurology Department of our local hospital between 2010 and 2012 (Lemos et al., 2015).

The patients enrolled had clinical semiannual evaluations and were followed until they developed dementia or until they had been cognitively stable for at least two years (follow-up *M*= 23.82 months). Eighty-eight out of the 100 aMCI patients met the follow-up criteria and comprise the longitudinal study group. From the 12 patients lost

to the clinical follow-up, 4 died and 8 declined to participate in the follow-up observation (considered as dropouts).

MCI patients were of the amnestic type (single or multi-domain) (Petersen, 2007) at baseline, and were selected according to Petersen's criteria (Albert et al., 2011; Petersen, 2004a). A neurologist completed a medical history with the patient and caregiver at baseline, and also conducted a general physical, neurological, and psychiatric examination of the patient. Standard tests included apolipoprotein E (ApoE) allele genotyping, laboratory, and imaging studies. A comprehensive battery was administered by experienced neuropsychologists. This included the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro, 1998), the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog; Guerreiro, Fonseca, Barreto, & Garcia, 2008; Mohs, Rosen, & Davis, 1983), and a comprehensive neuropsychological battery with normative data for the Portuguese population (Battery of Lisbon for the Assessment of Dementia; Guerreiro, 1998).Tests of interest for the present study within the neuropsychological battery included Logical Memory (LM; Immediate and Delayed Recall; Wechsler Memory Scale (WMS; Wechsler, 1987), and Verbal Paired-Associate Learning (VPAL; Immediate Recall). The Clinical Dementia Rating (CDR; Garrett et al., 2008; Morris, 1993) for global staging, and the Geriatric depression Scale (GDS-30; Barreto, Leuschner, Santos, & Sobral, 2008; Yesavage et al., 1983) to exclude severe depression (i.e., GDS-30 ≥ 20) were also administered.

All the available information (baseline cognitive testing, staging scales, clinical laboratory and imaging studies) was used to reach a consensus research diagnosis, headed by a board certified neurologist. A similar approach was used for semiannual follow-up evaluations. The baseline inclusion criteria for aMCI (single or multi-domain) were those proposed by Petersen (2007) and were operationalized as follows: 1) A subjective complaint of memory decline (reported by the subject or an informant); 2) An objective memory impairment (i.e., scores on standard memory tests > 1.5 SD below age/education adjusted norms) with or without deficits in other cognitive domains; 3) Normal general cognition suggested by normal scores on the MMSE and the ADAS-Cog; 4) Largely normal activities of daily living; 5) Absence of dementia, indicated by a CDR rating of 0.5. Exclusion criteria were a significant underlying medical or neurological illness revealed by lab tests or imaging; a relevant psychiatric

disease, including severe depression; CT or MRI demonstration of significant vascular burden (large cortico-subcortical infarct; extensive subcortical white matter lesions greater than 25%; uni- or bilateral thalamic lacunes; lacunes in the head of the caudate nucleus; > 2 lacunes) (Román et al., 1993).

Every six months, clinical, cognitive, and functional status was reassessed. Dementia was diagnosed according to the DSM-IV-TR (American Psychiatric Association, 2000) and AD was diagnosed according to the NINCDS-ADRDA criteria (McKhann et al., 1984). Conversion to AD required meeting clinical diagnostic criteria for probable AD, and was confirmed by the coordinator of the clinical study based on multiple types of assessments, and with an emphasis on clinician expertise and documentation of a functional decline (CDR). Patients in this study were classified has having undergone conversion based on: 1) Objective evidence on cognitive testing of deterioration to dementia using the MMSE and the ADAS-Cog scores and qualitative evaluation (i.e., impairment of memory plus other domains); 2) Changes in global CDR rating from 0.5 to 1 or more, confirming the cognitive profile of dementia and loss of autonomy. The onset of AD was defined as the date when the diagnosis was made.

All subjects were submitted to the same experimental research protocol. Informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of our local ethics committee.

Demographic and clinical characteristics of the population are shown in Table 4.1.

Procedure

At baseline, subjects were assessed using the Portuguese version of the Buschke's FCSRT (Buschke, 1984) adapted by Lemos, Martins, Simões, and Santana (2012). Materials and instructions for the FCSRT were provided by the original author (Buschke's FCSRT. Copyright, 2002. Albert Einstein College of Medicine of Yeshiva University, New York). The selection of the 16 stimulus words followed the same principles as the English version – intermediate frequency words were selected within a semantic category (frequencies in Portuguese in the CORLEX database) (Nascimento et al., 2003). In the present study, the FCSRT was not used in the diagnostic process.

The test starts by asking subjects to identify words in response to a unique category cue. The 16 items to be learned are presented four at a time on a card, distributed one word per quadrant. The subject is asked to search each card and point to and name aloud each item after its semantic cue is verbally presented. During this procedure, the subject is informed to learn the 16 words. The FCSRT version used in this study differs from the modified Grober-Buschke version used by Sarazin et al. (2007), as it does not include immediate cued recall in the learning phase. There are 3 recall trials, each preceded by 20 seconds of counting backward to prevent recall from short-term memory. Each recall trial consists of two parts. First, each subject has up to two minutes to freely recall as many items as possible. Next, verbally presented category cues are provided for items not retrieved by free recall. If subjects fail to retrieve the item with the category cue, they are reminded by presenting the cue and the item together. The sum of free and cued recall gives a measure of total recall (TR). The same procedure of recalling (free and cued) is done after a 30-minute interval, during which subjects are required to perform non-verbal tasks (Delayed Total Recall – DTR).

In this study, we used the total recall measures (immediate and delayed) in the analysis.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 19.0) (IBM SPSS, Inc., Chicago, IL). As data significantly deviated from normal distributions and homogeneous variances (verified using the Kolmogorov-Smirnov normality check and Levene homogeneity tests, respectively), a non-parametric statistical methods for group comparison was applied. Results with $p<.05$ were considered statistically significant. Demographic, clinical, and neuropsychological data were analyzed using the Mann-Whitney test for numerical data, and the Pearson χ^2 test for nominal data, allowing comparisons between the two groups of patients (aMCI-aMCI and aMCI-AD).

Survival curves methods were chosen for the analysis, as conversion to dementia occurred at different times and the observations were censored. Kaplan-Meier curves were used to illustrate the differences in progression to AD between the two groups. Survival time was calculated as the interval from the initial baseline evaluation to the

diagnosis of dementia. For patients who remained non-demented, survival time was censored at the date of the last clinical assessment. Variables were considered binary, as following: ApoE-ε4 allele carriers and non-carriers; memory tests with presence or absence of impairment according to the previously established cut-offs [LM and VPAL as 2 SDs below adjusted z-scores; Guerreiro, 1998; Silva et al., 2012]; FCSRT below standardized cut-offs for AD [TR≤27; DR≤8; Lemos et al., 2015]. Multivariate Cox proportional hazards regression models with forward selection procedure were used to estimate the effects of these variables on the relative risk of conversion from aMCI to AD. Hazard ratios (HR) with 95% confidence intervals (CI) were reported. The variance inflation factor (VIF) was used to check for the problem of multicollinearity among the predictor variables, considering a VIF < 5 as no evidence of multicollinearity; a 5 ≤ VIF ≤ 10 as moderate multicollinearity; and a VIF > 10 as significant multicollinearity amongst the variables.

Results

Baseline and follow-up characteristics

At baseline, 100 non-demented patients reporting subjective cognitive complaints with objective memory impairment were included. During the follow-up time (*M = 23*.82 months), 29 patients (33%) converted to dementia, and 59 (67%) did not. All the cases that progressed to dementia were diagnosed as AD (Figure 4.1).

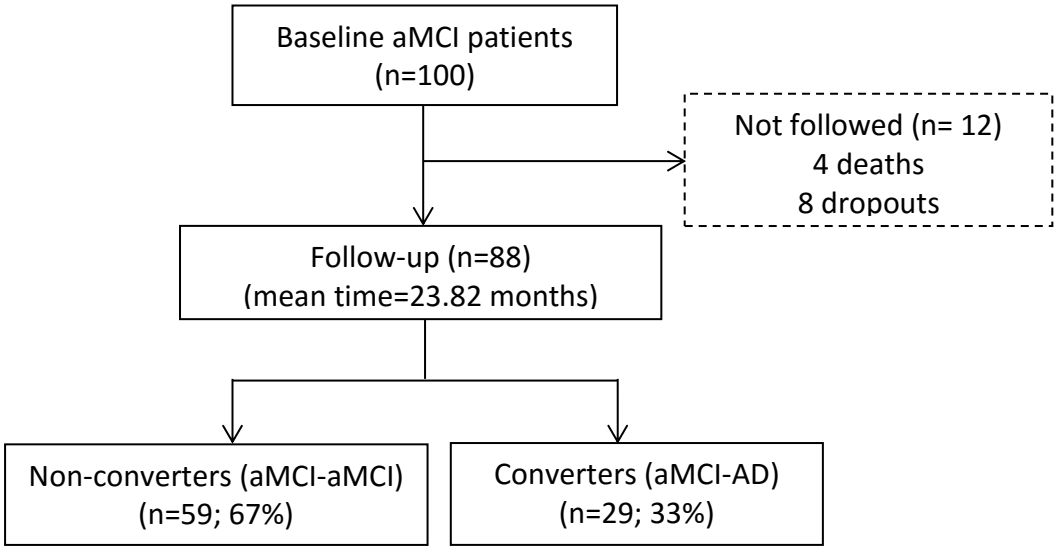

Figure 4.1 Study flow diagram

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease.

Demographical and clinical characteristics of the population are shown in Table 4.1. No statistically significant differences were found in age [*U* =763.5, *p* =.413], educational level (*U* = 809.5, *p* =.666), or gender [χ^2 (1) = 1.054, *p* = .305] between the two groups. Significant differences were found between ApoE-ε4 carriers and non-carriers among the groups [χ^2 (1) = 7.877, *p* = .005]. The follow-up time was not significantly different between the two samples [*U* =733.0, *p* =.277].

Table 4.1 Baseline demographical and clinical characteristics of the population

	Non-converters (aMCI-aMCI) (n=59)	Converters (aMCI-AD) (n=29)
Gender (m:f)	25:34	9:20
Age (years), mean (SEM)	69.63 (1.05)	67.00 (3.76)
Education Level, years	6.29 (0.54)	7.03 (0.83)
ApoE (ε4: non ε4 carrier)	20:39	19:10*
Follow-up time, months	24.62 (.93)	22.20 (1.39)

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease.
Note: Data are expressed as mean (SEM), except for gender and ApoE.
Comparisons between Non-converters-Converters were carried out by independent two-sample Mann-Whitney test or Pearson χ^2 test for nominal variables, where:
* aMCI-aMCI vs. aMCI-AD: *p* <.05.

A significant effect was found for the neuropsychological performance, at baseline, on almost all measures (MMSE: *U* =401.0, *p* <.001, ADAS-Cog: *U* =383.5, *p* =.001; LM IR: *U* =413.5, *p* <.05; LM DR: *U* =350, *p* <.05; FCSRT TR: *U* =333.5, *p* <.001; FCSRT DR: *U* =365, *p* <.001), except for VPAL (*p* =.190). As expected, on follow-up, the two global cognitive measures demonstrated significant differences (MMSE: *U* =212.5, *p* <.001, ADAS-Cog: *U* =194.5, *p* <.001) among the groups. When global scale comparisons were performed within groups between baseline and follow-up assessments, no differences were found for the aMCI-aMCI group (MMSE: *Z*=-1.871; *p*=.061; ADAS-Cog: *Z*=-1.056; *p*=0.291), but significant differences were found in the aMCI-AD sample (MMSE: *Z*=-3.141; *p*=.002; ADAS-Cog: *Z*=-3.478; *p*=.001) (Table 4.2).

Table 4.2 Neuropsychological performance of the population

	Non-converters (aMCI-aMCI) (n=59)		Converters (aMCI-AD) (n=29)	
	Baseline	*Follow-up*	Baseline	*Follow-up*
MMSE, score	27.90 (.27)	*27.37 (.38)*	25.48 (.48)**	*22.63 (.76)*$^{\#/\ddagger}$
ADAS-Cog, score	8.21 (.50)	*8.91 (.66)*	11.63 (.85)*	*16.31 (.84)*$^{\#/\ddagger}$
LM IR, score	6.28 (.41)		5.00 (.60)*	
LM DR, score	4.29 (.34)		2.55 (.48)*	
VPAL IR, score	11.86 (.61)		11.07 (.73)^{NS}	
FCSRT TR, score	31.59 (1.30)		19.97 (1.78)**	
FCSRT DR, score	10.39 (.60)		5.62 (.68)**	

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; MMSE – Mini-Mental State Examination; ADAS-Cog – Alzheimer's Disease Assessment Scale–Cognitive; FCSRT TR – Free and Cued Selective Reminding Test Total Recall.
Note: Data are expressed as mean (SEM).
Comparisons between Non-converters-Converters were carried out by independent two-sample Mann-Whitney test, where:
* At baseline, aMCI-aMCI vs. aMCI-AD: p <.05
** At baseline, aMCI-aMCI vs. aMCI-AD: p <.001
$^{\#}$ At follow-up, aMCI-aMCI vs. aMCI-AD: p <.001
^{NS} – Non significant.
Within groups, differences between baseline and follow-up were assessed by the Wilcoxon rank-sum test, where:
‡ Baseline vs. Follow-up: p <.05
In ADAS-Cog a higher score represents a higher level of impairment.

Relation between baseline neuropsychological performance and risk of developing AD

Figures 2.4 show the Kaplan-Meier estimates of the probability of conversion to AD in patients with aMCI for ApoE-ε4 allele and the neuropsychological tests (LM and FCSRT).

For ApoE, 49% of the ε4 allele carriers converted to AD, compared to 20% of ε4 non-carriers. The mean time of conversion was slightly reduced for ε4 allele carriers (29 vs. 31 months; χ^2 (1) = 3.978, p=.046) (Figure 4.2).

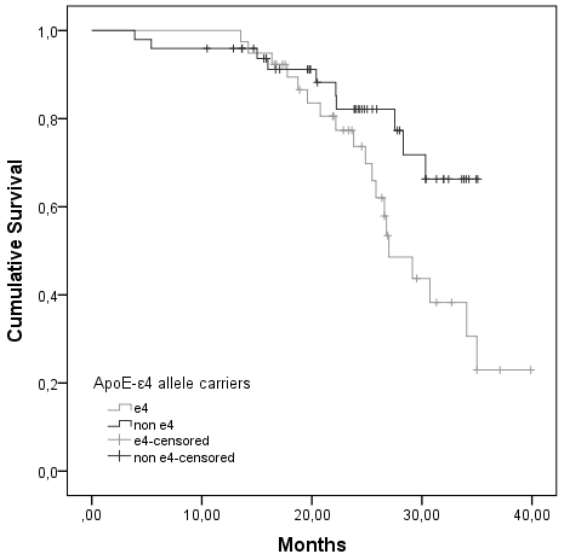

Figure 4.2 Kaplan-Meier survival curves for the conversion to Alzheimer's disease (AD) in patients with amnestic Mild Cognitive Impairment (aMCI) with regard to presence of ApoE-ε4 allele.

On WMS LM IR, 50% under the z-score threshold converted to AD, compared to 21% who were above the cutoff. The mean time to conversion was significantly reduced for those below the cutoff (24 vs. 34 months; χ^2 (1) = 8.738, *p*=.003). On WMS LM DR, 44% under the z-score threshold converted to AD, compared to 14% who were above the cutoff. The mean time to conversion was significantly reduced for those with impairment (27 vs. 36 months; χ^2 (1) = 9.748, *p*=.002) (Figure 4.3).

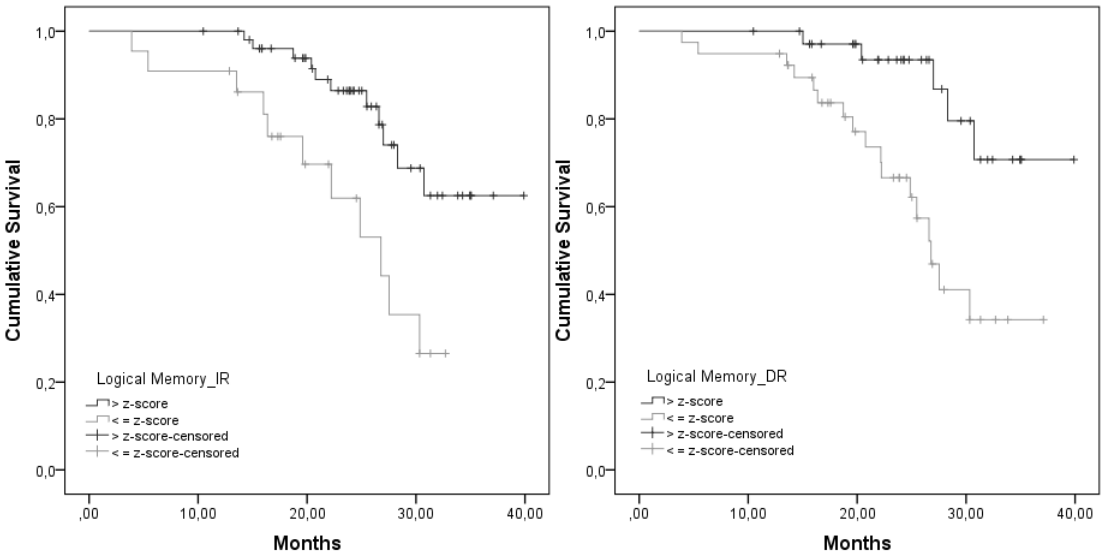

Figure 4.3 Kaplan-Meier survival curves for the conversion to Alzheimer's disease (AD) in patients with amnestic Mild Cognitive Impairment (aMCI) on WMS Logical Memory.
Abbreviations: IR – Immediate Recall; DR – Delayed Recall.

For subjects with FCSRT TR below cutoff, the conversion to AD occurred in 57% of the subjects, whereas a normal FCSRT resulted in 11% conversion events. Mean time to conversion was significantly reduced in patients with a pathological FCSRT profile compared to those with a normal FCSRT profile (25 vs 37; χ^2 (1) = 23.602, *p*<.001). For FCSRT DR, 54% of the subjects under the threshold converted to AD at follow-up, compared to 15% of those who were above the cutoff. The mean time to conversion was significantly different reduced in the aMCI group with an impaired performance (26 vs 36; χ^2 (1) = 16.176, *p*<.001) (Figure 4.4).

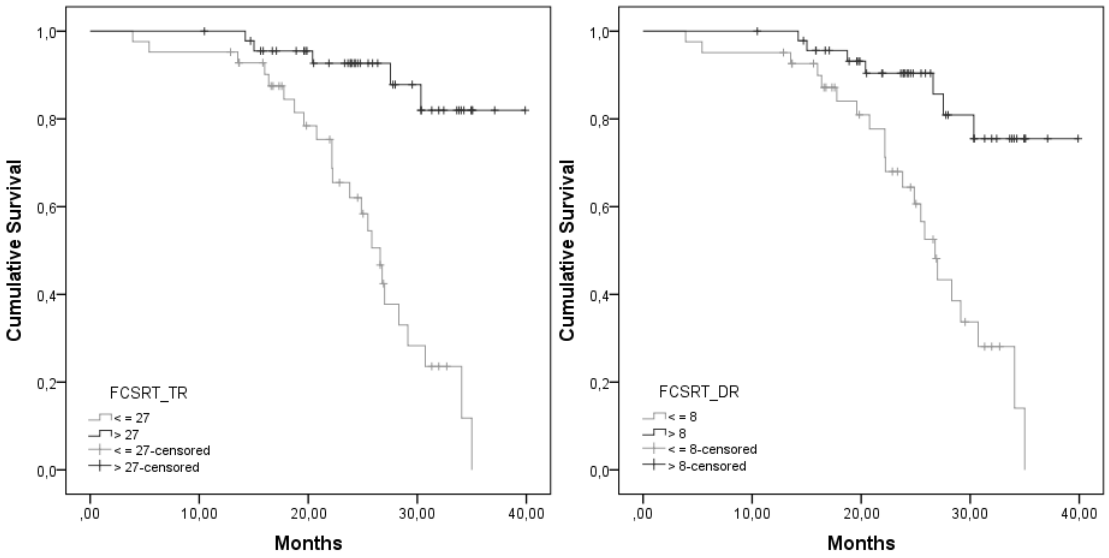

Figure 4.4 Kaplan-Meier survival curves for the conversion to Alzheimer's disease (AD) in patients with amnestic Mild Cognitive Impairment (aMCI), regarding the performance on the FCSRT.

Abbreviations: FCSRT – Free and Cued Selective Reminding Test; TR – Total Recall; DR – Delayed Recall.

Collinearity statistics showed that there was no evidence of significant collinearity among the predictor variables (all VIFs < 5, and on average: 1< VIF <3).

The FCSRT TR was the only variable that significantly predicted elevated risk of conversion to AD (HR = 6.945, 95% CI = 2.524-19.107, *p*<.001), with worse performance associated with elevated risk.

Discussion

The main objective of the present study was to investigate whether performance on the FCSRT would enhance the ability to predict incident AD in a group of aMCI

patients. Patients whose clinical presentation met criteria for aMCI (Petersen, 2007; Petersen, 2004b; Petersen et al., 1999, 2001) were specifically included in order to cover the full aMCI spectrum seen in the memory clinic – both patients who may have prodromal AD and patients that remain with a stable aMCI condition (Albert et al., 2011; Dubois et al., 2007, 2010). The outcome measure was progression to AD-type dementia according to the DSM-IV-TR (American Psychiatric Association, 2000) and the NINCDS-ADRDA (McKhann et al., 1984) criteria. The aMCI group included in the baseline was subdivided by conversion to AD (aMCI-AD) or stable aMCI (aMCI-aMCI) during the follow-up period. The two groups were matched for demographical variables, though significant differences were found concerning the distribution of the ApoE-ε4 allele and the neuropsychological performance (MMSE, ADAS-Cog, WMS LM IR and DR, and FCSRT IR and DR). Similar results have already been indicated as clinical predictors of progression to AD in aMCI patients (Baldeiras et al., 2010; Fleisher et al., 2007; Rabin et al., 2012). We observed a high rate of conversion during the follow-up time (23.82 months), where 33% of the aMCI population converted to AD. This high rate of conversion might indicate that prodromal AD was already present among aMCI patients at baseline. Comparisons within groups revealed no differences in the MMSE and ADAS-Cog between the two evaluation moments in the aMCI-aMCI group, but significant differences in the aMCI-AD sample. A survival analysis enhanced the contributions of the presence of ApoE-ε4 allele and the neuropsychological tests (LM and FCSRT) for the prediction of incident AD. Thus, the only variable that remained significantly associated with the risk of conversion to dementia during the follow-up was the FCSRT TR. Moreover, the mean time of conversion for aMCI patients with an impaired FCSRT TR was 25 months, whereas for subjects with a normal FCSRT, mean time to conversion was 37 months. The FCSRT has previously revealed its superiority among other neuropsychological tools, for detecting AD at its prodromal stage (Auriacombe et al., 2010; Lemos, Cunha, Afonso, Simões, & Santana, 2014; Mura et al., 2013; Rabin et al., 2012; Sarazin et al., 2007), and therefore is considered an ideal diagnostic tool for prodromal AD, according to the IWG-1 criteria (Dubois et al., 2007, 2010; Sarazin et al., 2007).

The FCSRT has shown to have better predictive validity than the commonly used WMS LM IR test both on the development of incident AD in a community based cohort with

memory complaints (Derby et al., 2013), and in MCI patients with a CSF profile for AD pathology (Wagner et al., 2012). Nevertheless, the recently IWG-2 criteria indicated that other memory tests, mainly those based on list-learning and delayed recall, also can be effective in the identification of the amnestic syndrome of AD. Thus, the IWG-2 concluded that list-learning memory tests such as the FCSRT (or other episodic memory tests with established high specificity for AD across the disease span) are preferred (Dubois et al., 2014).

A significant impairment in memory testing is essential to the diagnosis of both aMCI and AD (Albert et al., 2011; Dubois et al., 2007, 2010; Petersen, 2007; Petersen et al., 1999). A deficit in the delayed recall of episodic long-term memory would be particularly characteristic of initial AD (Perri, Serra, Carlesimo, Caltagirone, & Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's Disease, 2007), as it reflects the early involvement of medial temporal lobe structures. Genuine deficits in encoding and storage processes that are characteristic of AD must be distinguished from non-AD deficits that can also affect recall as a result of difficulties in attention, which are present in other geriatric conditions (Dubois et al., 2007). Low performance may reflect impaired encoding of the information, thus decreasing the consolidation of new verbal material (Belleville, Sylvain-Roy, de Boysson, & Ménard, 2008; Moulin, James, Freeman, & Jones, 2004). Therefore, the design of the test is very important, as an accurate assessment of memory depends on the quality of learning, which is later reflected in effective retrieval (Buschke et al., 1997). By controlling both encoding and retrieval with the same semantic cues, the FCSRT can isolate storage deficits due to hippocampal damage, and thereby identify the amnestic syndrome of AD, even in the early stages of the disease (Sarazin et al., 2007). This allows for differentiation of memory impairment due to attentional problems that may be present in other dementias not of the Alzheimer's type (Grober, Hall, Sanders, et al., 2008; Lemos, Duro, et al., 2014; Pasquier et al., 2001). The studies that determined the predictive value of the FCSRT for future conversion to dementia showed no evidence of accuracy superiority for delayed recall measures compared to immediate recall, supporting the hypothesis of a failure at the initial learning process (despite providing semantic cues), rather than forgetting due to inadequate storage of the information

(Carlesimo et al., 2011). Moreover, according to Carlesimo et al. (2011), the FCSRT is able to discriminate between memory deficits due to impaired storage processes, and deficits originated from a failure of encoding and/or retrieval. While a deficit in storage processes would be characteristic of AD, presumably due to its early hippocampal involvement, impairment in executive functions would be characterized by a deficit of elaborative encoding and strategic retrieval processes (present in other dementia syndromes and other geriatric conditions). Previous studies have shown that impairment in list-learning tests might predict accurately the conversion to AD (Chapman et al., 2011; Maruff et al., 2004; Rabin et al., 2009; Silva et al., 2012). Nevertheless, the IWG-1 and the IWG-2 criteria recommend a cued recall instrument to define memory impairment, such as the FCSRT (Dubois et al., 2007, 2010, 2014).

A previous cluster analysis study (Lemos et al., 2015) demonstrated an AD-alike pattern of impairment among the aMCI group with regard to performance on the FCSRT. aMCI patients with impaired FCSRT scores were similar to AD patients in terms of performance, and different from patients with normal FCSRT scores. The authors concluded that the heterogeneity of the aMCI group may be subdivided according to an AD-similar pattern of performance in the FCSRT profile.

Significant correlations between a poor performance on the FCSRT and AD biomarkers have also been shown with regard to medial temporal lobe (Sánchez-Benavides et al., 2014; Sarazin et al., 2010) and cerebrospinal fluid biomarkers (Wagner et al., 2012). Accordingly, a low performance in the FCSRT, along with evidence of abnormal CSF biomarkers, represent a combination of valid clinical markers for typical prodromal AD, as suggested by the IWG-2 diagnostic criteria (Dubois et al., 2014).

In sum, the FCSRT has been shown to differentiate aMCI from AD patients (Grober & Buschke, 1987; Ivanoiu et al., 2005; Lemos et al., 2015) at baseline, allowed for the division of the aMCI group according to an AD-alike pattern of impairment at baseline (Lemos et al., 2015), and was associated with the risk of conversion to AD in follow-up studies (Auriacombe et al., 2010; Petersen, 2007; Sarazin et al., 2010). This study corroborates the new AD criteria in conceptualizing the prodromal period preceding the onset of AD by using the FCSRT to evaluate the memory deficit. An early and accurate identification of individuals at a higher risk for AD is crucial, given that understanding the biological and cognitive processes occurring at the prodromal stage

may lead to novel therapeutic goals for disease prevention and/or treatment (Khachaturian et al., 2008), in addition to planning for caregiver assistance and economic burden.

The main limitation of this study is the strict focus on neuropsychological test data. Studies with the inclusion of other AD-biomarkers should be considered in the future.

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STUDY 5

Selective Reminding and Free and Cued Selective Reminding in Mild Cognitive Impairment and Alzheimer´s disease

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Abstract

The Selective Reminding Test (SRT) and the Free and Cued Selective Reminding Test (FCSRT) are multi-trial memory tests that use a common "selective reminding" paradigm that aims to facilitate learning by presenting only the missing words from the previous recall trial. While in the FCSRT semantic cues are provided to elicit recall, in the SRT subjects are merely reminded of the missing items by repeating them. These tests have been used to assess age-related memory changes and to predict dementia. The performance of healthy elders on these tests has been compared before, showing that twice as many words were retrieved from long-term memory in the FCSRT compared to the SRT. In this study we compared their properties and their accuracy in discriminating amnestic Mild Cognitive Impairment (aMCI, n=20) from Alzheimer's disease (AD, n=18). AD patients performed significantly worse than aMCI subjects on both tests. The percentage of items recalled during the learning trials was significantly higher for the FCSRT on both groups, and a higher number of items were later retrieved, showing the benefit of category cueing. Our key finding was that the FCSRT showed higher accuracy in discriminating aMCI from AD patients.

Introduction

The Selective Reminding Test (SRT; Buschke, 1973) and the Free and Cued Selective Test Reminding (FCSRT; Buschke, 1984; Grober & Buschke, 1987) are multi-trial memory tests that use a "selective reminding" paradigm, presenting only the words not recalled, instead of the entire list of the to-be-remembered words. This procedure, present in both the SRT and the FCSRT, is intended to facilitate learning by directing the subject's attention to the words not recalled on the previous trial.

The FCSRT differs from the SRT in that it includes a procedure that promotes attention and cognitive processing in the learning process. Subjects are told to search for items (e.g., hammer) in response to category cues (e.g., tool), instead of just the item itself. Another difference between the two tests is in the method used to remind subjects of the missed items during recall. In the SRT, subjects are simply reminded of the items that were not recalled on the previous trial; the items are merely represented. In the FCSRT, the category cue is presented for the missed item, to help the subject recall it by category. Cued recall has been shown to provide an estimate of all the items that the subject has stored, rather than just those that are freely recalled, and to be minimally affected by guessing (Grober, Gitlin, Bang, & Buschke, 1992). Using the same category cues during the learning and recall phases is thought to coordinate acquisition and recall, to ensure attention, and to promote deep semantic processing in the encoding phase, increasing its specificity to the memory process itself (Tulving & Osler, 1968; Tulving & Thomson, 1973).

These tests have been extensively investigated in the assessment of age-related memory changes as well as in the diagnosis and prediction of dementia. The SRT has been widely used to characterize the memory impairment in dementia in general (Sherwin, Chertkow, Schipper, & Nasreddine, 2011; Strauss, Sherman, & Spreen, 2006), as well as the memory profile of Alzheimer's disease (AD) in particular (Campo, Morales, & Martínez-Castillo, 2003; Degenszajn, Caramelli, Caixeta, & Nitrini, 2001; Hall et al., 2007; Starkstein, Boller, & Garau, 2005).

The FCSRT, with its cued selective reminding paradigm, has been used to characterize the memory dysfunction typical of both AD (Brown & Storandt, 2000; Buschke, Sliwinski, Kuslansky, & Lipton, 1997; Grober & Kawas, 1997; Grober, Hall, Lipton, et al.,

2008; Mahieux et al., 2009; Vogel, Mortensen, Gade, & Waldemar, 2007) and of amnestic Mild Cognitive Impairment (aMCI; Ivanoiu et al., 2005; Saka, Mihci, Topcuoglu, & Balkan, 2006; Wenger, Negash, Petersen, & Petersen, 2010). It has shown both differences and similarities in the profile of memory dysfunction in the two disorders. For instance, the FCSRT indicated a similar profile of memory dysfunction in some individuals with aMCI and AD (Onen, Henry-Feugeas, Roy, Baron, & Ravaud, 2008; Petersen et al., 1999; Sánchez-Benavides et al., 2010). The similarity was especially clear in aMCI-patients who had a higher risk of conversion to AD (Petersen et al., 1995; Sarazin et al., 2007).

The FCSRT was recently recommended by the International Working Group on Alzheimer's disease (Dubois et al., 2007) due to its high sensitivity and specificity in the differentiation of AD patients from healthy controls (Grober, Sanders, Hall, & Lipton, 2010) as well as from individuals with other dementia types (Buschke et al., 1997).

Grober, Merling, Heimlich, and Lipton (1997) compared the performance of healthy elders on both the SRT and the FCSRT to determine which test produces better recall in normal aging, as well as to identify the factors that account for superior recall. They studied 33 very elderly (average age = 88.6) subjects and a group of 23 less-elderly subjects (average age = 76.4). Twice as many words were retrieved from long-term memory in FCSRT compared to the SRT. This improvement in free recall may be attributed to the cued method of reminding of the FCSRT.

In the current study, these same two tests were compared to determine which is more sensitive in discriminating aMCI from AD, and to determine whether, as previously found, the FCSRT is more sensitive in discriminating aMCI from AD. We hypothesized, as did (Grober et al., 1997), that a higher percentage of words would be recalled in FCSRT than SRT in both groups because of the paradigm that underlies the FCSRT, which promotes attention and semantic processing. As that procedure is thought to minimize the effects of mild cognitive decline, the FCSRT should enhance the accuracy in detecting AD patients, where attention and semantic processing are more impaired. The AD patients are less able to use the assistance provided by the FCSRT, in contrast to the aMCI group, where attention and semantic processing have not yet significantly deteriorated.

Materials and Methods

Participants

The clinical study sample included 21 aMCI patients (14 women and 6 men) and 18 AD patients (11 women and 7 men), recruited at the Dementia Clinic of the Neurology Department of our local University Hospital. The diagnostic investigation involves a standard clinical evaluation, extensive psychological and cognitive assessment, laboratory tests, and imaging studies. Certain laboratory tests (including chemistry profile, CBC count, thyroid function tests, vitamin B12 and folic acid level, syphilis and Lyme serology), imaging studies (CT, MRI, or SPECT), and Apolipoprotein E allele genotyping were always performed. Positron Emission Tomography, Cerebrospinal Fluid analysis, and genetic studies were more selectively done, largely in younger patients. The psychological battery administered included: 1) Cognitive tests: the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro et al., 2008), the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog; Guerreiro, Fonseca, Barreto, & Garcia, 2008; Mohs, Rosen, & Davis, 1983), and a comprehensive neuropsychological battery with normative data for the Portuguese population (BLAD; Guerreiro, 1998) exploring memory as well as other cognitive domains. 2) The Clinical Dementia Rating (CDR; Garrett et al., 2008; Morris, 1993) was used for global staging. 3) The Geriatric Depression Scale (GDS-30; Barreto, Leuschner, Santos, & Sobral, 2008; Yesavage et al., 1982) was used to exclude severe depression.

These auxiliary exams were used to support diagnoses of a multidisciplinary team headed by a board certified neurologist, based on international consensus diagnostic criteria. The MCI group included patients classified as “amnestic” (single or multi-domain) (Petersen, 2007) and was selected according to Petersen’s criteria (Albert et al., 2011; Petersen, 2004): 1) A subjective complaint of memory decline (reported by the subject or an informant); 2) Objective memory impairment (defined as scores on standard memory tests >1.5 SD below age/education adjusted norms) with or without deficits in other cognitive domains; 3) Normal general cognition indicated by normal scores on the MMSE and ADAS-Cog; 4) Largely normal daily life activities; 5) Absence of dementia (CDR = 0.5). The mean age of aMCI subjects was 69.8 years (SD = 7.88; range

= 52 – 80); their mean educational level was 6.6 years (SD = 4.55; range = 2 – 17). MMSE scores ranged between 22 and 30, with a mean of 26.95 (SD = 2.39).

The criteria for the diagnosis of AD were those in the Diagnostic and Statistical Manual of Mental Disorders – fourth edition (DSM-IV-TR; American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA; McKhann et al., 1984, 2011). The AD group only included patients with mild severity (CDR = 1 and MMSE ≥ 17 points). Moreover, to be eligible for this particular study, patients had to be stable, without acute significant events or recent or in-progress changes in medication. Other exclusion criteria were: Neurological/psychiatric conditions other than aMCI or AD; CT or MRI demonstration of significant vascular disorder (large cortico-subcortical infarct; extensive subcortical white matter lesions (> 25%); uni- or bilateral thalamic lacunes; lacunes in head of caudate nucleus; more than 2 lacunes (Román et al., 1993). The mean age for AD subjects was 73.89 years (SD = 6.97; range = 57 – 83); their mean educational level was 8 years (SD = 4.52; range = 3 – 17). MMSE scores ranged between 17 and 26, with a mean of 21.56 (SD = 2.89).

The two groups did not differ on demographical variables: age [t (36) = -1.686, p= .101], educational level (U = 140.50, p = .251), and gender [χ^2 (1) = 3.789, p = .052]. Performance on the MMSE, as expected, was worse for AD patients compared to aMCI subjects (U = 25.50; p <.001).

The same experimental research protocol was used for all subjects. Informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of our local ethics committee.

Procedure

- Selective Reminding Test (SRT)

In a first session, subjects performed the Portuguese adapted version of the SRT Afonso, 2010; Buschke, 1973). For Trial 1, subjects read a list of 12 unrelated words presented one at a time on index cards at 5 second intervals. Mispronunciations are corrected by the examiner. Immediately after reading all the words, subjects are given 120" to recall as many words as possible, in any order. Subsequent learning trials (total

of 12) involve the selective presentation of only those items not recalled on the immediately preceding trial. The subject is asked to verbally repeat them. A cued-recall trial is presented after the last selective reminding trial, which is defined as the 3rd consecutive trial on which all 12 words are recalled (up to 12 trials). For cueing in the SRT, the first two or three letters of each word are presented on an index card, and the subject is asked to recall the corresponding word from the list. Following the cued-recall trial, a multiple-choice recognition trial is presented. The subjects are not forewarned of a delayed recall trial, given 30 minutes after the multiple-choice recognition trial.

Of the possible variables that can be computed, we selected: 1) the total of immediately recalled words across trials (SRT Total IR), 2) the total of words recalled after the 30 minute interval (SRT Total DR – delayed recall), 3) long-term storage (LTS – words recalled twice in a row, assumed to be in long-term/permanent storage from that point on), and 4) short-term storage (STS – the remaining words not in LTS).

- Free and Cued Selective Reminding Test (FCSRT)

Subjects were then given, in a second moment, the Portuguese version of the FCSRT (Buschke, 1984; Grober & Buschke, 1987; Lemos, Martins, Simões, & Santana, 2012). Materials and instruction of the FCSRT were provided to our group by the original author (Buschke's FCSRT. Copyright, 2002. Albert Einstein College of Medicine of Yeshiva University, New York). Sixteen items are to be learned. The 16 items to be learned are presented four at a time on a card, distributed in four quadrants, one item per quadrant. The test starts by asking subjects to identify words in response to a unique category cue, each one. The subject is asked to search each card and point to and name aloud each item after its semantic cue was aurally presented. During this procedure, the subject is informed to learn the 16 words. Next, there are three recall trials, each preceded by 20 seconds of counting backward to prevent recall from short-term memory. Each recall trial consists of two parts. First, each subject is given up to 120" to recall as many items as possible. Next, aurally presented category cues were provided for items not retrieved in *free* recall. If subjects failed to retrieve the item with the category cue, they were reminded by presenting the cue and the item together. The sum of *free* and *cued* recall gives a measure of total recall (Immediate

Recall - IR). The same recall procedure (free and cued) is done after a 30 minute interval (Delayed Recall - DR). The selected measures to be analysed within the FCSRT were the total of immediately words recalled across the 3 trials (sum of the *free* and *cued* recalls - FCSRT Total IR), as well as the total of words recalled on delayed trials (sum of the *free* and *cued* recalls - FCSRT Total DR).

Statistical analysis

Based on the methodology described by Berres, Zehnder, Bläsi, and Monsch (2008), all raw scores were transformed into demographically adjusted z-scores for comparisons of performance between the two groups, on both tests (SRT - Afonso, 2010; FCSRT – (Lemos, Simões, Santiago, & Santana, 2015). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 19.0) (IBM SPSS, Inc., Chicago, IL). Statistical significance was set at $p<.05$. To determine whether the *z*-scores of the tests variables were significantly different between the two groups, we performed independent two-sample *t*-tests. Cronbach's alpha was used as an index of internal consistency, independently for each test. Convergent validity was assessed with Spearman's correlation coefficients between the total immediate recall (IR) and the total delayed recall (DR) of both SRT and FCSRT.

To compare recall from LTS between tests, a measure of consistent retrieval among the three common learning trials was computed for each patient, as follows: the number of words that were recalled on two successive trials without reminding (SRT) or cueing (FCSRT) was considered the consistent recall score.

To account for the fact that the list length and the number of trials differs between the SRT and the FCSRT, the number of items recalled during free recall was divided by the total number of items, yielding a percentage of items recalled (PIR-IR – immediate recall), on the first three trials. The same procedure was used for the delayed recall (DR) – percentage of items recalled (PIR-DR).

A series of binary logistic regressions, using the enter method, were performed to assess the effect of the immediate and delayed PIR's of both the SRT and the FCSRT on the differentiation between aMCI and AD patients. A Linear Discriminant Analysis (LDA) classificatory model, with an enter method, was performed to determine which

measure better distinguished the two groups. Equal a priori classification probabilities were used for LDA to avoid biases from the data sets.

Results

The means, standard deviations, and ranges of the z-scores of the selected SRT and FCSRT variables are presented in Table 5.1. *P*-values of independent two-sample *t*-test (see Table 5.1) revealed that AD patients performed significantly worse ($p<.001$) on all variables.

Table 5.1 Performance on the SRT and on the FCSRT (*z*-scores)

	aMCI (*n*=20)		AD (*n*=18)		*p*-value
	Mean (*SD*)	Range	Mean (*SD*)	Range	
SRT Total IR	-1.3 (0.97)	-3.23 to 0.44	-2.5 (0.83)	-4.33 to -0.67	.001
SRT Total DR	-1.34 (0.99)	-2.79 to 0.28	-2.566 (0.38)	-2.79 to -1.64	.001
SRT STS	1.41 (1.05)	-0.51 to 3.15	2.84 (0.93)	0.86 to 4.06	.001
SRT LTS	-1.41 (1.05)	-3.15 to 0.51	-2.97 (0.93)	-4.06 to -0.86	.001
FCSRT Total IR	-1.67 (2.22)	-6.33 to 1.10	-5.31 (0.94)	-6.87 to -3.43	.001
FCSRT Total DR	-1.88 (2.3)	-6.09 to 0.98	-5.76 (0.99)	-7.10 to -3.57	.001

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; SRT –Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall; STS – Short-term Storage; LTS – Long-term storage; FCSRT –Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall.

Psychometric properties

Cronbach's alpha was 0.929 for immediate recall and 0.802 for delayed recall for the SRT; it was 0.926 for immediate recall and 0.881 for delayed recall on the FCSRT, indicating overall good reliability of the tests.

The selected measures (Total IR and Total DR) for the two tests were significantly positively correlated (Total IR: $r = .638$, $p < .001$; Total DR: $r = .665$, $p < .001$), indicative of convergent validity.

Group differences

Figure 5.1 shows the mean PIR on each learning trial for the SRT and the FCSRT, for the two groups. The mean PIR revealed a significantly higher number of items recalled on FCSRT than SRT for each trial for the aMCI group (Trial 1: $Z=-3.922$; $p<.001$; Trial 2: $Z=$-

3.118; *p*=.002; Trial 3: *Z*=-3.455; *p*=.001). In contrast, for the AD group, no comparisons between the SRT and FCSRT reached significance; and there was a similar pattern of performance in the three learning trials for both tests.

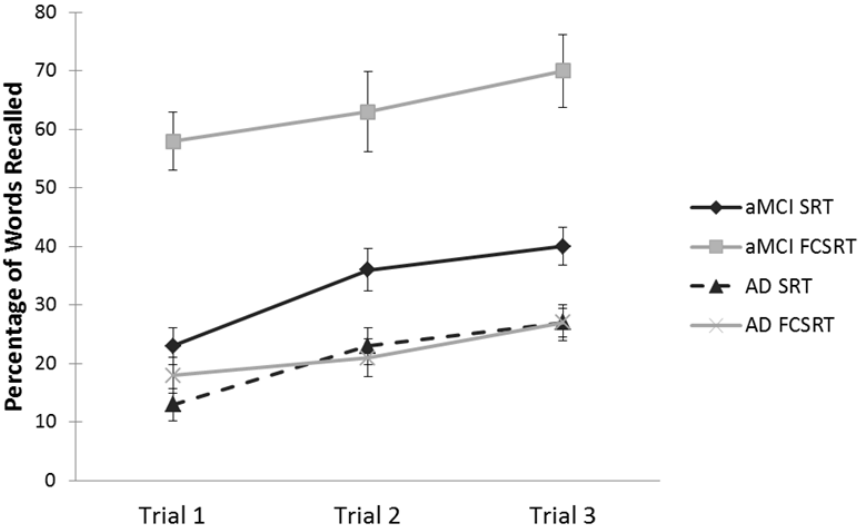

Figure 5.1 Percentage of words recalled (PIR) on the first three trials of the Selective Reminding Test (SRT) and the three trials of the Free and Cued Selective Reminding Test (FCSRT), between aMCI and AD. Error bars indicate standard errors.

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; SRT –Selective Reminding Test; FCSRT –Free and Cued Selective Reminding Test.

In SRT recall is tested immediately after reminding, allowing one to measure both short-term (STS) and long-term storages (LTS). The LTS comprises the words that did not demand reminding (assumed to be in LTS after being recalled twice in a row), whereas the STS consists of words which required reminding on the previous trial (difference between the total number of items and the words of LTS). Unlike SRT, recall in FCSRT reflects only LTS, as the 20 second of interference prevents recall from STS.

Figure 5.2 shows the mean percentage of consistent retrieval on the SRT and the FCSRT for trials 1 and 2; and 2 and 3, between the two groups. The mean PIR for the aMCI group revealed a significantly higher number of items recalled on FCSRT than SRT on each trial (Trial 1: *Z*=-3.922; *p*<.001; Trial 2: *Z*=-3.118; *p*=.002; Trial 3: *Z*=-3.455; *p* =.001). In contrast, for the AD group, none of the comparisons reached significance. That is, again, we found a similar pattern of performance across the three learning trials on both tests for the AD group, in contrast to the superior performance of the aMCI group on the FCSRT compared to the SRT.

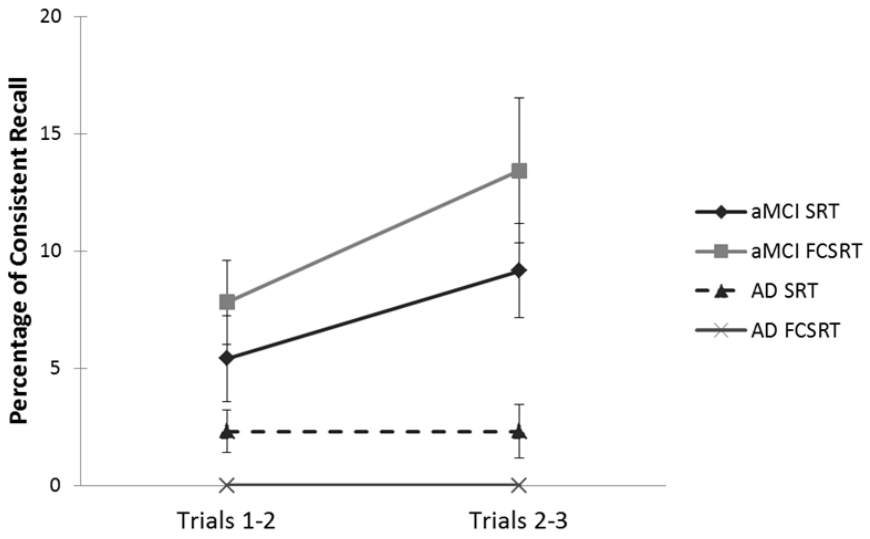

Figure 5.2 Percentage of consistent retrieval for trials 1 and 2, and 2 and 3 on the Selective Reminding Test (SRT) and the Free and Cued Selective Reminding Test (FCSRT), between aMCI and AD. Error bars indicate standard errors.

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; SRT –Selective Reminding Test; FCSRT –Free and Cued Selective Reminding Test.

The delayed mean PIR revealed a significantly higher number of items recalled on FCSRT than SRT on both groups (aMCI: Z =-3.400; p =.001; AD: Z =-3.006; p =.003).

When analyzing the performance on the total immediate (sum of the three learning trials), and delayed PIR's of both the SRT and the FCSRT, a significant difference was found between aMCI and AD patients (.05 < p <.001) (Table 5.2). The AD patients had worse performance than the aMCI group.

Table 5.2 Total percentage of words recalled between the two clinical groups on the SRT and on the FCSRT

	aMCI (*n*=20)		AD (*n*=18)		
	Mean % (*SD*)	Range	Mean % (*SD*)	Range	*p*-value
SRT PIR-IR	33.06 (13.27)	8.33 to 52.78	21.14 (9.86)	8.33 to 47.22	.004
SRT PIR-DR	30.83 (21.48)	0 to 66.67	5.09 (8.15)	0 to 25	.001
FCSRT PIR-IR	63.96 (25.56)	10.42 to 95.83	22.11 (10.77)	4.17 to 43.75	.001
FCSRT PIR-DR	64.69 (28.48)	12.50 to 100	16.67 (12.31)	0 to 43.75	.001

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; SRT –Selective Reminding Test; FCSRT –Free and Cued Selective Reminding Test; PIR-Percentage of Items Recalled; IR – Immediate Recall; DR – Delayed Recall.

Logistic regression revealed a significant effect on both recalls of the FCSRT [$B_{FCSRT\ PIR-IR} = -.095;\ X^2_{wald}(1) = 8.057;\ p = .005; OR = .910;$ $B_{FCSRT\ PIR-DR} = -.070;\ X^2_{wald}(1) = 6.702;\ p = .010; OR = .933$].

All measures were analyzed independently, as predictor variables, to highlight their relative contribution in discriminating the two groups, through a Linear Discriminant Analysis (LDA). All Wilks' lambdas were significant at *p*<.05. The SRT PIR-IR (λ Wilks =.788; $\chi^2(1)$ = 8.454; *p*=.004; RCanonical =.460) revealed an accuracy of 65.8% in classifying the subjects; while the FCSRT PIR-IR (λ Wilks =.464; $\chi^2(1)$ = 27.232; *p*<.001; RCanonical =.732) was the predictor with higher accuracy (86.8%) in the subjects classification; the SRT PIR-DR (λ Wilks =.612; $\chi^2(1)$ = 17.441; *p*<.001; RCanonical =.623) had an accuracy of 81.6% in discriminating the groups; and the FCSRT PIR-DR (λ Wilks =.452; $\chi^2(1)$ = 28.221; *p*<.001; RCanonical =.741) revealed an accuracy of 84.2% in the subjects classification (Table 5.3).

Table 5.3 Classification results of the SRT and the FCSRT

			Predicted Group Membership	aMCI (*n*=20)	AD (*n*=18)
PIR - IR	SRT	Count (%)	aMCI	13 (65)	7 (35)
			AD	6 (33.3)	12 (66.7)
	FCSRT	Count (%)	aMCI	16 (80)	4 (20)
			AD	1 (5.6)	17 (94.4)
PIR - DR	SRT	Count (%)	aMCI	14 (70)	6 (30)
			AD	1 (5.6)	17 (94.4)
	FCSRT	Count (%)	aMCI	16 (80)	4 (20)
			AD	2 (11.1)	16 (88.9)

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; PIR-Percentage of Items Recalled; IR – Immediate Recall; DR – Delayed Recall; SRT –Selective Reminding Test; FCSRT –Free and Cued Selective Reminding Test.

Discussion

The aim of this research was to compare the SRT and the FCSRT in distinguishing aMCI from AD. We compared the performance of aMCI and AD patients on the two tests, analysing their properties and diagnostic accuracy.

Both tests showed different levels of impairment in the aMCI and AD groups.

As expected AD patients performed significantly worse than aMCI subjects on both memory tests. Psychometrically, both tests had good internal reliability. Also, the variables selected from the two tests (total immediate recall and total delayed recall) were significantly positively correlated, indicating convergent validity. To eliminate differences stemming from different list length and number of trials on the SRT and FCSRT, we converted the raw scores to percentages, for immediate and delayed recall. For the aMCI patients, the percentage of items recalled across the three learning trials was significantly higher for FCSRT than SRT: More items were retrieved, showing the benefit of category cues in the FCSRT for the aMCI group, compared to the mere selective reminding in the SRT. In contrast, for the AD group, the pattern of performance was similar across the trials on both FCSRT and SRT. The data for consistently retrieved words yielded similar results: A significantly higher number of items was recalled on FCSRT than SRT for the aMCI group, whereas AD patients' did not differ on FCSRT versus SRT. For the delayed trial, on both groups, significantly more items were recalled on FCSRT compared to SRT.

For the SRT, the delayed recall (81.6%) enabled a higher accuracy of classification than the immediate recall (65.8%), whereas, for the FCSRT, the difference between classification accuracy was very small (FCSRT PIR-IR: 86.8%; FCSRT PIR-DR: 84.2%). We believe that while the FCSRT benefits aMCI patients during learning - their learning trials are better than on SRT - that benefit is not seen with AD patients, presumably because their semantic processing is impaired. Both sets of patients did better on delayed recall on the FCSRT than on SRT, except with regards to accuracy. We did not, on delayed recall, find the differential benefit of the FCSRT over the SRT for aMCI subjects compared to AD subjects. Thus, it appears that the AD group benefitted from the repetition involved in the learning phase of the SRT (total of 12 trials), which justifies the superior accuracy found in the delayed recall. While the semantic cueing plays an effective role during learning, regardless of the delayed recall, memory tests of unrelated list of words, such as the SRT, seems to require extra learning trials to reach higher values of accuracy at the level of delayed recall.

Our results suggest that the reminding paradigms that underlie both the SRT and the FCSRT are useful in characterizing the memory impairment found in aMCI and AD

patients. However, the results also suggest that the FCSRT, with its category cueing procedure, yields better accuracy in distinguishing between aMCI and AD. As noted earlier, the FCSRT procedure supports and fosters both attention and semantic cognitive processing in the learning process. It is also used in the retrieval phase, where the category cue is presented for the missed item. It differs in this regard from the SRT, where subjects are merely selectively reminded of the items that were not recalled on the previous trial, by re-presenting them. Some authors have pointed out that mere repetition facilitates new learning (Hayman, Macdonald, & Tulving, 1993); others have stressed that new information is encoded in episodic memory through semantic memory - that semantic processing in the encoding phase facilitates learning, and, consequently, retrieval of stored information (Tulving & Osler, 1968; Tulving & Thomson, 1973). We found this in the present study of individuals with memory impairment: The use of semantic cues (FCSRT) improved subsequent recall more than just repeating the items not retrieved previously (SRT). The procedure - the method of reminding in FCSRT - not only improved recall in comparison to SRT procedures, but also yielded better characterization of the process of AD spectrum memory impairment. The superiority of the FCSRT has been previously reported in differentiating AD patients from individuals in other groups, e.g., healthy controls, and patients with other dementias (Buschke et al., 1997; Grober, Hall, Sanders, & Lipton, 2008; Grober et al., 2010). That led the International Working Group on Alzheimer's disease (Dubois et al., 2007) to suggest the use of the FCSRT to objectively assess the memory impairment of these patients. Grober et al. (1997) also found the FCSRT more efficient in promoting learning and memory than the SRT in normal aging: twice as many words were retrieved from long-term memory in the FCSRT, suggesting that the improvement in free recall was due to the procedure - the method of reminding involved in the FCSRT.

Our study is consistent with prior research indicating that different memory test paradigms and procedures may yield distinct patterns of performance. Regular word list tests demand reproduction of a list of unrelated words. They thus require an active effort to organize information both during encoding and retrieval. In contrast, tests with semantically organized material (such as the FCSRT) allow for more passive learning, and demand less active implementation of retrieval strategies (Perri, Fadda,

Caltagirone, & Carlesimo, 2013). We surmise that the structured paradigm that underlies the FCSRT, which supports attention and semantic processing, minimizes the effects of mild cognitive decline, resulting in a higher percentage of recalled words. We further surmise that this may also account for the superiority of the FCSRT in detecting demented patients. Demented patients may be sufficiently impaired that they are not able to use the supports the FCSRT provides, in contrast to those with mild cognitive decline, whose apparent memory difficulties may reflect a lack of use of semantically-based encoding strategies, rather than a true retention problem.

Limitations of our current study: We had a relatively small sample size. This gives us less confidence that the results will generalize to the broader population of aMCI and AD patients. We also did not have a control group and it would be desirable to compare controls, aMCI and AD individuals simultaneously, fully to characterize the continuum of memory dysfunction.

We believe our study shows that the paradigm of cued reminding that supports elements important to the encoding and retrieval conditions is superior to mere selective reminding without cueing. The FCSRT can also result in economy of time and effort. That may have the advantage of reducing patient fatigue in achieving learning, as it is more efficient than mere SRT: The three learning trials of the FCSRT were found to be adequate; they elicited more recalled words than the twelve trials that may be needed for the SRT. Of course, these results need to be confirmed in studies using larger samples. It will also be important to conduct studies that examine the correlation of performance on the tests with AD biomarkers. We suggest studies comparing memory tests that use different paradigms. Finally, we suggest the need for longitudinal studies, where aMCI subjects are followed over time, to better understand the accuracy of these instruments in predicting conversion to dementia.

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STUDY 6

The Free and Cued Selective Reminding Test and the Wechsler Memory Scale in discriminating Mild Cognitive Impairment from Alzheimer's disease

Adapted from: **Lemos, R.**, Cunha, C., Marôco, J., Afonso, A., Simões, M. R., & Santana, I. (2014). Free and Cued Selective Reminding Test is superior to the Wechsler Memory Scale in discriminating mild cognitive impairment from Alzheimer's disease. *Geriatrics & Gerontology International.* doi:10.1111/ggi.12374 [Epub ahead of print]

Abstract

The Logical Memory (LM) and the Verbal Paired Associative Learning (VPAL) are subtests from the Wechsler Memory Scale commonly used to characterize the memory deficit of amnestic Mild Cognitive Impairment (aMCI) and Alzheimer's disease (AD). The Free and Cued Selective Reminding Test (FCSRT) was suggested to assess the memory impairment of AD spectrum patients by the International Working Group on AD. In this study, we compared the properties of the tests and their accuracy in classifying aMCI and AD. A group of aMCI (n=85) and of AD (n=43) were included. The reliability and the validity of the three tests were analyzed.

AD patients revealed a significant pattern of worst impairment on all tests than aMCI. The FCSRT was able to classify more subjects as having memory impairment in the aMCI group rather than the WMS subtests. The FCSRT proved to be good in discriminating the two groups in both lower and higher educational levels, while the LM was more useful in higher educated subjects.

Although the instruments had good results, the FCSRT was more accurate in discriminating MCI from AD and less influenced by the educational level.

Introduction

Memory impairment is essential for the diagnosis of amnestic Mild Cognitive Impairment (aMCI; Petersen et al., 1999, 2001) and Alzheimer's disease (AD; American Psychiatric Association, 2000; McKhann et al., 1984, 2011), and a strong predictor of dementia's development (Dubois et al., 2007; Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999). A compromise of the episodic long-term memory is the characteristic profile of mild AD (Perri, Serra, Carlesimo, Caltagirone, & Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's Disease, 2007), since it reflects the early involvement of the hippocampus and its related structures. Moreover, these structures are critical in memory consolidation and tasks of delayed recall are particularly sensitive to hippocampal dysfunction. However, performance in delayed recall and consolidation also reflects the quality of learning, therefore paradigms that control and superimpose reinforcement to the encoding process may increase test acuity (Belleville, Sylvain-Roy, de Boysson, & Ménard, 2008; Buschke, Sliwinski, Kuslansky, & Lipton, 1997; Moulin, James, Freeman, & Jones, 2004; Wang & Zhou, 2002).

Standard criteria for the diagnosis of both aMCI and AD require an objective validation of the memory dysfunction (American Psychiatric Association, 2000; Dubois et al., 2007; McKhann et al., 1984, 2011; Petersen et al., 2001). Therefore, the test used to identify this memory impairment should be highly accurate (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994), and individual deviations must be concretely specified along with its cut-off values (Petersen, 2004a).

Valid and accurate neuropsychological tests must have good diagnostic classification properties. In terms of memory, a significant impairment in neuropsychological testing is essential to the diagnosis of both aMCI and AD (Dubois et al., 2007; Portet et al., 2006).

Despite the modifications on the operationalization of the MCI criteria (Jak et al., 2009; Petersen et al., 2009; Visser & Verhey, 2008; Winblad et al., 2004) no specific memory test was suggested for the diagnosis of aMCI. On the other hand, the International Working Group (Dubois et al., 2007, 2010) proposal for the early diagnosis of AD suggested the use of the Free and Cued Selective Reminding Test (FCSRT; Buschke,

1984; Grober & Buschke, 1987) to objectively assess the memory impairment of AD spectrum patients.

The FCSRT (Buschke, 1984) was designed to coordinate acquisition and retrieval by using the same cues to control learning and elicit effective cued recall. Moreover, this test provides a measurement of memory under conditions that control attention and cognitive processing, in order to obtain an assessment of memory unconfounded by normal age-related changes in cognition. The utility of this paradigm has been widely reported in AD (Brown & Storandt, 2000; Carlesimo, Perri, & Caltagirone, 2011; Grober & Kawas, 1997; Grober et al., 2008; Mahieux et al., 2009; Sarazin et al., 2010; Vogel, Mortensen, Gade, & Waldemar, 2007) and MCI (Ivanoiu et al., 2005; Saka, Mihci, Topcuoglu, & Balkan, 2006; Wagner et al., 2012). The similar profile of memory dysfunction has been described between MCI and AD (Petersen, 2004b; Petersen et al., 1999), and in MCI subjects with a higher risk of conversion to AD (Petersen, 2007; Sarazin et al., 2010). A poor performance on the FCSRT has also shown a high correlation with atrophy in the medial temporal lobe (Sánchez-Benavides et al., 2010; Sarazin et al., 2010), and was significantly associated with cerebrospinal fluid AD-biomarkers (Rami et al., 2011; Wagner et al., 2012).

The Wechsler Memory Scale (WMS; Wechsler, 1987), particularly the subtests Logical Memory (LM) and Verbal Paired Associative Learning (VPAL), have been widely used in the characterization of the memory deficit of both AD (Galvin, Fagan, Holtzman, Mintun, & Morris, 2010; Gould et al., 2005) and MCI (Guo, Zhao, Chen, Ding, & Hong, 2009; Rabin et al., 2009; Tremont, Miele, Smith, & Westervelt, 2010). Furthermore, performance on the WMS has been associated with a higher rate of conversion to AD as compared to other episodic memory tests (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Silva et al., 2012; Tierney et al., 1996). Moreover, the LM subtest is suggested for the assessment of memory by the Alzheimer's Disease Neuroimaging Initiative study (Crane et al., 2012; Kennedy, Schneider, Cutter, & Alzheimer's Disease Neuroimaging Initiative, 2012).

Even though the paradigms that underlie the FCSRT and the subtests of the WMS are different, some recent studies have proved the superiority of the FCSRT in predicting prodromal AD (Derby et al., 2013; Wagner et al., 2012).

In the present study we aimed at comparing the performance of aMCI and AD patients on the WMS-R subtests LM and VPAL and on the FCSRT. Our main goal was to determine which test is more accurate in classifying aMCI and AD.

Materials and methods

Participants

The study included 85 aMCI patients and 43 AD patients, recruited at Neurology Department of the Coimbra University Hospital. Diagnostic investigation included: standard biochemical laboratory tests, imaging studies (CT or MRI), SPECT and Apolipoprotein E allele genotyping. The aMCI group was selected according to Petersen's criteria (Albert et al., 2011; Petersen, 2004b) and included patients classified as "amnestic" (single or multi-domain) (Petersen, 2007). The standard criteria for the diagnosis of AD were the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000); and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA; McKhann et al., 1984, 2011). The AD group selected for this study only included patients with a global staging of mild dementia [Clinical Dementia Rating (CDR; Morris, 1993) = 1 and Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) ≥ 17 points]. Moreover, to be eligible we considered that patients had to be in a stable condition and we defined as exclusion criteria neurological/psychiatric conditions other than aMCI or AD, and CT/MRI demonstration of significant vascular burden (Román et al., 1993).

All subjects were submitted to the same experimental research protocol and performed both the WMS-R subtests and the FCSRT. Informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of our local ethics committee.

Procedure

A comprehensive neuropsychological assessment battery that included the following tests and scales was carried out:

The CDR (Garrett et al., 2008; Morris, 1993) as a global staging classificatory and independent of the other neuropsychological measures. Because comparisons

between the FCSRT and the WMS subtests are part of our main goal analysis, and in order to avoid an eventual diagnostic circularity that may bias the results interpretation, CDR was used as the major classificatory instrument, independent of the neuropsychological measures. Groups were classified as CDR = 0.5 to define MCI and CDR = 1.0 to define AD.

The Geriatric Depression Scale (GDS-30; Barreto, Leuschner, Santos, & Sobral, 2008; Yesavage et al., 1982) to exclude severe depression (score ≥ 20).

Cognitive instruments as the MMSE (Folstein et al., 1975; Guerreiro, Silva, et al., 2008), the Alzheimer Disease Assessment Scale-Cognitive (Guerreiro, Fonseca, Barreto, & Garcia, 2008; Mohs, Rosen, & Davis, 1983), and a comprehensive neuropsychological battery validated for the Portuguese population (Guerreiro, 1998; Silva et al., 2012) exploring memory and other cognitive domains. Tests of interest for the present study included: the LM (immediate - IR and delayed recalls - DR) and the VPAL (IR), both from the WMS.

The FCSRT [Buschke's FCSRT. Copyright, 2002. Albert Einstein College of Medicine of Yeshiva University, New York. (Buschke, 1984; Lemos, Martins, Simões, & Santana, 2012)] to assess verbal memory, under a semantic cued selective reminding paradigm. Category cues are provided for items not retrieved by free recall. If subjects fail to retrieve the item with the category cue, they are reminded by presenting the cue and the item together. The sum of free and cued recall gives a measure of total recall (IR). The same procedure of recalling (freely and cued) is done after a 30 minute interval (DR).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Inc., version 19.0, Chicago, IL). When data significantly deviated from normal distributions (verified using the Kolmogorov-Smirnov normality check and Levene homogeneity tests), we choose to apply non-parametric statistical methods. Results with $p<.05$ were considered statistically significant. Descriptive statistics were used for sample's characterization, and the Mann-Whitney test; the Pearson χ^2 test; and the independent two-sample *t*-test allowed the group comparisons. Cronbach's alpha was considered as an index of internal consistency and was measured

independently for each test. The convergent validity was assessed through Spearman's correlation coefficients between the WMS-R subtests and the FCSRT on both recalls.

The neuropsychological assessment was standardized according to the norms for the Portuguese population and impairment on the memory tests was defined as scores in the impaired range [aMCI: 1.5 SDs and AD: 2 SDs below age and education-adjusted mean on LM and VPAL (Guerreiro, 1998; Silva et al., 2012); FCSRT below standardized cut-offs (Lemos, Simões, Santiago, & Santana, 2015)], allowing a categorical subdivision of "normal" or "abnormal". The significance of accordance between these dichotomous classifications was carried out through the McNemar test.

The accuracy of the tests for the distinction between the diagnosis of aMCI and AD was assessed through the receiver operating characteristics (ROC) curve analysis implemented in MedCalc (version 12.7) (MedCalc Software, Acacialaan). The areas under the curve (AUC) can vary between 0.5 and 1, with larger AUC indicating better diagnostic accuracy. The optimal cut-off points for each measure of both the WMS-R subtests and the FCSRT that generated the highest Youden index were selected, thus indicating maximization of accuracy. For the analysis of the predictive value we calculated, for each cut-off point, the sensitivity, specificity, the positive predictive value (PPV), the negative predictive value (NPV), and the classification accuracy. The ROC curves were compared according to their AUC (DeLong, DeLong, & Clarke-Pearson, 1988).

A series of binary logistic regressions, using the Forward (conditional) method, were performed to assess the effect of the different memory tests and of the demographic characteristics (age, education and gender) on the differentiation between aMCI and AD patients.

Results

Sample characterization

Demographic and clinic characteristics of the population are shown in Table 6.1. No statistically differences were found on age [$t(126) = -1.173$, $p = .243$], educational level ($U = 1533.5$, $p = .124$), or gender [$\chi^2 (1) = .031$, $p = .859$] between the two groups.

As expected, a significant effect was found for MMSE (U =507, p <.001) as AD patients performed poorly.

Table 6.1 Demographic and clinic characteristics of the population

	aMCI (n=85)	AD (n=43)
Gender (m:f)	33:52	16:27
Age (years)	70.34 (0.84)	72.07 (1.23)
Education Level (years)	6.81 (0.49)	8.07 (0.75)
MMSE (score)	26.95 (0.42)	22.77 (0.50)*

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; MMSE – Mini-Mental State Examination.
Note: Data are expressed as mean (SEM).
Comparisons between aMCI-AD patients were carried out by independent two-sample sample *t*-test, Mann-Whitney or Pearson χ^2 test for non-homogenous variables, where:
*aMCI vs. AD: p <.05.

Psychometric properties

Within this analysis the Cronbach's alpha confirmed an overall good reliability of the tests, for the total sample: LM (IR: 0.840; DR: 0.851), VPAL (0.867), FCSRT (IR: 0.896; DR: 0.873).

The recalls of the tests were significantly and positively correlated which is indicative of convergent validity (IR: LM and VPAL r =.592, p<.001; LM and FCSRT: r =.605, p<.001; VPAL and FCSRT: r =.575, p<.001; DR: LM and FCSRT: r =.677, p<.001).

Group differences and diagnostic classification accuracy of the tests

AD patients had a worse performance, in all measures (p<.001) (Table 6.2).

Table 6.2 Performance on the tests

		aMCI (n=85)	AD (n=43)
LM	IR	5.95 (.31)	2.95 (.37)**
	DR	3.72 (.28)	.94 (.22)**
VPAL	IR	11.48 (.44)	8.34 (.56)**
FCSRT	IR	28.56 (1.20)	15.09 (1.50)**
	DR	9.12 (.50)	3.80 (.51)**

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; LM – Logical Memory; VPAL – Paired Associate Learning; FCSRT –Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall.
Note: Data are expressed as mean (SD).
Comparisons between aMCI-AD patients were carried out by the Mann-Whitney test for non-homogenous variables, where:
** aMCI vs. AD: p <.001.

The standardized performance (dichotomous classification) of the two samples on the WMS-R subtests and on the FCSRT was compared in order to determine which test was better in classifying the memory impairment. Table 6.3 presents the general frequency of the classification for each test.

Table 6.3 Frequency of the dichotomous classification on the tests

		aMCI (n=85)		AD (n=43)	
		Abnormal	Normal	Abnormal	Normal
LM	IR	25	75	81	19
	DR	54	46	98	2
VPAL	IR	6	94	44	56
FCSRT	IR	68	32	91	9
	DR	74	26	93	7

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; LM – Logical Memory; VPAL – Paired Associate Learning; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall.
Note: Data are expressed as percentage (%).

In terms of classification, the FCSRT categorized more subjects, mainly on the aMCI group, as having memory impairment than the WMS-R subtests. For AD's, the DR of the LM captured slightly more patients. Among all tests, the VPAL had a higher number of misclassifications, as more subjects were categorized as "normal" in terms of memory impairment.

Table 6.4 presents the cross-tabulation of the classification among all the tests (i.e, the frequency of one test in respect to another).

In this analysis, classification of subjects is compared between the tests, by means of comparing how many subjects are classified the same way or differently. For aMCI subjects the only comparison that had no significant difference was between the two recalls of the FCSRT; however there was an effective change in the classification of performance between the two recalls of LM, between LM and VPAL, and between the WMS-R subtests and FCSRT (both recalls). On the other hand, on AD patients, there were no differences in terms of classification among the LM and the FCSRT, nor between the two recalls of the FCSRT; still the two recalls of the LM subtest had differences among them, as had the VPAL subtest when compared with all the other tests.

Table 6.4 Cross-tabulation of the dichotomous classification among all the tests

	Test			LM		VPAL		FCSRT			
				DR		IR		IR		DR	
				Ab	N	Ab	N	Ab	N	Ab	N
aMCI (n=85)	LM	IR	Ab	95	5**	14	86**	90	10**	90	10**
			N	40	60	3	97	61	39	69	31
		DR	Ab			9	91**	87	13*	84	16*
			N			3	97	49	51	64	36
	VPAL	IR	Ab					100	0**	100	0**
			N					66	34	72,5	27,5
	FCSRT	IR	Ab							97	3 ^{NS}
			N							26	74
AD (n=43)	LM	IR	Ab	100	0*	48	52*	94	6 ^{NS}	97	3 ^{NS}
			N	88	12	25	75	75	25	75	25
		DR	Ab			45	55**	90	10 ^{NS}	93	7 ^{NS}
			N			0	100	100	0	100	0
	VPAL	IR	Ab					100	0**	100	0**
			N					82	18	86	14
	FCSRT	IR	Ab							97	3
			N							50	50 ^{NS}

Abbreviations: aMCI – amnestic Mild Cognitive Impairment; AD – Alzheimer's disease; LM – Logical Memory; VPAL – Paired Associate Learning; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall; Ab – Abnormal; N - Normal.
Note: Data are expressed as percentage (%).
Comparisons between classifications among tests were carried out by the McNemar test for related categorical variables, where:
*p<.05;
**p<.001;
NS – Non significant.

In order to evaluate the diagnostic accuracy of the tests, the ROC curves were performed: LM [IR - fair AUC of .786 (95% CI = .705 - .853), DR - good AUC of .812 (95% CI = .733 - .876)], VPAL had a fair AUC of.743 (95% CI = .657 - .817), FCSRT [IR: .819 (95% CI = .741 - .881), DR: .811 (95% CI = .733 - .875)]. No statistically differences were found between AUC's (DeLong et al., 1988) The optimal cut-off scores for maximum accuracy of each total recall measure are described in Table 6.5.

Table 6.5 Diagnostic classification accuracy of the tests

		Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	Classification accuracy
LM	IR	≤4	.786	77	75	75	77	76
	DR	≤2.5	.812	91	69	75	88	80
VPAL	IR	≤8.5	.734	69	75	73	71	72
FCSRT	IR	≤21	.819	77	74	75	76	76
	DR	≤8	.811	93	57	68	89	75

Abbreviations: LM – Logical Memory (maximum score =21.5); VPAL – Paired Associate Learning (maximum score =21); FCSRT –Free and Cued Selective Reminding Test; IR – Immediate Recall (maximum score =48); DR – Delayed Recall (maximum score =16); AUC – area under the operating characteristics curve; PPV - positive predictive value; NPV - negative predictive value.
Note1: Sensitivity, Specificity, PPV, NPV and Classification Accuracy values are expressed in percentage.
Note2: Cut-off values indicate the minimum score required for absence of signal.

In order to assess the test that better defined the likelihood of having AD, a series of binary logistic regression was performed. In this analysis demographic variables were included as covariates. Significant effects were found for LM DR, FCSRT IR, and education on the logit modelling the probability of being AD [($B_{LM\ DR} = -.434;\ X^2_{wald}(1) = 8.329;\ p = .004; OR = .648$), ($B_{FCSRT\ IR} = -.079;\ X^2_{wald}(1) = 6.988;\ p = .008; OR = .924$) and ($B_{education} = .128;\ X^2_{wald}(1) = 5.557;\ p = .018; OR = 1.137$)]. The other tests/recalls did not reach significance on the distinction between aMCI and AD, neither did age or gender.

Therefore, we divided the levels of education of the participants into two different groups (lower education group: ≤ 6 years of education and higher education group: > 6 years of education) in order to analyze the impact of the cognitive tests on the differentiation between aMCI and AD. A new series of binary logistic regression was performed for all the tests, on the differentiation between aMCI and AD. On the lower education group, the FCSRT IR was the only measure reaching significance ($B_{FCSRT\ IR} = -.120;\ X^2_{wald}(1) = 13.759;\ p < .001; OR = .887$), with the models showing an accuracy of 82% in the subjects classification; with a specificity of 91%, and a sensitivity of 58%. Furthermore, on the higher education group, significant effects were found both on the LM DR ($B_{LM\ DR} = -.531;\ X^2_{wald}(1) = 7.071;\ p = .008; OR = .588$) and on the FCSRT IR ($B_{FCSRT\ IR} = -.104;\ X^2_{wald}(1) = 4.745;\ p = .029; OR = .901$), with the models showing an accuracy of 76% in classification; with a specificity of 79%, and a sensitivity of 70%.

Discussion

The general purpose of this research was to compare the performance of aMCI and AD patients on the WMS-R subtests (LM and VPAL) and on the FCSRT. Our main goal was to determine which test was more accurate in classifying aMCI and AD. In order to achieve our proposal we analyzed the tests' properties by comparing the performance of aMCI and AD patients.

Overall, the tests revealed good psychometric properties with a good internal consistency, and were significantly and positively correlated indicating convergent validity.

When comparing the performance of both samples, the AD patients revealed a significant pattern of worst impairment on both recalls of all tests than aMCI, as expected.

In order to realize which test was better in classifying the memory impairment on the two groups, the standardized scoring was used to classify the performance in a dichotomous way ("abnormal" *versus* "normal"). The FCSRT was able to classify more subjects as having memory impairment in the aMCI group rather than the LM or the VPAL subtests. On the AD sample, the DR of the LM included slightly more patients with memory impairment than the other tests. The VPAL subtest had a higher number of misclassifications. When the classification of subjects is compared between tests, i.e. matching how many subjects are classified the same way or differently among the instruments, different results were found on aMCI and on AD patients. On aMCI subjects the only comparison that had no significant difference in the classification was between the two recalls of the FCSRT. Still, for AD patients, the lack of differences in terms of classification is more extended among the instruments and recalls. There were no differences of grouping among the LM and the FCSRT, nor between the two recalls of the FCSRT. The effective change in the classification performance between the different tests in aMCI patients might be the result of the different paradigms that underlie the tests, as they have a milder impairment in memory. As for AD patients, with a greater impact in memory performance, the impairment is extensive to almost all the tests thus resulting in a consistent classification among them. While to classify

the impairment of aMCI patients we may need to use different memory instruments, to capture the deficit of AD's a single episodic memory test may be enough.

When comparing the diagnostic accuracy of the tests in discriminating between aMCI and AD patients, the ROC curves confirmed that the VPAL subtest is the less accurate in discriminating the two pathological groups. The DR of both the LM and FCSRT was more sensitive on discriminating aMCI from AD patients, but were less specific, while the IR had similar values of accuracy.

Moreover, the educational level showed to greatly influence the patients' discrimination, along with the DR of the LM and the IR of the FCSRT. Several studies have been showing that education has a great impact on the cerebral organization of cognitive skills and on the consequent performance on neuropsychological instruments (Ardila, Ostrosky-Solis, Rosselli, & Gómez, 2000; Jefferson et al., 2011). Therefore, the levels of education of the participants were divided into lower education group and higher education group to analyze the impact of the cognitive tests on the differentiation between aMCI and AD. The results showed that while the FCSRT (IR) was good to discriminate aMCI from AD patients in both groups, the LM (DR) was only useful to differentiate the two samples in the higher educated group. This is an important issue for countries with a significant percentage of low educated elders, like Portugal.

The LM test requires more attention, greater learning ability, and better language comprehension, as it provides a more specific examination of the episodic memory system (closely resembling everyday memory), as well as how language affects the memory system (Lezak, Howieson, & Loring, 2004). Therefore, it is reasonable to assume that lower education adults have less ability to remember and to describe everyday speech than higher education adults (Baek et al., 2011). Nevertheless, in FCSRT (Buschke, 1984) the influence of language should be restricted to the semantics of words, since it has proved to be independent of education effects (Grober, Lipton, Hall, & Crystal, 2000; Lemos et al., 2015).

Previous studies have showed the high discriminative validity of the FCSRT for dementia (Grober et al., 2000; Sánchez-Benavides et al., 2010), its superiority, related to LM, to discriminate aMCI from AD (Wagner et al., 2012), and its better predictive

value, in comparison to LM, for identifying individuals with memory complaints who will develop AD (Derby et al., 2013).

A weakness of this study is the sample size; ideally these results would be confirmed in a larger population. Other limitations of the present study were that it was based in standardized scoring and that it focused only on neuropsychological data and other biomarkers were not considered.

In sum, the present study results suggest that the VPAL subtest of the WMS-R does not qualify for the distinction of the memory impairment between aMCI and AD patients. Although the LM subtest of the WMS-R and the FCSRT proved to be accurate in discriminating the two groups, the FCSRT may be preferred as it proved to be independent of education effects and can be used in patients of lower and higher education thresholds.

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STUDY 7

The Free and Cued Selective Reminding Test distinguishes Alzheimer's disease from Frontotemporal Dementia

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Abstract

Memory impairment is often present in frontotemporal dementia (FTD) as a result of an inefficient use of learning strategies, sometimes leading to a misdiagnosis of Alzheimer's disease (AD). The Free and Cued Selective Reminding Test (FCSRT) is a memory test that controls attention and acquisition, by providing category cues in the learning process. The main goal of this study was to show the usefulness of the FCSRT in the distinction between behavioral (bv-) FTD and AD. Three matched subgroups of participants were considered: bv-FTD (n=32), AD (n=32), and a control group of healthy adults (n=32). Results proved that while AD patients exhibited an overall impairment in FCSRT, bv-FTD subjects showed to benefit more from the controlled learning through category cues. AD patients were 25 times more likely to have an impaired FCSRT. The FCSRT has shown its utility in the distinction between bv-FTD and AD, therefore increasing the diagnostic accuracy.

Introduction

Memory impairment is one of the most common complaints in the ageing population, and one of the most prevalent symptoms in patients with neurological disorders. In the field of dementia, a deficit in memory is significant as it may indicate the onset of Alzheimer's disease (AD) or it may pose as a risk factor for the subsequent development of AD (Dubois et al., 2007; Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999). An accurate diagnosis of AD is primarily based on an individual's performance on cognitive tests that are designed to detect memory impairment with high sensitivity and specificity (Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994). Moreover, the design of the test is very important as an accurate assessment of memory depends on the quality of learning, which is later reflected in an effective retrieval (Buschke, Sliwinski, Kuslansky, & Lipton, 1997). However, memory impairment is not necessarily evidence of an AD-related memory disorder and can be present in other conditions (e.g. Mild Cognitive Impairment, Depression). In patients with AD, the amnestic profile is typically characterized by poor learning and rapid memory decay over relatively short periods, often concurrent with damage to the mesio-temporal structures, such as the hippocampus (Squire, Stark, & Clark, 2004). Though there is some evidence that the memory consolidation problems often observed in patients with frontotemporal dementia (FTD) may also be linked to hippocampal atrophy (Lindberg et al., 2012; Muñoz-Ruiz et al., 2012; van de Pol et al., 2006), memory deficits in FTD are more typically reflective of poor organization and lack of efficient learning strategies. Thus, this results in a defective encoding of memory leading to an inability to implement effective retrieval strategies, due to an involvement of the prefrontal cortex (Blumenfeld & Ranganath, 2007). It is of clinical importance that deficits in encoding and storage processes that are so characteristic of AD can be distinguished from non-AD memory deficits that may have a different etiology. The accurate diagnosis of the episodic memory deficit, so often observed in AD patients, may be improved upon the use of test paradigms that provide information at encoding and retrieval – encoding specificity (Buschke et al., 1997). One way of controlling the acquisition and retrieval of information is to use the same cues to direct learning and produce effective cued recall. The encoding specificity procedure has shown to promote deeper engagement

with attentional and semantic processing in the encoding phase of memory, and it also controls the conditions of retrieval (Tulving & Osler, 1968; Tulving & Thomson, 1973). Furthermore, memory tests that require the ability to control acquisition and retrieval may optimize encoding specificity and thus may be more sensitive to the early signs of dementia (Buschke, 1987) than tests that use different paradigms.

The Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984) is a memory test that controls attention and cognitive processing, requiring subjects to search for items in response to their category cues, in the learning process. Moreover these same category cues are given later to participants in order to elicit the recall of the items not retrieved on the free recall trial, thus controlling acquisition and retrieval. Performance on the cued recall trial provides an estimate of the items that the subject has stored, and it has been shown that this estimate is minimally affected by guessing (Grober, Gitlin, Bang, & Buschke, 1992).

The utility of this cued selective reminding paradigm in the detection of AD-related memory dysfunction has been widely reported (Brown & Storandt, 2000; Grober, Buschke, Crystal, Bang, & Dresner, 1988; Grober & Buschke, 1987; Grober & Kawas, 1997; Grober, Hall, Lipton, et al., 2008; Ivanoiu et al., 2005; Vogel, Mortensen, Gade, & Waldemar, 2007). A poor performance on the FCSRT has also shown a high correlation with atrophy in the medial temporal lobe (Habert et al., 2011; Sánchez-Benavides et al., 2010; Sarazin et al., 2010), and was significantly associated with cerebrospinal fluid (CSF) biomarkers of AD, thereby supporting the accuracy potential of this paradigm in the early detection of AD (Rami et al., 2011; Wagner et al., 2012).

Furthermore, the potential of the FCSRT being used as a clinical diagnostic tool is bolstered by International Working Groups proposal (Dubois et al., 2007, 2010) that it could be used to assess memory in patients with suspected AD, given its high sensitivity (Grober, Hall, Sanders, & Lipton, 2008; Grober, Sanders, Hall, & Lipton, 2010).

FTD is the second most prevalent type of dementia and typically occurs much earlier in life than AD, overcoming Lewy Body dementia (Harvey, Skelton-Robinson, & Rossor, 2003) which is more common later on. The frontal or behavioral variant (bv-FTD) is the most common subtype accounting for approximately half of all FTD cases (Johnson et al., 2005; H Seelaar et al., 2008). Despite the heterogeneity in its clinical presentation,

bv-FTD is characterized by an insidious onset and a progressive decline that is marked by personality and/or behavioral changes (McKhann et al., 2001; Neary et al., 1998). The cognitive deficits of bv-FTD include impairments on executive function, attention, working memory, poor abstraction and difficulty in shifting mental set leading to perseverative tendencies (Neary et al., 1998; Weder, Aziz, Wilkins, & Tampi, 2007). It is also usually associated with bilateral symmetrical frontal and anterior temporal atrophy (Neary et al., 1998; Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011). Research has shown that the specific pattern of impairment of bv-FTD includes a relative sparing of memory and visuospatial functions in comparison to executive functions which are most commonly affected (Rascovsky et al., 2011). However, since impairment in executive functioning can limit effective learning in patients with bv-FTD, decrements in performance on conventional memory tests may result either from primary memory deficits or as a result of executive and attention deficits that hinder the use of learning and retrieval strategies (Wang & Miller, 2007). Therefore, the memory impaired profiles of patients with bv-FTD and AD may appear similar when memory is assessed with tests that place demands on frontal and/or attentional processes. In order to distinguish between these cognitive profiles, memory may be more accurately assessed with tests that overcome this limitation by controlling for attentional and executive processes. Consequently, bv-FTD patients should theoretically benefit from controlled learning procedures, like the category cueing FCSRT paradigm as this profile of memory impairment seems to be useful in the differentiation between bv-FTD and AD patients (Pasquier, Grymonprez, Lebert, & Van der Linden, 2001).

The main goal of this study was to show the utility of the FCSRT in the distinction between patients with bv-FTD and patients with AD, which may improve the accuracy of the diagnosis. Additionally, we aimed to characterize the memory impairment in patients with bv-FTD in comparison with AD patients. Our hypothesis was that the proposed cognitive mechanisms underlying these memory deficits would differentiate the two pathologies. This would be revealed as bv-FTD patients may benefit more from the controlled learning conditions which involves category cueing, than AD patients.

Methods

Participants

The total sample included 96 subjects divided into 3 subgroups: (i) 32 bv-FTD patients, (ii) 32 AD patients, and (iii) 32 cognitively healthy adults. The clinical study sample was recruited at the Neurology Department of the Coimbra University Hospital.

Study eligibility was restricted to patients with a comprehensive clinical, and neuropsychological evaluation, with a validated battery for the Portuguese population (Guerreiro, 1998), as well as a full investigation using biochemical, structural, and functional imaging (magnetic resonance imaging and single photon emission computed tomography, and/or positron emission tomography), which are essential to exclude other causes of dementia and to establish the clinical diagnosis.

The bv-FTD group included only patients with a diagnosis of the behavioral variant of FTD, established by a multidisciplinary team according to international criteria (Neary et al., 1998; Rascovsky et al., 2011). All the individuals who displayed the FTD-related Primary Progressive Aphasic syndromes (non-Fluent or semantic dementia) (Gorno-Tempini et al., 2011) or mixed clinical syndromes were excluded from the study. In order to better characterize the study group, all patients with bv-FTD were further evaluated using the following instruments: the Montreal Cognitive Assessment (Freitas, Simões, Alves, & Santana, 2012), the Frontal Assessment Battery (Dubois, Slachevsky, Litvan, & Pillon, 2000), the Maze-Tracing Task (Lezak, Howieson, & Loring, 2004), the Comprehensive Affect Testing System (Schaffer, Wisniewski, Dahdah, & Froming, 2006), the Neuropsychiatric Inventory (Cummings, Mega, Gray, Rosenberg-Thompson, Carusi, & Gornbein, 1994), and the Frontal Behavior Inventory (Kertesz, Nadkami, Davidson, & Thomas, 2000) (data not shown).

The AD group included patients diagnosed by a multidisciplinary team consensus based on international criteria for probable AD [(DSM-IV-TR; American Psychiatric Association, 2000); NINCDS-ADRDA; (McKhann et al., 1984, 2011)]. This group was recruited to match the patients with bv-FTD by gender, age, education level, and severity of cognitive decline (mild forms), as assessed by the Clinical Dementia Rating scale (CDR; Garrett et al., 2008; Morris, 1993). Besides the comprehensive clinical/neuropsychological standard evaluation, AD patients underwent the following

specific investigation: the Montreal Cognitive Assessment (Freitas et al., 2012), and the Alzheimer Disease Assessment Scale (Guerreiro, Fonseca, Barreto, & Garcia, 2008; Mohs, Rosen, & Davis, 1983).

The following patient exclusion criteria were established at the outset of the study: an unstable clinical condition, with significant comorbidities; high severity dementia (only patients with CDR≤1 and Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro, Silva, et al., 2008) ≥15 points were included in the study); recent pharmacotherapy changes; recent psychiatric comorbidity (clinically diagnosed within 6 months prior to the current neuropsychological evaluation); and significant motor, visual or auditory deficits, all of which may influence the cognitive assessment.

The control group comprised 32 cognitively healthy adults belonging to the local community (recruited among the patients' spouses, hospital or university staff, or their relatives), that were age, education, and gender matched to the patients. They had no history of neurological or psychiatric relevant condition, including alcohol or drugs abuse or head trauma, and no significant motor, visual or auditory deficits which could influence the neuropsychological performance. All control subjects were assessed using the following instruments: a complete sociodemographic questionnaire; an inventory of current clinical health status, past habits and medical history; the MMSE; the CDR; and the Geriatric Depression Scale (GDS-30; Barreto, Leuschner, Santos, & Sobral, 2008; Yesavage et al., 1982). All control subjects had normal MMSE scores (mean 29.06); were fully autonomous, according to the information obtained through a general practitioner and/or an informant; and had no Depression (depressive complaints were evaluated through a clinical interview and the GDS-30, and subjects with a score of 20 or more points were excluded).

The study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of our local ethics committee. After obtaining an Informed consent, all the participants, were submitted to the same experimental research protocol.

Demographic and clinical characteristics of the population are shown in Table 7.1.

Procedure

Subjects were assessed using the Portuguese version of the FCSRT (Lemos, Martins, Simões, & Santana, 2012). Materials and instructions of the FCSRT were provided by

the original author (Buschke's FCSRT. Copyright, 2002. Albert Einstein College of Medicine of Yeshiva University, New York). The FCSRT (Buschke, 1984; Grober & Buschke, 1987) is a multi-trial memory test that uses a "selective reminding" paradigm by presenting only the words not recalled, instead of all the to-be-remembered words, thus directing the subject's attention to the words not recalled on the previous trial.

The test starts by asking subjects to identify words or pictures in response to a unique category cue. The 16 items to be learned are presented four at a time on a card, distributed by one word per quadrant. The subject is asked to search each card and point to and name aloud each item after its semantic cue was aurally presented. During this procedure, the subject is informed to learn the 16 words. There are three recall trials, each preceded by 20 seconds of counting backward to prevent recall from short-term memory. Each recall trial consisted of two parts. First, each subject had up to two minutes to freely recall as many items as possible. Next, aurally presented category cues were provided for items not retrieved by *free* immediate recall (Free IR). If subjects failed to retrieve the item with the category cue, they were reminded by presenting the cue and the item together (Cued IR). The sum of *free* and *cued* recall gives a measure of *total* immediate recall (Total IR). The same procedure of recalling (freely and cued) is done after a 30 minute interval, during which subjects are required to perform non-verbal tasks (Delayed Recall – DR), allowing the measure of the Free DR, Cued DR, Total DR). A percentage of retention was also computed, by comparing the total number of items recalled freely and on delayed recall to the total of items (free and cued) recalled on the third learning trial.

Besides the FCSRT, other neuropsychological tests were performed in order to attain other cognitive functions and evaluate the different performance between the two pathological groups: the Digit Span (Forward and Backward recall versions) of the WAIS-III (Wechsler, 2008) to assess immediate and working memory; the Trail Making Test (A and B) (Partington & Leiter, 1949) to measure speed of attention, working memory, sequencing and mental flexibility; the semantic verbal fluency task to evaluate the spontaneous production of words (food and animals) (Garcia, 1984); and the Brief Visuospatial Memory Test-Revised (BVMT- R; Benedict, 1997) as a measure of both visuospatial ability (copy) and visual memory (immediate and delayed recalls, learning and retention).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 19.0) (IBM SPSS, Inc., Chicago, IL). When data significantly deviated from normal distributions (verified using the Shapiro-Wilk normality check and Levene homogeneity tests) we did therefore choose to apply non-parametric statistical methods. Results with $p<.05$ were considered statistically significant. Descriptive statistics were used for sample's characterization; comparisons between means were performed with the use of the general linear model [one-way analysis of variance (ANOVA)] with post-hoc Tukey for multiple comparisons or the Kruskal-Wallis one-way ANOVA for k samples with pairwise comparisons with adjusted *p* value. The χ^2 test was used for comparisons between categorical variables. Cronbach's alpha reliability coefficient was considered as an index of internal consistency, and analyzed separately for the immediate and delayed recalls. Non-parametric Wilcoxon test was used to compare the performance between the learning trials among each group.

A logistic regression model was fit to the data with impairment on both total immediate and total delayed recalls of the FCSRT as the outcome, and dementia subtype was a significant predictor in order to determine the sensitivity and the specificity of the FCSRT measures for distinguishing AD from bv-FTD.

Results

Sample characterization

Demographical and clinical characteristics of the population are shown in Table 7.1. No statistically significant differences were found on age [$F(2,93) = .280$, $p = .756$], educational level (χ^2_{KW} (2) =.115, p =.944), or gender [χ^2 (2) = 2.248, p = .325] between the three groups.

As expected, a significant effect was found for the MMSE performance (χ^2_{KW} (2) =58.427, p =.000) among the three groups. Therefore, multiple comparisons revealed that both bv-FTD (p =.05) and AD (p <.001) performed poorly on the MMSE, when compared to control subjects and AD patients had a worst performance, when compared to bv-FTD subjects (p <.001).

Table 7.1. Demographical and clinical characteristics of the population

	Control subjects (n=32)	bv-FTD (n=32)	AD (n=32)
Gender (m:f)	22:10	22:10	17:15
Age (years)	68.59 (1.27)	68.56 (1.19)	69.72 (1.27)
Education Level (years)	7.06 (0.86)	6.97 (0.84)	6.91 (0.87)
MMSE (score)	29.06 (0.20)	26.88 (0.43)*	21.22 (0.70)*/†
CDR (score)	0 (0)	1 (0)	1 (0)

Abbreviations: bv-FTD – behavioral frontotemporal dementia; AD – Alzheimer's disease; MMSE – Mini-Mental State Examination; CDR – Clinical Dementia Rating
Note: Data are expressed as mean (SEM).
Comparisons between Controls- bv-FTD, Controls-AD and bv-FTD-AD patients were carried out by a one-way ANOVA with post-hoc Tukey tests, Kruskal-Wallis 1-way ANOVA for k samples with pairwise comparisons, or χ^2 test, where:
*Controls vs. bv-FTD: p <.05; Controls vs. AD: p <.001;
† bv-FTD vs. AD: p <.001.

Preliminary tests

Concerning the performance on the preliminary neuropsychological tests, main effects were found in all of them, except for the Forward Digit Span. The multiple comparison analysis showed that AD patients were impaired in all other measures, whereas the bv-FTD group performed significantly worse than controls on the Trail Making Test (p <.05), Verbal Fluencies (p <.05), BVMT recalls and learning (p <.001). Still, bv-FTD patients did not differ significantly from controls on the Backward Digit Span, BVMT-R copy and retention. The two clinical groups had a similar performance on the Backward Digit Span, Verbal Fluency (food) and BVMT-R learning (for details see Table 7.2).

Psychometric properties – internal consistency reliability of the FCSRT

Internal consistency reliability of the FCSRT was estimated using Cronbach's alpha. Within this analysis the Cronbach's alpha of the FCSRT as an index of internal consistency was .914 for the IR and .852 for the DR on the total study sample, confirming an overall good reliability of the test scores. This reliability coefficient was also computed for each clinical group [α (bv-FTD): IR = .813; DR = .667 and α (AD): IR = .799; DR = .862].

Table 7.2 Performance on the preliminary tests

	Controls (n=32)	bv-FTD (n=32)	AD (n=32)	χ^2_{KW}	*p* value
Digit Span (Forward)	6.78 (0.32)	6.09 (0.35)	5.91 (0.32)	4.366	NS
Digit Span (Backward)	4.19 (0.36)	3.16 (0.32)	2.84 (0.24)	7.804	=.02*
Trail Making Test A (time/sec.)	89.03 (7.48)	143.78 (16.18)	198.75 (14.50)	26.937	<.001**
Trail Making Test B (time/sec.)	213.81 (20.86)	374.34 (34.22)	544.97 (19.57)	41.723	<.001**
Verbal Fluency (food)	15.59 (0.82)	11.84 (0.73)	9.47 (0.58)	26.893	<.001[#]
Verbal Fluency (animals)	13.81 (0.88)	9.59 (0.75)	7.06 (0.51)	34.712	<.001**
BVMT-R Copy	11.66 (0.12)	11.13 (0.40)	9.44 (0.65)	12.603	=.002[†]
BVMT-R Total IR	16.53 (1.34)	7.06 (1.14)	2.91 (0.48)	51.011	<.001[§]
BVMT-R Learning	4.00 (0.42)	1.63 (0.30)	0.72 (0.21)	33.226	<.001[‡]
BVMT-R Total DR	7.00 (0.57)	3.03 (0.56)	0.38 (0.16)	57.924	<.001[¥]
BVMT-R Retention (%)	90.50 (2.72)	63.44 (7.42)	14.41 (5.13)	42.339	<.001[††]

Abbreviations: bv-FTD – behavioral frontotemporal dementia; AD – Alzheimer's disease; BVMT-R – Brief Visuospatial Memory Test-Revised; IR – Immediate Recall; DR – Delayed Recall
Note: Data are expressed as mean (SEM).
Comparisons between Controls- bv-FTD, Controls-AD and bv-FTD-AD patients were carried out by a Kruskal-Wallis 1-way ANOVA for k samples with pairwise comparisons, where:
* Controls vs. AD: $p < .05$.
**Controls vs. bv-FTD: $p < .05$; Controls vs. AD: $p < .001$; bv-FTD vs. AD: $p < .05$.
[#] Controls vs. bv-FTD: $p < .05$; Controls vs. AD: $p < .001$; bv-FTD vs. AD: NS.
[†] Controls vs. bv-FTD: NS; Controls vs. AD: $p < .05$; bv-FTD vs. AD: $p < .05$.
[§] Controls vs. bv-FTD: $p < .001$; Controls vs. AD: $p < .001$; bv-FTD vs. AD: $p < .05$.
‡ Controls vs. bv-FTD: $p < .001$; Controls vs. AD: $p < .001$; bv-FTD vs. AD: NS.
[¥] Controls vs. bv-FTD: $p < .001$; Controls vs. AD: $p < .001$; bv-FTD vs. AD: $p < .001$.
[††] Controls vs. bv-FTD: NS; Controls vs. AD: $p < .001$; bv-FTD vs. AD: $p < .001$.
NS = not significant ($p > .05$).

Group differences (FCSRT)

When analyzing the performance on the FCSRT selected measures (free, cued, total recalls, and retention), the bv-FTD and the AD groups were impaired relative to controls on the free and total recalls (p<.001); nevertheless, only the AD group was impaired on the two cued recalls (p<.001) and on the percentage of retention (p<.05). There was also a significant difference between the bv-FTD and AD patients in all the FCSRT selected measures (Table 7.3).

Table 7.3 Performance on the FCSRT

	Controls (n=32)	bv-FTD (n=32)	AD (n=32)	χ^2_{KW}	*p* value
FCSRT Free IR	21.84 (0.92)	12.94 (1.16)	3.41 (0.67)	64.157	<.001*
FCSRT Cued IR	17.41 (0.59)	13.63 (1.18)	7.72 (1.11)	28.902	<.001†
FCSRT Total IR	39.25 (0.94)	26.56 (2.18)	11.13 (1.61)	55.752	<.001*
FCSRT Free DR	8.72 (0.35)	4.28 (0.49)	0.72 (0.34)	65.618	<.001§
FCSRT Cued DR	5.34 (0.30)	4.09 (0.42)	2.03 (0.34)	29.242	<.001†
FCSRT Total DR	14.06 (0.30)	8.38 (0.77)	2.75 (0.55)	62.742	<.001‡
FCSRT Retention (%)	-36.72 (1.98)	-37.11 (2.92)	-23.24 (2.95)	14.835	=.001††

Abbreviations: bv-FTD – behavioral frontotemporal dementia; AD – Alzheimer's disease; FCSRT – Free and Cued Selective Reminding Test; IR – Immediate Recall; DR – Delayed Recall.
Note: Data are expressed as mean (SEM).
Comparisons between Controls- bv-FTD, Controls-AD and bv-FTD-AD patients were carried out by the Kruskal-Wallis 1-way ANOVA for k samples with pairwise comparisons, where:
*Controls vs. bv-FTD: p <.05; Controls vs. AD: p <.001; bv-FTD vs. AD: p <.001.
† Controls vs. bv-FTD: NS; Controls vs. AD: p <.001; bv-FTD vs. AD: p <.05.
§ Controls vs. bv-FTD: p <.001; Controls vs. AD: p <.001; bv-FTD vs. AD: p <.001.
‡ Controls vs. bv-FTD: p <.001; Controls vs. AD: p <.001; bv-FTD vs. AD: p <.05.
†† Controls vs. bv-FTD: NS; Controls vs. AD: p <.05; bv- FTD vs. AD: p <.05.
NS = not significant (p >.05).

The learning slopes (along the three trials) among the three groups are shown in Figure 7.1. Comparing the performance between the learning trials among each group, results showed a significant improvement on free recall, on both clinical groups, between trials 2 and 3 (bv-FTD: Z=-3.137; p=.002; AD: Z=-2.449; p<.05), but not between trials 1 and 2 (p>.05). The control group revealed an improvement between the three trials (Trials 2-1: Z=-3.704; p<.001; Trials 3-2: Z=-4.131; p<.001). In order to analyze the impact of cueing, the same comparisons were done for the total (free + cued) recalls along the three learning trials. Whereas the bv-FTD (Trials 2-1: Z=-3.423; p=.001; Trials 3-2: Z=-3.408; p=.001) and the control (Trials 2-1: Z=-4.610; p<.001; Trials 3-2: Z=-3.779; p<.001) groups showed a significant improvement between the three trials, the AD group only benefited from cueing between the third and second trials (Trials 2-1: Z=-.558; p>.05; Trials 3-2: Z=-3.567; p<.001).

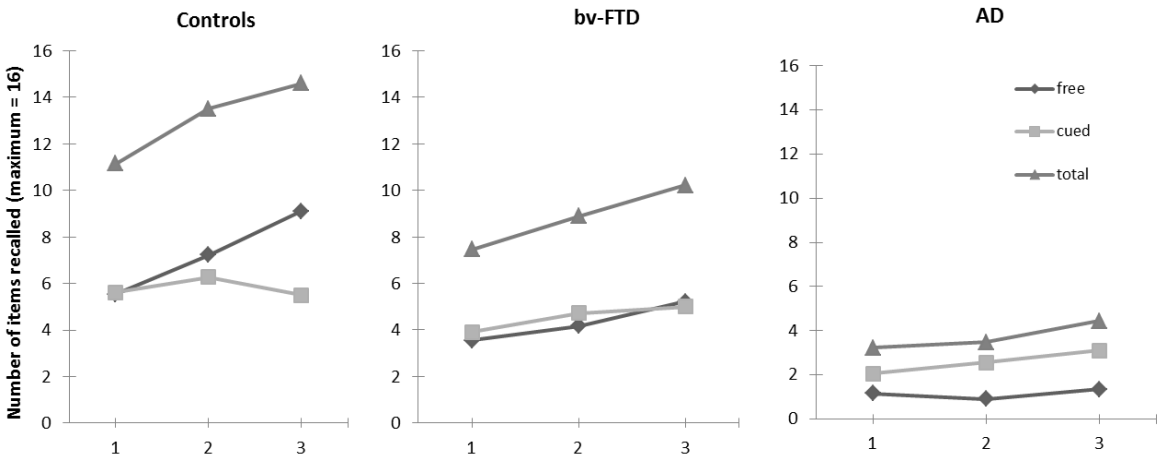

Figure 7.1. Free, cued and total recalls (mean) in the FCSRT along the first, second and third learning trials.
Abbreviations: bv-FTD – behavioral frontotemporal dementia; AD – Alzheimer's disease.

Established cut-off scores (Lemos, Simões, Santiago, & Santana, 2015) for AD were used to determine the sensitivity and the specificity of the total immediate and total delayed recalls of the FCSRT for patients with AD versus bv-FTD. A logistic regression model was fit to the data; impairment on both total immediate and total delayed recalls of the FCSRT were used as the outcome; dementia subtype was a significant predictor in order to determine the sensitivity and the specificity of the FCSRT measures for distinguishing AD from bv-FTD ($B_{Dementia\ Subtype} = 3.219$; $X^2_{wald}(1) = 15.542$; $p < .001; OR = 25.000$). The model showed an accuracy of 78.1% against a baseline value of 54.8% (i.e. when the classification is performed randomly) in the subjects' classification, with a specificity of 71.4%, and a sensitivity of 90.9%. Sixty-three percent (20/32) patients with bv-FTD had an intact FCSRT, whereas only six percent (2/32) of AD patients scored normally. Patients with AD were 25 times more likely to have impaired FCSRT than patients with bv-FTD.

Discussion

The main objective of this study was to show the utility of the FCSRT in distinguishing bv-FTD from AD patients. Furthermore, we aimed to contribute to the characterization of the memory impairment observed in patients with bv-FTD in comparison with AD patients.

The FCSRT showed an overall good reliability with high indexes of internal consistency for the immediate recall and for the delayed recall trials, in this sample of Portuguese participants.

Moreover, the FCSRT showed an accuracy of 78.1%, with 71.4% of specificity and 90.9% of sensitivity, allowing us to identify ninety-four percent of patients with AD and discard sixty-three percent of patients with bv-FTD, indicating that an impaired FCSRT performance emphasizes the significance of episodic memory deficits in patients with AD. Patients with AD were 25 times more likely to have impaired FCSRT performances than patients with bv-FTD.

Another aim of this study was to compare the pattern of memory impairment on FCSRT in patients with bv-FTD and AD. We observed that both groups were relatively impaired to the control group on the free and total (immediate and delayed) recalls trials. Furthermore, only the AD group showed impairment on the cued recall trial and on the percentage of items retained. Our initial hypothesis was that the mechanisms underlying the memory deficits observed in these groups would differentiate the two pathologies, as bv-FTD patients may benefit more from the controlled learning with the use of category cues, than AD patients. Our results confirmed that, although bv-FTD patients were impaired on the total recall trials, cueing was more efficient for patients with bv-FTD than AD. In addition, bv-FTD patients showed an impaired delayed recall but their ability to retain information was spared, i.e., when delayed recall performance was compared to performance on the third learning trial.

The slopes of the groups' performances were compared on free recall of the three learning trials. Our results showed that the control group performance improved incrementally over the three trials while both the clinical groups' improvement was restricted to just the second and third trials. The impact of cueing resulted, overall in a significant improvement over the three trials for both the bv-FTD and control groups. However, this effect was only observed between the second and third trials in the AD group. These results showed a pattern of impairment for the AD group independently of the recall (free or total); whereas the bv-FTD group appeared to benefit from cueing which was reflected in a marked improvement in the performance on the total recall trial. The concept of cueing, inherent in the design of the FCSRT, requires subjects to search for items in response to already given category cues in the learning process,

controlling for both attention and cognitive processing. This method of cueing showed an improvement of the retrieval ability in bv-FTD patients, which has not been observed with tests that employ other methods of cueing (Glosser, Gallo, Clark, & Grossman, 2002). It has been reported that learning and memory ability are based on the integrity of the temporal and frontal lobe regions of the brain. These are regions which may play different roles depending on the task demands and test characteristics. Much evidence suggests that basic learning and retrieval aspects of memory are supported by the medial temporal lobe. Specifically, it is well documented that the hippocampus plays a significant role in the formation and memorization of associations between novel non-related items (Squire, 1992). On the other hand, the frontal lobes have also been shown to be implicated in learning and memory processes, contributing to efficient working memory, conditional learning, and encoding strategies (Cummings & Miller, 2007). The FCSRT is a memory test that controls for attention and executive processing, by introducing category cues during the learning process. Additionally, the same cues are used to elicit recall of the items not retrieved on the free recall trial, and thereby control acquisition and retrieval.

Our study demonstrated memory impairment in patients within the early stages of bv-FTD. This is common in the early stages of the disease, sometimes leading to a misdiagnosis of AD (Wittenberg et al., 2008). In the FCSRT, free and cued recalls were poorer in bv-FTD patients than in controls, and free recall was as poorer in bv-FTD patients than in AD patients, which is consistent with the findings reported by Pasquier et al. (2001). Providing a semantic cue to bv-FTD patients showed a significant increase in recall performance, suggesting that there may be impairment in retrieval processes when encoding processes are controlled for. The rates of forgetting did not differ between bv-FTD patients and control subjects, which was assessed by comparing the retention percentages of the two groups, indicating that the bv-FTD group had a relatively intact storage processes. In sum, poor free and total recall performance rates, both in learning and after a delay, were observed in both dementia groups; low scores in cued recalls, and a lower rate of retention were representative of AD, while an improvement with category cueing and spared retained items were suggestive of bv-FTD. The design characteristics of memory test paradigms may account for the distinct pattern of performance of patients with different types of dementia. Regular

word list tests demand a reproduction of a list of unrelated words, thus requiring an active effort to organize information at both encoding and retrieval, however, tests with semantically organized material (such as story recall tests or the FCSRT) allow for more passive learning and implementation of less demanding retrieval strategies (Perri, Fadda, Caltagirone, & Carlesimo, 2013). Therefore, while AD patients are expected to be impaired on both paradigms, bv-FTD patients are more likely to have deficits on regular word list tests than tests which require the participant to organize semantic information (Pasquier et al., 2001; Perri et al., 2013), which is consistent with the findings from the present study. Concerning the performance on the neuropsychological tests that measure other cognitive functions, the bv-FTD group showed impairment on attention, working memory, and spontaneous production of words, and spared visuospatial ability and retention. These findings are congruent with the brain structures reported to be implicated in these abilities and often compromised in this disease. Comparison of the two clinical groups revealed that, although bv-FTD patients had better results than AD's on most neuropsychological measures, the two samples had similar performances on the Backward Digit Span, Verbal Fluency (food) and BVMT-R learning tasks. A general pattern of impairment for both bv-FTD and AD patients in the executive domain has already been reported by several authors, confirming that there was no difference of performances between these two groups (Gregory, Orrell, Sahakian, & Hodges, 1997; Hodges et al., 1999; Walker, Meares, Sachdev, & Brodaty, 2005). These findings reinforce the idea that executive functions, although expected to be impaired in cases of frontal lobe damage, should not be the only focus of attention in the differential diagnosis between AD and bv-FTD (Giovagnoli, Erbetta, Reati, & Bugiani, 2008). Nevertheless, executive measures that rely on both frontal (compromised in bv-FTD) and parietal (compromised in AD) regions comprise a similar pattern of performance in both disease groups. Thus frontally specific executive measures are expected to inform the diagnosis of bv-FTD and therefore, should be selected (Possin et al., 2013). Moreover, in our study, the main pattern of dissociation between bv-FTD and AD was the impairment of parieto-occipital related functions which seems to be exclusive to AD. Furthermore, information regarding aspects of social cognition including personality and/or behavioral disorders was taken into consideration during the diagnosis of bv-FTD.

An accurate differential diagnosis between AD and bv-FTD is of crucial importance. Given that FTD is the second cause of primary degenerative dementia and has overlapping symptoms with AD, a misdiagnosis can occur. Deficits in memory are common in FTD patients and may be overlooked due to a greater prominence of behavioral and/or personality disturbances. For these reasons, it is more informative to use memory tests that control for the learning deficit often observed in FTD patients so as to elicit the retrieval of stored information. This may aid to isolate the memory deficit more typical in AD patients and thereby increase the accuracy of a diagnosis. The FCSRT has shown these potentialities in the present study. However, future research would benefit by including other types of dementias in order to confirm the accuracy values of the FCSRT in informing a diagnosis for AD.

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The goal of this discussion is to briefly analyse the main results achieved during the FCSRT's work plan that was previously presented in the respective research papers (either published, or submitted for publication). We organized and divided this discussion chapter into the following topics: *Description of Chapter I* (*Transcultural adaptation*, *Psychometric validity and Clinical validity of the FCSRT); Highlights and limitations of these studies; Future outlook; and Conclusions*.

Description of Chapter I

The general purpose of this chapter was to explore, in a clinical perspective, the properties and validity of the FCSRT on a memory clinic basis for the AD spectrum early diagnosis, in Portugal. Our scientifical purpose was to contribute to the hot topic discussion concerning new proposals for the early diagnosis of AD (Dubois et al., 2007, Dubois et al.,2014 Albert et al.,2011). Our investigation was initiated soon after the publication of the IWG-1 framework criteria for AD (Dubois et al., 2007), which specifically suggest the use of cued recall measures, based on encoding specificity to assess the memory impairment of AD spectrum disorders, such as the FCSRT (Buschke, 1984; Grober & Buschke, 1987).

After the FCSRT transcultural adaptation process, we started a validation set of studies that tried to cover both psychometric and clinical validity in a memory clinic basis. According to the defined initial objectives we were especially interested in AD spectrum disorders (MCI and mild AD). A longitudinal study, i.e., prediction of conversion to AD, supported our baseline results regarding the FCSRT utility. We also included a group of behavioural variant of frontotemporal dementia (bv-FTD) patients with the purpose of isolating the amnestic syndrome of the hippocampal type as representative of typical-AD. All these points are in line, and corroborate, the arguments of the IWG-1 (Dubois et al., 2007) in favour of the use of the FCSRT in the objective assessment of memory in AD spectrum disorders.

By adapting and validating the FCSRT, we also contributed to the increase of Portuguese-adapted neuropsychological instruments' availability (in general) and to present a different paradigm of verbal memory evaluation (in particular).

Some of the studies reported here were not defined initially, but were projected during the progress of this work plan in order to respond to questions that have arisen in the meantime and to enrich and corroborate the achieved results. This argument applies to Studies 6 (Lemos, Cunha, et al., 2014), 5 (Lemos, Afonso, et al., 2015) and 3 (Lemos, Marôco, et al., 2015). In Study 6 (Lemos, Cunha, et al., 2014), we took advantage of the data acquired during the regular neuropsychological assessment through the use of the Battery of Lisbon for the Assessment of Dementia (BLAD; Guerreiro, 1998) that includes the Logical Memory (LM) and Verbal Paired Associative Learning (VPAL) subtests from the Wechsler Memory Scale (WMS). This comprehensive neuropsychological battery is used to characterize the cognitive profile of patients and therefore helps to reach a differential diagnosis. Study 5 (Lemos, Afonso, et al., 2015) was developed taking advantage of a masters' Psychology student work plan. As such, the patients included in that project, that have performed the SRT (Afonso, 2010), were further assessed with the FCSRT. We designed this study in line with the previous work of Grober, Merling, Heimlich, and Lipton, (1997) that compared the performance on both the Selective Reminding Test (SRT) and the FCSRT in healthy aging, but adjusted it to pathological aging by means of discrimination between aMCI and AD patients. Study 3 (Lemos, Marôco, et al., 2015) was designed after Study 2 (Lemos, Simões, et al., 2014) but both comprise the same samples. The need for assessing the construct related validity of the FCSRT in the AD spectrum disorders has arisen after the publication of Study 2 (Lemos, Simões, et al., 2014), but it is our understanding that the two studies could have been developed together and converged in a complete construct and diagnostic validities study of the memory assessment of AD spectrum disorders throughout the use of the FCSRT.

Transcultural Adaptation

We started by adapting the FCSRT to the Portuguese population, as decribed in Study 1 (Lemos, Martins, Simões, & Santana, 2012), taking into account linguistic and cultural adequacy criteria. The principle required by the FCSRT authors (Buschke, 1984; Grober & Buschke, 1987) was followed, i.e., intermediate frequency words were selected within a semantic category present in the original version instead of a simple translation from English to Portuguese words. The semantic categories were selected

from a total of sixteen available in the original version. The other criteria used in the selection of words/items derived from linguistic characteristics of Portuguese language.

Moreover, we took into consideration the *International Test Commission (ITC) guidelines for translating and adapting tests*, specifically the test development and adaptation recommendation that insures that "the adaptation process takes full account of linguistic and cultural differences among the populations for whom adapted versions of the test or instrument are intended" (International Test Comission, 2005, p. 7). Whenever applicable, the Portuguese version sought to respect the equivalence to the FCSRT's original version, according to the model of Herdman, Fox-Rushby, and Badia (1998).

The FCSRT adaption constituted the first step of the present work plan, therefore essential to the following validity studies and accurate interpretation of its related results.

Psychometric Validity of the FCSRT

A complete analysis, in terms of the psychometric properties of an instrument, is a valuable advantage that results in an important contribution to outline a more systematic and comprehensive neuropsychological evaluation. This project includes studies of the psychometric properties: *internal consistency*, *concurrent* and *construct validities*.

In the case of the FCSRT, information on the psychometric properties of its paradigm is scarce in the literature and limited to the modified Grober-Buschke (GB) procedure (Grober, Ocepek-Welikson, & Teresi, 2009). The GB modified version differs from the FCSRT as it includes an immediate cued recall during the learning phase after the identification of a group of four items that are very often pictures rather than words.

Internal consistency: Cronbach's alpha coefficient was considered as an index of FCSRT's reliability and was analysed on both the immediate (IR) and delayed (DR) recalls. Results showed an overall good reliability of the test among all the studied samples, with values of 0.915 for the IR and 0.879 for the DR on the AD spectrum validation study (Study 2; *n*=271: 100 aMCI subjects, 70 AD patients and 101 control elders; Lemos, Simões, Santiago, & Santana, 2014) and 0.914 for the IR and 0.852 for

the DR on the FDT/AD comparison research (Study 7; *n*=96: 32 FTD subjects, 32 AD patients and 32 matched controls; Lemos, Duro, Simões, & Santana, 2014). Moreover, in Study 6 (*n*=128: 85 aMCI subjects, and 43 AD patients; Lemos, Cunha, et al., 2014) we found an overall good reliability of the FCSRT (IR: 0.896; DR: 0.873), and the WMS subtests [LM (IR: 0.840; DR: 0.851), VPAL (0.867)], for the total sample. In Study 5 (*n*=38: 20 aMCI subjects, and 18 AD patients; Lemos et al., 2015) similar good reliabilities were found both on the FCSRT (IR: 0.926; DR: 0.881) and the SRT (IR: 0.929; DR: 0.802). Our FCSRT results are comparable to the good reliability coefficients reported by Grober et al. (2009) for the GB version (Cronbach's alpha ranging from 0.85 to 0.88) on all the three available forms among patients from a geriatric centre.

Concurrent validity: Modest positively significant correlations were verified among the FCSRT and other verbal memory tests, such as the SRT (IR: *r* = .638; DR: *r* = .665) (Study 5; *n*=38: 20 aMCI subjects, and 18 AD patients; Lemos et al., 2015) and both the LM (IR: *r* =.605; DR: *r* =.677) and VPAL (*r* =.575) subtests of the WMS (Study 6; *n*=128: 85 aMCI subjects, and 43 AD patients; Lemos, Cunha, et al., 2014). While AD patients revealed a significant pattern of worse impairment than aMCI on all tests, the FCSRT showed a higher accuracy in discriminating the two groups and was less influenced by the educational level. Furthermore, Zimmerman et al. (2015) reported a modest association (r=0.36) between the FCSRT free recall and the WMS LM I subtest among healthy elders.

Construct validity is an important concept that relates to the importance of validating a psychometric test for use in a particular clinical population (American Educational Research Association, American Psychological Association, 1999). The goal is to guarantee that the psychological instrument is accurately evaluating the underlying dimension(s), rather than something different, in the clinical population in which it is being used (Maroof, 2012). In the study of Grober et al. (2009), the factor analysis indicated a single construct or dimension, on the three GB test forms, which the authors presume to be memory ability. The modified GB version comprises only a free recall from the test (learning) phase and does not include a delayed measure. Since we used the FCSRT regular version that comprises both IR and DR, we decided to test two models using confirmatory factor analysis (CFA) to provide further evidence of FCSRT's construct related validity: a one-factor structure based on the model proposed by

Grober et al. (2009) that accounts for the unidimensionality of memory ability; and a two-factor model, considering the two factors - learning (total recall) and retention (DR) (Study 3; *n*=271: 100 aMCI subjects, 70 AD patients and 101 control elders; Lemos, Marôco, Simões, & Santana, 2015). Our results indicated that both models revealed similar adequate fit values; still, the appropriated convergent validity and the lack of discriminant validity supported the two-factors as measuring the same construct – memory ability).

As an exception, the *inter-rater reliability* is not comprised in our studies because the FCSRT has a dichotomous scoring, i.e. recalled word=1 and missed word=0; therefore this property does not apply for this particular test. Even though we have not analysed the *test-retest reliability* in our longitudinal study (Study 4; Lemos et al., 2015), Zimmerman et al. (2015) reported good values of test-retest reliability for the FCSRT (free recall – 0.80; total recall – 0.83) on two visits in a randomised counterbalanced design study, among healthy elders.

In sum, the possibility of a complete analysis along with the psychometric properties of an instrument is a valuable advantage that results in an important contribution to outline a more systematic and comprehensive neuropsychological evaluation.

Clinical Validity of the FCSRT

According to the ITC, another essential guideline that should be provided by the test developers when adaptating psychological tests, is related to "information on the evaluation of validity in all target populations for whom the adapted versions are intended" (International Test Comission, 2005, p. 7). Moreover, valid and accurate neuropsychological tests must show good diagnostic classification properties which means, in terms of memory, that a significant impairment in neuropsychological testing is essential to the diagnosis of both aMCI and AD (Dubois et al., 2007, 2014; Portet et al., 2006).

Having this notion in mind, and also the importance that the FCSRT represents to the IWG-1 and the IWG-2, we started by validating the FCSRT for aMCI and AD through the analysis of the diagnostic accuracy and the suggestion of its cut-off scores (Study 2: Lemos, Simões, Santiago, & Santana, 2014; and Study 3: Lemos, Marôco, et al., 2015).

Concerning our samples' general cognitive profile, the brief cognitive evaluation (Mini-Mental State Examination) revealed a poor performance of patients, when compared to control subjects, and also showed a worse pattern of impairment of AD patients in comparison to aMCI. More importantly, the performance on the FCSRT was able not only to distinguish the clinical groups from the control group, but also to separate the degree of impairment between the pathological samples. The AD group was significantly worse when compared to the aMCI sample. This gradual pattern of impairment among normal ageing, MCI, and AD has already been reported (Boeve et al., 2003; Petersen, 2004; Petersen et al., 1999), and supported by Saka, Mihci, Topcuoglu, and Balkan (2006) that found enhanced cued recall paradigms to highly and moderately discriminate AD and MCI from controls, respectively.

Study 2 (Lemos, Simões, Santiago, & Santana, 2014) enabled the analysis of the impact of the FCSRT measures (free, cued, and total) among the two recalls (IR and DR) on the likelihood of having aMCI or AD, where significant effects were found for the two total recall trials. Total recall, which is the sum of the free and the cued recalls, reflects the amount of information that is stored spontaneously and facilitated by the subject. Accordingly, the cut-off scores were set at ≤35 for total IR and ≤12 for total DR, in the aMCI group, and at ≤27 for total IR and ≤8 for total DR in the AD group. Moreover, the DR measure showed to be more sensitive, although the IR presented a higher value of specificity, showing the importance of having a delayed measure to account for the milder forms of cognitive decline (Ivanoiu et al., 2005) such as MCI. In Study 3 (Lemos, Marôco, et al., 2015), the unidimensional construct of the FCSRT enabled us to add a global score for FCSRT (summation of the two recalls). Thus, this total recall (TR) was the predictor with higher accuracy (68.3%) in the classification among the three groups (controls, aMCI, and AD), followed by the IR (67.9%), and the DR (65.7%). Nonetheless the similar results in accuracy among all the recalls, we believe that the outcomes from the two-factor model construct validity of the FCSRT allow to additionally support the importance of including both total (learning) and delayed (retention) recalls. The immediate recall provides qualitative and quantitative information regarding learning, while the delayed recall report memory consolidation/retention that is particularly sensitive to the hippocampal dysfunction present in AD spectrum disorders. In fact, both learning and retention correspond to the process of memory functioning. This

shows the significance of a delayed recall to comprise the milder forms of cognitive decline (Albert et al., 2011; Grober & Kawas, 1997; Ivanoiu et al., 2005; Sánchez-Benavides et al., 2014) such as aMCI, and avoid the inclusion of false negatives that can happen when learning is the only memory measure tested. According to Salmon (2000), clinically, measures of the ability to learn and retain new information are quite useful in differentiating between healthy aging elders and AD patients, and delayed recall trials revealed to be more effective than measures of learning across trials. As such, in Study 3 we suggested a new possibility in terms of using the FCSRT in AD spectrum disorders. According to our results, the FCSRT recalls may be used and reported: i) independently (for a qualitative approach of the retained material), ii) as a composed result/global value (for a more simple way of reporting the result), or iii) as a single unit (in order to reduce patients' fatigue, or on follow-up evaluations).

As the IWG-1 criteria (Dubois et al., 2007) aimed to capture the earliest stages of the disease (AD) and some cases of aMCI may be considered as a preclinical phase of AD or prodromal AD (Dubois et al., 2007, 2010), we analysed and compared the performance of the two pathological groups on Study 2 (Lemos, Simões, Santiago, & Santana, 2014). As such, and in order to better understand an AD-like profile of impairment among MCI patients, we subdivided the MCI group into MCI-MCI and MCI-AD sub-groups according to the previously established cut-offs. Results showed that almost half of the subjects (46%) had an AD-like pattern of impairment. Among the three pathological groups, the performance on the FCSRT had an overall profile of MCI-MCI>MCI-AD=AD. Furthermore, the MCI-AD group showed a significantly increased distribution of the ApoE-ε4 allele when compared to the MCI-MCI group, but with an equivalent frequency to that observed in the AD group. A cluster analysis, based on the cognitive performance, supported a two cluster solution with MCI-MCI subjects on the first group, and a combination of the MCI-AD and AD patients on the second. With this novel approach we believe that the heterogeneity of the MCI group may be subdivided according to an AD-similar pattern of performance in respect to the FCSRT profile, as early as at baseline, thus facilitating the capture of the earliest stages of AD as defended by Dubois et al. (2007). Although we assume that our results should be correlated with AD biomarkers, a poor performance on the FCSRT has previously shown a high correlation with the medial temporal lobe, by means of atrophy

(Diamond et al., 2007; Sánchez-Benavides et al., 2010, 2014; Sarazin et al., 2010; Wenger, Negash, Petsersen, & Petersen, 2011), hypoperfusion (Habert et al., 2011) and hypometabolism (Van Der Gucht et al., 2014), and was also significantly associated with CSF profile of AD (Rami et al., 2011; Wagner et al., 2012; Xie et al., 2014).

Thereafter, a *longitudinal* study was conducted in order to investigate whether the performance on the FCSRT would enhance the ability to predict conversion to AD in an aMCI group (Study 4; *n*=88; Lemos et al., 2015). Both the group of 29 converters and the group of 59 stable MCI were matched for demographical variables, though significant differences were found concerning the neuropsychological performance and also the presence of the ApoE-ε4 allele. There was a high rate of conversion during the follow-up time (23.82 months), as 33% of the aMCI population converted to AD. This rate of conversion is in line with what is expected for a memory clinic, thus attesting the validity of the study. Moreover, it corroborates the concept of prodromal AD. An impaired FCSRT IR was the only variable (compared to WMS LM and the presence of the ApoE-ε4 allele) significantly associated to the risk of conversion to dementia, with a mean time to conversion of 25 months. Thus, the FCSRT demonstrates utility for detecting AD at its prodromal stage, supporting its use as a valid clinical marker. Other researchers have already described the utility of cued recall paradigms for the purpose of predicting AD (Dickerson, Sperling, Hyman, Albert, & Blacker, 2007; Ivanoiu et al., 2005; Koric et al., 2013; Mura et al., 2014; Rabin et al., 2012; Sarazin et al., 2007).

In sum, our studies showed that the FCSRT was able to differentiate aMCI from AD patients at baseline (Study 2; Lemos, Simões, et al., 2014), allowed for the division of the aMCI group according to an AD-alike pattern of impairment (MCI-MCI and MCI-AD) (Study 2; Lemos, Simões, et al., 2014), and was associated with the risk of conversion to AD in follow-up studies (Study 4; Lemos et al., 2015)**.**

We also aimed at comparing the FCSRT, in terms of accuracy for the memory impairment of AD spectrum disorders, with other declarative memory tests with no support for encoding or cue for retrieval – free recall procedures. Our results showed in Study 6 (Lemos, Cunha, et al., 2014) that the FCSRT was able to classify more subjects as having memory impairment in the aMCI group (74%) rather than the WMS

subtests (LM – 54% and VPAL – 6%). On the AD sample, the DR of the LM included slightly more patients with memory impairment than the other tests. The VPAL subtest had a higher number of misclassifications. Previous studies slightly more effectiveness of the FCSRT in detecting very mild AD (Brown & Storandt, 2000), in association with CSF biomarkers indicative of AD in subjects with MCI (Wagner et al., 2012), and in predicting individuals with memory complaints who will develop incident AD (Derby et al., 2013), when compared to the WMS LM. Our study also showed that while the FCSRT was good in discriminating aMCI from AD both in lower and higher education levels, the LM was more useful in higher educated subjects. This is an important issue for countries with a significant percentage of low educated elders, like Portugal.

The IWG-1 also states the imperative need of distinguishing deficits in encoding and storage processes (characteristic of AD) from non-AD deficits that can also affect DR (Dubois et al., 2007), thus supporting the presence of an amnestic syndrome of the hippocampal type as representative of typical-AD spectrum disorders. Others showed that the FCSRT was able to differentiate AD patients from other forms of dementia in general (Grober, Hall, Mcginn, et al., 2008), and specifically from VaD (Grober, Hall, Sanders, & Lipton, 2008; Grober et al., 2010; Traykov et al., 2005) and FTD (Basely, Ceccaldi, Boyer, Mundler, & Guedj, 2013; Bertoux et al., 2014; Pasquier, Grymonprez, Lebert, & Van der Linden, 2001). Accordingly, in Study 7 (Lemos, Duro, Simões, & Santana, 2014) we showed the utility of the FCSRT in the distinction between patients with *bv-FTD* and patients with AD, therefore improving the accuracy of the diagnosis. Comparisons between AD and FTD, in Study 7, revealed that FTD subjects benefited from the controlled learning through category cues, as their performance was spared on both the cued recalls and the percentage of retention. Moreover, the FCSRT had a classification accuracy of 78.1%, allowing us to identify ninety-four percent of patients with AD and discard sixty-three percent of patients with bv-FTD, indicating that an impaired FCSRT performance emphasizes the significance of episodic memory deficits in patients with AD. Patients with AD were 25 times more likely to have an impaired FCSRT than bv-FTD patients. Moreover, the method of cueing inherent to the FCSRT showed an improvement of the retrieval ability in bv-FTD patients, which has not been observed with tests that employ other methods of cueing (Glosser, Gallo, Clark, &

Grossman, 2002). The pattern of impairment was the following: poor free and total recall performance rates, both in learning and after a delay, were observed in both AD and bv-FTD groups; low scores in cued recalls, and a lower rate of retention were representative of AD; while an improvement with category cueing and spared retained items were suggestive of bv-FTD. The achieved results within this study allowed us to conclude that it is more informative to use memory tests that control the learning deficit often observed in FTD patients so as to elicit the retrieval of stored information. This may aid to isolate the memory deficit more typical in AD patients and thereby increase the accuracy of a diagnosis.

Highlights and Limitations

It is our understanding that we were able to reach the main purpose of the present work plan – explore, in a clinical perspective, the properties and validity of the FCSRT on a memory clinic basis for the AD spectrum early diagnosis, in Portugal. Additionaly, we believe to have scientifically contributed to the discussion concerning new proposals for the early diagnosis of AD (Dubois et al., 2007, Dubois et al.,2014 Albert et al.,2011).

Noteworthy, the pathological samples included in all the works from this thesis were recruited at the Neurology Department of the Coimbra University Hospital, which is a reference center, both for clinical and research purposes, where patients and clinical staff have access to the most recent and sophisticated supplementary means of clinical diagnosis. This setting enables the differential diagnosis to be made accurately.

As previously reported, some studies were not defined initially, but were developed in order to better integrate the results achieved during the progress of this project.

A common and solid characteristic of all the studies is the fact that the pathological groups and the control sample were always equivalent, in terms of demographical variables (age, educational level, or gender).

An important point to be highlighted is the use of the Clinical Dementia Rating as the major (staging) classificatory instrument, in Study 6 (Lemos, Cunha, et al., 2014), independently of the neuropsychological measures. The rationale for this choice was the fact that comparisons between the FCSRT and the WMS subtests were part of our

main goal analysis, and it was done in order to avoid diagnostic circularity that may bias the results' interpretation.

One main limitation across all the reported studies is the relatively small size of the samples. In terms of the healthy elders group, we did not intend to work throughout a normalization study, as we are aware that it requires a significantly higher number of subjects. Instead, we prioritized having a reasonable number of controls to compare the clinical samples and therefore allowing us to proceed to all the validation studies. In terms of recruitment of the control group, we included cognitively healthy adults belonging to the local community that were recruited among the patients' spouses, hospital or university staff, or their relatives. Our main guidelines were taking into consideration the demographical aspects of the pathological samples that were being included and also making sure that these control subjects had no history of neurological or psychiatric relevant condition (including abuse of alcohol or drugs or head trauma) neither significant motor, visual or auditory deficits which could influence the neuropsychological performance. We excluded all subjects with a score of 20 or more points (severe depression) in the Geriatric Depression Scale. Despite all the instruments used to assure that these subjects had no cognitive impairment, we are aware that a comprehensive neuropsychological evaluation that included validated instruments (mainly to assess memory domain), along with other supplementary diagnostic means, would have been more accurate. Nonetheless, including more instruments to the battery and questionnaires used during our assessment would certainly increase significantly the time of evaluation and consequentially discourage subjects to participate in our study.

The FCSRT requires subjects to read the printed words during the test administration. This circumstance automatically disregards illiterate subjects to be included. We are aware that in Portuguese geriatric populations the number of illiterates is still high and that a low education is representative of this age group. Nevertheless, in our studies, the absence of an education significant effect enabled us to verify that the FCSRT can be used in the classification of subjects without the need of adjustment for different educational levels.

We have exclusively included MCI patients of the amnestic type and this is in line with our main objective of studying (typical) AD spectrum disorders. These patients have a higher risk of conversion to AD, and their memory deficit reflects the early involvement of the hippocampus and its related structures, and therefore they were intentionally chosen. This circumstance discourages the inclusion of other MCI subtypes, and consequently one must be advised against generalizing the obtained results to all the MCI subtypes.

In terms of psychometric properties, we tried to cover all the possible variables in our analysis. The temporal stability was not analysed in our longitudinal study, as subjects only performed the FCSRT at baseline; therefore, we were not able to compare the performance on the FCSRT at different moments.

Our main objective was mainly to capture the earliest stages of AD by examining the pattern of performance in a memory test but it is important to state that neuropsychological tests unaided are not enough to characterize patients as prodromal AD. In order to reach that purpose, and to support the suggestions of the IWG criteria, the results should be corroborated with AD clinical biomarkers – which we do not present at the current thesis.

Future Outlook

It is our understanding that the process of validating an instrument is always an open project. Therefore, we could develop a challenging normalization process, throughout the inclusion of a significantly higher number of healthy subjects that takes into consideration all the country-representative variables.

The further expansion of the validation studies for other clinical populations is also an exciting future plan, as well as the development of concurrent validation investigations with the use of other neuropsychological memory tests.

A mandatory continuity of this project is the development of a correlational study that includes data from the FCSRT with AD clinical biomarkers. This study may certainly enrich all the results achieved throughout the present thesis and will expectedly support the concepts developed by the IWG criteria.

Conclusions

The FCSRT is a verbal memory test that involves the use of a selective reminding paradigm with semantic cueing. Because it showed high sensitivity and specificity in the differentiation of AD from healthy controls and other dementias, the IWG framework criteria for AD suggested its use in the assessment of the memory impairment of typical AD spectrum disorders.

The work presented in this thesis showed the process of transcultural adaptation of the FCSRT to the Portuguese population, and explored its psychometric and clinical validities. The results allowed us to confirm the FCSRT as a valid and accurate test, as well as a useful tool in the objective characterization of the amnestic syndrome associated with AD. We highlight our contributions to the development neuropsychological instruments to be used in Portugal in the field of ageing and dementia, and also to the the operationalization in a research and clinical perspective of the international IWG framework criteria for AD.

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CHAPTER II

"Do you know where my husband is?" she cried.
At first I Just laughed, but as she turned more anxious, grabbing my hand and shaking, I saw she was serious. That´s when I became speechless. The reason for my reaction is that I am her husband."

(Bill P., whose wife suffers from Alzheimer's disease)
In *What you need to know about Alzheimer's,* JOHN MEDINA

In this chapter we review the progress that has been made in the scientific research on visual functions in the AD spectrum. In particular, we will focus on studies that directly addressed low and high-level visual functions in both AD and MCI groups suggesting the visual perception assessment as an additional diagnostic tool for improving the knowledge of AD spectrum disorders.

Background

As reported earlier, while the first symptoms of AD patients are usually related to memory deficits, cognitive dysfunction in at least one other domain – such as reasoning and judgment, visuospatial abilities, or language – is often affected (McKhann et al., 2011).

Current cognitive neuroscience models explain memory functions in terms of multiple independent systems that process different types of information by using distinct encoding, storage and retrieval operations. A similar conceptual framework applies to vision concerning sensory, perceptual and attentional processes.

Apart from the objective memory deficit, visual brain systems may be altered in the AD spectrum (Cronin-Golomb, 2004). Although distinct types of memory functions have been explicitly and extensively studied in AD and MCI, the same does not hold true for visual functions. Nevertheless, the effects of normal ageing on visual perception and visual cognition are well established (Greenlee & Sekuler, 2014; Mateus et al., 2013). More recent studies revealed that, despite the visual cortical deficits in AD, other parts of the visual system may be affected such as the optic nerve and the retina (Tzekov and Mullan, 2014), the pupil (Frost et al., 2013), the macular part of the retina (Garcia-Martin et al., 2014; Mandas et al., 2014; Nolan et al., 2014) and eye movements (Molitor, Ko, & Ally, 2015; Peltsch, Hemraj, Garcia, & Munoz, 2014).

Visuospatial processing is supported by two main cortical pathways (Figure II): i) the dorsal pathway, which comprises a network of occipito-parietal regions involved in spatial vision and motion perception; and ii) the ventral stream, which consists of a network of occipito-temporal regions that underlie recognition of object shape properties (Milner & Goodale, 2008).

Adapted from: **Lemos, R**., Patrício, M., & Castelo-Branco, M. (2015). Visual Function in the Alzheimer´s disease spectrum: a review. (*submitted to publication*).

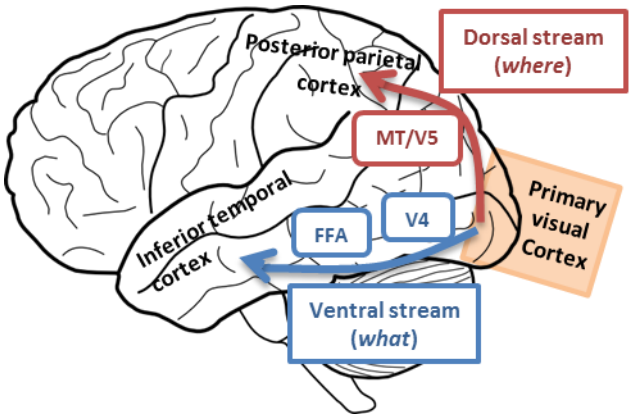

Figure II Dorsal and Ventral parallel visual pathways.
Visual processing in the brain is handled, in part, by two processing pathways extending from primary visual cortex: the dorsal visual stream (*where*), which projects from the primary visual cortex to the parietal lobe and is involved in object spatial location functions; and the ventral visual stream (*what*), that spreads from the primary visual cortex to the temporal lobe and is responsible for object identification as well as shape and face processing. *(Adapted from Milner and Goodale, 2008)*

Studies focusing on vision are important because not only the medial temporal lobe regions are affected in early AD, but also ventral and dorsal regions that may be important for predicting AD and understanding its pathophysiology (Jacobs et al. 2015; McKee et al. 2006; Rizzo et al. 2000; Villain, Chételat, et al. 2010; Villain, Fouquet, et al. 2010). Moreover, recent evidence indicated that sensory and motor changes may precede the cognitive symptoms of AD, with strong evidence for neuropathologic changes in the olfactory, visual, auditory, and motor systems (Albers et al., 2015).
MCI reduces attention capacity and slows down attention switching, but a fine dissection of visual and attentional deficits and their link to retinocortical and occipito-parietal damage has not yet been attempted. The need to assess multiple domain loss within the visual system is even more obvious in what concerns MCI. Nevertheless, there is a relatively low number of studies concerning visual function in MCI, becoming even lower if one considers its link with other cognitive domains.

The visual impairment in AD spectrum disorders

<u>Behavioural and Psychophysical evidence</u>

AD is associated with disturbances in basic visual, complex visual and oculomotor functions, leading these patients and their caregivers to report frequent visuospatial difficulties. The broad range of visual system disorders in AD may result from the concentration of neuropathology in visual association cortex and optic nerves in this disease (Mendez, Tomsak, & Remler, 1990). Previous reviews on the spectrum of visual system disturbances found in AD focused on: visual field deficits, prolonged visual evoked potentials, depressed contrast sensitivities, abnormal eye movement recordings, and high-order complex visual disturbances (Mendez et al., 1990); nerve fiber deficits, and functional losses in the magnocellular pathway (CS and temporal processing) (Valenti, 2010); the broad-band pathway, glaucoma, and the ventral and dorsal streams of vision (Kirby, Bandelow, & Hogervorst, 2010); visual spatial cognition (Possin, 2010).

There is a relative lack of visual function studies in MCI, especially when compared with the amount of research in AD. This fact may be due to its more recent categorization. Some studies in the literature report about high-level visual functions, showing visual search or attentional impairment to be present in MCI subjects. These are indeed impaired in some functions early on, but other functions seem to be preserved. Additionally, it is noteworthy to point out that these studies usually do not include a large enough number of subjects, which preclude random effects analyses that can be generalized to the population. Yet, it is important to investigate how visual function is affected in MCI and compare the patients to AD and control subjects. Another important goal is assessing the potential conversion predicting value of the visual function status.

In the in the following paragraphs we look into how different dimensions of the visual function were addressed, by comparing available evidence in AD and in MCI.

- Visual acuity, contrast sensitivity (CS) and colour vision

Given their different neural substrates, it is relevant to analyse low-level visual functions (visual acuity, chromatic and achromatic CS) separately from intermediate or high level visual functions.

In the specific case of AD, impairment in primary visual functions is relatively well known and it is described in many studies (Rizzo et al. 2000). Visual acuity decreases

along the course of the disease although ophthalmological comorbidity (eg. cataract, glaucoma and age related macular degeneration) have to be considered in order to isolate the specific effects due to cortical pathological ageing (Wolin, 1994).

Rizzo et al. (2000) have provided one of the most extensive studies analysing visual function in AD. The authors aimed to "test the hypothesis that AD produces both ventral and dorsal visual pathway deficits while sparing basic sensory functions" and correlate such deficits with disease severity. For that purpose, they assessed a large number of visual functions by using tasks such as static (Sloan letter shapes) and dynamic visual acuity tasks. Subjects were asked to identify five letters which were moving in the dynamic task. Additionally, spatial CS was assessed using Pelli charts - which measure performance from low to medium spatial frequencies, stereoacuity - by using the stereopsis Titmus test, and colour vision - by means of Pseudoisochromatic plates. In the latter test, 12 pseudoisochromatic plates made of coloured circles of different size, hue and lightness were employed. Participants were asked to identify the target figure, or else to trace any perceived pattern with their finger. Although it is often claimed that this serves as a ventral visual stream probe, this task does not really dissect low and high level visual function. Results suggested that AD pathology affects visual functions (colour vision), but several basic visual sensory functions were spared. In another article by Rizzo and Nawrot (1998) the ability to identify 2D target shapes was measured (Sloan acuity letters) in a dynamic visual acuity task, where "form and contour cues were conspicuously available when the shapes were stationary". The specificity of this task was not fully examined, yet AD patients performed in a similar way as controls. Wijk et al. (2002) have also reported preserved colour perception ability in AD patients.

Mendola et al. (1995) found significant deficits in AD patients in tests of colour discrimination, stereoacuity, CS, and letter-identification with backward masking. In this study it was found that low level sensory functions were seemingly not spared. Performance in the backward masking task was the most sensitive predictor of the AD group status. Results for static binocular acuity were normal in this study. The results found for low level vision in this study were similar to those obtained by Rizzo et al. (2000). Moreover, these similar results were obtained with different measures of the same visual functions, in particular colour vision ("City University Colour Vision test",

"Farnsworth D-15 test", and "Lanthony New Colour test") vs. the "Standard Pseudoisochromatic Plates" used by Rizzo et al. (2000) and achromatic CS. The only visual function diverging in these two studies was stereoacuity, for which in this study an impairment in the AD group was found, in contrast to the study of Rizzo et al. (2000) which did not report a significant group difference. Other studies describing the importance of understanding visual changes in AD population, showing AD deficits in colour discrimination, stereoacuity, CS, and backward masking (Cronin-Golomb 1995; Cronin-Golomb et al. 1991, 1995; Rizzo et al. 1992). On the other hand, Pache et al. (2003) reported an unspecific colour vision deficiency in AD patients that proved to be independent of the severity of the disease. Bassi et al. (1993) reported the performance of an AD group on visual functions of colour vision, CS and stereoacuity. This article did not report differences to have been found for the colour vision task, suggesting that this can be due to age-related co-morbidity; stereoacuity was impaired in the dementia groups; and low spatial frequency CS was the only function impaired in the AD group. The authors concluded that AD patients show deficits in several visual functions; nevertheless only deficits in CS seemed to be specific to AD.

Cronin-Golomb (2004) commented that "spatial frequency CS is the most studied visual function in AD". This function reflects the "minimum amount of contrast that an observer needs to resolve a stimulus of a given size", which is probably relevant concerning deficits in daily function in elderly people. The deficits in CS shown by AD patients are often described as the visual image being viewed through a filter and it is called the "Alzheimer filter", and the impaired CS at low facial frequencies contributes to AD patients poor face discrimination (Cronin-Golomb et al., 2000). Neargarder et al. (2003) have reported distinct results in the performance of AD patients among several CS measures. It is possible that the variability of CS results in different studies can be due to differences in acuity or other characteristics of the subjects studied, or due to the visual characteristics of the target and the scene complexity (Neargarder & Cronin-Golomb, 2005). Accordingly, Cormack et al. (2000); Cronin-Golomb et al. (2007); Gilmore and Levy (1991); Gilmore et al. (2005); Nolan et al. (2014); Risacher et al. (2013); Valenti (2013) corroborated the CS deficits in AD patients, which were independent of AD higher-level cognitive (memory) disturbances impairment (Kéri, Antal, Kálmán, Janka, & Benedek, 1999). Trick et al. (1995) showed that the visual field

loss in AD is most pronounced in the inferonasal and inferotemporal arcuate regions but also involves the central field. Furthermore, AD proved to affect later central visual functions than peripheral ones (Schlotterer, Moscovitch, & Crapper-Mclachlan, 1984). Moreover, AD subjects also proved to benefit from increasing contrast, presumably by compensating for their CS deficit (Hutton, Morris, Elias, & Poston, 1993; Laudate et al., 2012).

Research of visual function on MCI comprises mainly high-level visual functions, like attention or visual search tasks. The literature available on low level visual functions is scarce. However, Risacher et al. (2013) proved an early deficit in CS to be present in amnestic MCI patients.

- Motion Perception

The involvement of occipito-parietal regions in AD may lead to visuospatial disorientation and consequently patients may get lost even in familiar surroundings. The occipito-parietal cortex involves processing the radial patterns of visual motion that create optic flow and guide movements through the environment by showing one's direction of self-movement. Tetewsky and Duffy (1999) studied whether AD patients are impaired in perceiving visual patterns of optic flow, suggesting a perceptual mechanism of visuospatial disorientation. These authors showed that AD greatly impairs the ability to see radial patterns of optic flow, and concluded that this may interfere with the use of visual information to guide self-movement and maintain spatial orientation.

Rizzo and Nawrot (1998) published a study about the performance of a group of AD patients in tasks requiring the perception of movement and shape. In one of the experiments they tested the perception of motion direction using “Random-Dot-Cinematograms” (RDC) stimuli. These stimuli “present a motion signal amid spatially random background noise and allow for variation of spatial displacement and temporal intervals at programmable exposure durations”. AD had significant effects on the perception of SFM but had relative sparing of dynamic visual acuity and motion direction discrimination. Rizzo et al. (2000) studied movement perception, by using either a motion direction discrimination task that required subjects to indicate the perceived direction of the motion in the stimulus after a 195 ms presentation, and a

two-alternative forced-choice SFM task where the observer had to report the shape of the presented object. AD patients revealed to be impaired in the latter task.

More conspicuous evidence for impairment in AD has been found with high level motion tests. Using measures of horizontal motion and radial optic flow, Duffy et al. (2000) found an impairment in AD patients' performance, when compared with two control groups (young - YN and elderly normal - EN). Nevertheless, the AD group could be divided in two sub-groups considering the performance: about half of the AD subjects had similar thresholds as compared to those seen in the EN group, while the other half showed much higher radial optic flow thresholds than horizontal motion thresholds. These results not only confirm the recognition of visual motion processing deficits in AD patients, but also demonstrate a selective impairment in radial optic flow perception that can be linked to navigational deficits. These deficits found in AD do not seem to reflect impairments in basic visual function, but somewhat reflect high level dysfunction of the visual extrastriate cortex, and are consistent with the notion that higher level deficits tend to dominate.

Kavcic et al. (2011) showed that AD was associated with poorer heading direction and speed perception at lower temporal periodicity, with smaller effects of spatial texture, using the radial patterns of visual motion in optic flow. AD patients were particularly impaired by motion incoherence created by adding randomly moving dots to the optic flow, when compared to young, middle-aged and older normal subjects.

Tippett and Sergio (2006) examined the accuracy of movements requiring a visuomotor transformation in neurologically healthy elderly subjects and patients diagnosed with AD, using a task where they had to make sliding finger movements over a clear touch-sensitive screen. The latter was positioned in three spatial planes and patients were asked to displace a cursor from a central target to one of four peripheral targets viewed on a monitor. Significant main effects were observed on reaction time and movement time measures, as well as significant increases in task completion errors, in the patient population. Furthermore, the performance was affected more by the visual feedback changes relative to the plane location changes. The authors suggest that the integration of eye and hand information may be impaired in AD. In a later article involving some of the same authors, the ability to successfully complete procedures involving short-term spatial visuomotor memory tasks and tasks

involving increasingly complex visuomotor transformations was examined in the same groups (Tippett et al. 2007). Overall, these new results revealed that AD patients show substantial declines in their ability to process and integrate visual information to produce motor responses, therefore providing evidence that AD can affect anatomical regions supporting vision for action.

Hawkins and Sergio (2014) used kinematic measures, under conditions that place demands on visual-spatial and cognitive-motor processing, to suggest that the impairments observed in individuals at increased AD risk may reflect inherent brain alteration and/or early neuropathology disrupting the reciprocal communication between hippocampal, parietal, and frontal brain regions required to successfully prepare and update complex reaching movements. Such impairment may affect activities of daily living, and could serve as a sensitive measure of functional ability in at-risk AD adults.

Nevertheless, in MCI most of the evidence comes from neuroimaging studies that do not directly measure performance. However, a study by Mapstone et al. (2003) did evaluate the performance of an MCI group and an AD group, in comparison with young and older control groups, on motion detection (horizontal and radial optic flow) and spatial orientation (Money Road Map Test) tasks. The results showed an impairment of MCI patients in radial motion detection. The AD group performed worse than the MCI group both in spatial orientation and in the radial motion detection. The performance in the horizontal motion detection was similar for all groups. This study reveals a correlation between radial optic flow results and spatial orientation scores across all groups that proved to be independent of memory deficits, thus supporting the existence of a link between impaired optic flow perception and visuospatial disorientation. This result may explain why AD patients may readily become spatially lost, because of their visual perceptual impairments rather than forgetting their path or location, in line with the idea that visuospatial impairment is independent of memory processing. MCI patients showed selective impairments in the radial motion tasks, and all patients who were impaired in one radial optic flow task were impaired in the other, but not in the processing of horizontal motion stimuli. This may imply that some MCI patients have significant visual perceptual deficits along with memory impairment, whereas others have memory impairment without significant visual

perceptual deficits. This finding led the authors to suggest a visuospatial variant of MCI.

- Visual Attention

Concerning visual attention, Rizzo et al. (2000) have studied it using two tasks: the useful field of view (UFOV) and the starry night task. The former used the Visual Attention Analyser, Model 2000, which includes three subtests to provide a measure of speed of visual processing discrimination, divided attention and selective attention. The latter tests the subject's ability to detect "on" and "off" signals presented to both hemifields, since the performance depends on an observer's visual sensory function and ability over time to sustain visual attention across a spatial array. The AD group was significantly worse on both tasks of visual attention.

Foster et al. (1999) investigated selective attention in AD patients, using a visual search procedure. Patients showed deficits, as expressed by increased reaction time, both on simple and conjoined feature search tasks; and had also more difficulty in detecting targets on the right side of hemispace and in more peripheral locations.

Parasuraman et al. (2000) studied spatial attention and visual search in an AD group, comparing it with two healthy control groups. They showed that the AD group was impaired both in accuracy and reaction time in a cued visual search task where the subjects had to identify a target in different conditions. Participants had to search for feature or conjunction targets in a search display preceded by a cue that varied in validity (valid, invalid or neutral), size and precision of spatial localization. The cue size effect was evident both in feature and conjunction search, but it was reduced both in AD and older control group, when compared with the younger control group. Nonetheless, the AD group seemed to benefit from precise cues in spatial attention.

Tales et al. (2002) studied the performance of AD patients on a visual attention task. They showed that the performance when detecting a target (visual search) may depend on the type of target used. Two types of cues were used: endogenous cues – that have a meaning, are learnt and require conscious recruitment of attentional processes; and exogenous cues – which automatically attract attention and are suggested (ex: the automatic orienting triggered by a flash of light). Cueing effects were found, for both type of cues, for either the two control groups (younger and

older age-matched) and the AD group. Nevertheless, the AD patients showed a normal performance for the endogenous cueing condition and impairment when exogenous cues were used, implying that automatic attention processes are affected in AD, while controlled attention is spared. The exact neural mechanism underlying these deficits remains to be explored.

In another study, Tales, Butler, et al. (2002), asked whether AD was particularly affected by the features (orientation and lightness) of the target and if performance depends on some shifting of attention, during a visual search task. Two non-conjunction control conditions were employed: the first was a pre-attentive, single-feature, "pop-out" task, detecting a vertical target among horizontal distractors; whereas the second was a single-feature, partly attentive task in which the target element was slightly larger than the distractors - a "size" task. The results suggested that AD patients had a particular impairment in the conjunction task but not in the single-feature size or pre-attentive tasks. This may imply that AD particularly affects those mechanisms which compare across more than one feature type, and spares the other systems and is not therefore simply an 'attention-related' impairment.

Distinctions across putative mechanisms were explored in a study by Tales et al. (2004). These authors concluded that AD patients are impaired on visual search tasks as a combination of both inefficacy on attention shifting and target processing factors. The ease of attention shifting was manipulated in this visual search task, by controlling both target salience and task difficulty, where AD patients showed greater effects of manipulations.

Butter et al. (1996) studied two AD groups, one with and another without visual symptoms, along with a healthy control group. The article explored the assumption that the high level visual-spatial dysfunction in AD patients can explain their visual symptoms. The battery administered included the assessment of visual-spatial skills, form identification, colour vision, and visual memory. The results showed that the two AD groups differed significantly, in which concerns visual-spatial test scores. It was concluded that visual symptoms in AD are related primarily to high level visual-spatial deficits.

One may conclude at this point that visual attention is impaired in AD at different levels. These deficits have been linked to dysfunction of the posterior parietal cortex

and associated networks, and are qualitatively and quantitatively different from the visual attentional changes in normal ageing.

Studies on the time course of visual attention, that examine how quickly attention can be directed to and for how long attention remains directed at a stimulus, have suggested a temporary functional blindness in MCI patients – incapacity to attend a second stimulus presented within 500 ms of the first one. This phenomenon is known as the attentional blink or attentional dwell time (Perry & Hodges, 2003). These authors have examined the neural correlates of this phenomenon and its relationship to mechanisms that control attention in a MCI group. Their paradigm was divided in two situations: in the first one, subjects had to identify both a number and a letter that were rapidly and sequentially presented on a visual display – the effect that the need to identify the first stimulus had on the ability to identify the second was used as a measure of the attentional blink. In the second situation, subjects were asked to identify only one of the two stimuli – the ability to ignore the first stimulus was a function of their top-down attentional control. Results showed that MCI patients had a normal performance on the attentional dwell time task, but top-down inhibitory attentional control was impaired. This dissociation suggests that these two aspects of visual attention have a distinct neural basis.

Levinoff et al. (2005) used three reaction time attentional tasks to assess the nature of focused attention impairments in AD and in MCI, in comparison with a normal elderly control group. The experiment was divided in three tasks: 1) a simple reaction time task – where subjects had to respond as rapidly as possible to a single stimulus – as a measure of psychomotor speed; 2) a choice reaction time task (CRT) – where participants had to carry out one of two response options based on the nature of the stimulus that was presented – obtaining a focused attention measure; 3) a cued choice reaction time task (CCRT) – where cues are provided before the stimulus presentation – assessing a cueing effect. The results showed that AD patients were slower on the three situations, while MCI patients were only impaired on CRT and CCRT, which provides evidence for impaired focused attention and the inability to benefit from a cue in both the MCI and AD groups.

Visual attention mechanisms have an important relationship (bottom-up or top-down) with other brain functions, such as mnemonic, high-level cognitive, perceptual and

sensory (feedback effects in the latter). Within this context, Tales et al. (2005) studied the ability for visual search in both MCI and AD patients. In the visual search task, participants had to find a target element that was one of the symbols "<" or ">" (i.e., a black left or right-pointing arrow). These were presented alone or amongst distracter elements with the same shape as the target but rotated, pointing up or down ("^" or "v"). Results indicated a similar performance between MCI and control groups when the target appeared alone but when it appeared surrounded by distractors, the reaction time of MCI responses increased significantly. AD patients were impaired on both conditions. The pattern of results displayed by the MCI group indicated that patients who appear clinically to suffer only from a deficit in memory also exhibit a deficit in visual attention-related processing, even though not as severe as those with AD.

- Object Perception

Object perception in AD has rarely been separated from amnestic deficits. In this manner, it remains difficult to prove a specific domain-specific deficit of object or more specifically face perception in AD. Testing memory for faces and names has been widely applied in clinical contexts, and it has been claimed that this provides highly sensitive indices of episodic and semantic memory performance (Werheid & Clare, 2007). The elucidation of specific object perception deficits and their contribution to such performance measures remains to be established.

In the experiment of Rizzo et al. (2000) the observer reported the shape of the object presented in each trial, in a two-alternative forced-choice task. Results of this study showed that the amount of signal needed for threshold discrimination of SFM is higher in the AD group.

Cronin-Golomb (2004) stated that "deficits in spatial contrast sensitivity result in increased difficulty in face discrimination" not only in healthy elderly individuals but especially in patients with AD. They have found that a reduced face size influences contrast sensitivity at different spatial frequencies, resulting in normal face discrimination for only that face size. This suggests that it is important to control for low level mechanisms when assessing object perception in AD.

In the previously reported study of Rizzo and Nawrot (1998) AD patients were impaired in perceiving shapes defined by motion cues (SFM task). These findings suggest that even if retinal pathology cannot be excluded, it alone cannot explain the pattern of the defects observed. The deficits in the processing of complex motion patterns are likely to have a cortical basis and are probably related with lesions in visual extrastriate cortex.

Surprisingly, few studies are available to study object perception in MCI. Most of the evidence comes from neuroimaging studies (see Neuroimaging section). To make issues even more complicated most of these do not directly measure performance. The problem is that MCI is not explicitly defined in most of the studies dealing with object perception. A good example is a study of visual object and face processing in mild-to-moderate AD (Tippett et al. 2003). The authors suggested that small, but in most cases reliable, impairments in visual perception, which are independent of degree of cognitive decline, could be found. Deficits in basic shape processing influenced performance on some higher level visual tasks. Poor performance on face processing, or the deficit on object naming, seemed however to be related to high level semantic-lexical impairment.

Neurophysiological evidence

Visual task and performance-related oscillatory activity and its synchronization may prove to provide important biomarkers in AD and MCI research (Uhlhaas & Singer, 2006). This is the case because, as pointed by these authors, synchronization of oscillatory responses in the beta and gamma-band is involved in a variety of cognitive functions, such as perceptual grouping, attention-dependent stimulus selection, routing of signals across distributed cortical networks, sensory-motor integration, working memory, and perceptual awareness. However, evidence in this respect is quite tentative Jackson and Snyder (2008). It is nevertheless to be expected that new fingerprints will be identified and that extended application of Electroencephalography (EEG) and event related potential (ERP) studies will provide novel biomarkers of MCI and early AD.

- Retina and subcortical structures

Yin et al. (2008) have revived the idea that retinal (glaucoma) and cortical age related degenerations (AD) may share similar mechanisms, in a theory-driven hypothetical paper. This idea was also explored in animal models (Ding et al., 2008; Ning, Cui, To, Ashe, & Matsubara, 2008).

Paquet et al. (2007) had suggested that that the retinal nerve fibre layer (RNFL) seemed to be involved early during the course of amnestic MCI. Berisha et al. (2007) had similar results and further showed that retinal abnormalities in early AD include not only a specific pattern of RNFL loss, but also narrow veins, and decreased retinal blood flow. Bambo et al. (2014) and; Kesler et al. (2011) found significant correlations between visual function tests and RNFL thickness with the severity of AD. Interestingly, melatonin receptor profiles in the retina are also altered in AD (Savaskan et al., 2007), suggesting that changes in circadian biology can have a retinal basis in this disease.

- Visual cortical pathways

Most of the efforts to elucidate the neurophysiology of visual processing in AD concern brain imaging, although EEG/ERP studies are also available. Unfortunately, no systematic attempts have yet been made in human research to assess retinotopic maps in AD and MCI.

An EEG source image study that suggested the existence of three different neural patterns in aged individuals, while viewing a visual stimulus: i) left hippocampus and midbrain in mild AD, ii) left lateral orbitofrontal gyrus, left nucleus accumbens, caudate nucleus, thalamus, posterior cinguli, right precuneus, right superior parietal lobe in MCI, and iii) right lateral-medial orbitofrontal gyrus, caudate nucleus, thalamus, right lateral occipito-temporal gyrus in elderly controls (Haupt, González-Hernández, & Scherbaum, 2008). However this study must be taken with caution, because it is arguable that EEG source mapping can reliably reach deep structures.

Stothart et al. (2015) used visual evoked potentials (VEPs) to assess the functional integrity of visual association area processing in AD and amnestic MCI. Results were interpreted as suggesting that changes in VEPs in AD may be a consequence of the microscopic AD pathology found in the extrastriate cortex, and that therefore neural measures of visual processing may help to better characterize subgroups of aMCI patients likely to develop AD. Fix et al. (2015) examined the diagnostic accuracy of

flash VEPs in MCI subjects, and speculated that MCI have compromised cholinergic functioning that result in impaired visual processing.

Yener et al. (2014) compared visual sensory-evoked oscillations and event-related oscillations in MCI to explore brain dynamics. The topography of oscillatory responses showed to differ depending on stimuli and tasks: visual sensory responses are highest over occipital and cognitive responses over frontal regions. A group effect was observed in MCI indicating that visual sensory and cognitive circuits behave differently indicating preserved visual sensory responses, but decreased cognitive responses.

Neuroimaging

The diagnosis of dementia is still essentially grounded on clinical criteria, but neuroimaging can often aid in providing further assessment. The identification of AD histological alterations is still mandatory for a definitive diagnosis, according to the most recent diagnostic criteria for AD (Dubois et al., 2007, 2014; McKhann et al., 2011). Nevertheless, the higher specificity correlation between amyloid deposition in the Pittsburgh compound B-Positron emission tomography (PiB-PET) and AD pathology in post-mortem studies enabled this functional neuroimaging technique to be considered as a valid pathophysiological marker of brain fibrillar amyloid pathology (Dubois et al., 2014). Accordingly, it is included in the more recent framework criteria both as a pathophysiological biomarker (Dubois et al., 2014) and as a biomarker of Aβ accumulation (Jack et al., 2011).

One cannot overemphasize the importance of post-mortem studies which in fact represent the diagnostic golden standard (Huddleston & Small, 2005). These studies have shown that initial amyloid deposits are formed in temporal, parietal and frontal lobes (Huddleston & Small, 2005). Visual cortex and primary sensorimotor cortex are apparently only affected in the latest stage of the disease (Braak & Braak, 1997). These notions are however at odds with recent neuroimaging results (in particular the functional imaging techniques) and represent a major challenge for future studies. One should, however, take into consideration the fact that visual functions actually span from the occipital, parietal, temporal and even frontal networks.

Although initially amyloid is deposited in temporal, parietal and frontal lobes, the first symptoms of AD are associated to neocortical-hippocampal deficits. It is becoming

clear that brain imaging is changing the way we view this and other causes of dementia, and that this trend will increase, which will probably force upcoming adjustments of the accepted diagnostic criteria (American Psychiatric Association, 2000; Dubois et al., 2007, 2010, 2014; McKhann et al., 1984, 2011).

Through neuroimaging techniques, either structural [Magnetic Resonance Imaging (MRI)], or functional [functional MRI (fMRI), nuclear imaging: Single-photon emission computed tomography (SPECT), and fluorodeoxyglucose-Positron emission tomography (FDG-PET), and PiB-PET], clinical investigations aim to achieve a better way to diagnose and monitor AD (Huddleston & Small, 2005).

- Structural Imaging

MRI and Computed Tomography (CT) are useful tools to identify non-degenerative and potentially treatable causes of dementia (Huddleston & Small, 2005; Klöppel et al., 2008). High-resolution volumetric MRI has increased the capacity to identify the various forms of the frontotemporal lobar degeneration spectrum and some forms of parkinsonism or cerebellar neurodegenerative disorders (Vitali, Migliaccio, Agosta, Rosen, & Geschwind, 2008). Patterns of cortical and subcortical abnormalities on MRI can be very informative in this regard.

To be useful in diagnosis, the structural MRI should help distinguish early stage AD from normal ageing (Klöppel et al., 2008).

Regardless of visual function-related regions, a study by Frisoni et al. (2007) using MRI allowed distinguishing between individuals affected by AD with early and late forms. Those affected early on show greater atrophy of the parietal and occipital lobes. On the other hand, the individuals affected later on had increased atrophy of the hippocampus (Frisoni et al., 2007).

Finally, among the new MRI methods, diffusion-weighted MRI is also slowly entering the clinical arena. Tensor-based morphometry (TBM) may indeed help detect regional structural brain differences between patients with AD or MCI and controls (Hua et al., 2008). This technique may become quite important because in addition to the deterioration of the cortical grey matter, also the brain white matter (WM) is affected. Indeed, Bozzali et al. (2002) have demonstrated that the deterioration of WM is due to wallerian degeneration of fiber tracts due to neuronal loss in cortical associative areas.

This study showed that WM pathology is not homogeneously distributed, preferably involving the fibres connecting association cortices, the corpus callosum and as well as pathways linking temporal, frontal, and parietal lobes in the detriment of little involvement of motor (internal capsule) or early visual pathways (optic radiations). Moreover, Cooley et al. (2014) had examined WM abnormalities of brain regions, including those associated with visual processing. Using diffusion tensor imaging (DTI) the authors studied a group of "probable MCI" compared to a group of cognitively healthy subjects, by comparison with a brief cognitive screening tool. Results indicate that there were posterior WM microstructural changes in individuals with probable MCI. These differences demonstrated that WM abnormalities are evident among individuals with cognitive impairment in regions beyond those commonly associated with AD and anterior brain ageing patterns. In another study, Nishioka et al. (2014) used DTI to analyse the visual pathway in healthy controls, MCI and AD patients. Their findings indicate that WM damage extends to the visual system, namely to the optic nerves and the splenium of the corpus callosum, and may help explain the visual deficits experienced by AD patients

- Functional Imaging

Functional MRI (fMRI)

fMRI is a promising technique to evaluate the dynamic changes in the degenerating brain. If successful in the detection of early functional damage it might allow for studies of early intervention to slow or prevent disease progression (Petrella, Coleman, & Doraiswamy, 2003). Smith et al. (1999) showed that cognitively normal individuals at high risk for AD, with family history of AD and corresponding apolipoprotein E allele status, demonstrated decreased brain activation in the mid- and posterior inferotemporal regions bilaterally during visual naming and letter fluency tasks. The authors claim to have provided evidence of a window of opportunity for disease-modifying treatment before the onset of symptomatic AD.

Concerning high level regions, a study has attempted to characterize activity in putative human V4, the right fusiform face area (FFA) (face task) and superior temporal sulcus (STS) (for a motion task) (Sauer, Ffytche, Ballard, Brown, & Howard,

2006). As reported by the authors, these differences could be explained by behavioural performance, failing to reach significance in the covariance analysis.

Thiyagesh et al. (2009) claim to be the first ones to explore the neuroanatomy of depth and motion perception in AD, during an fMRI study. AD patients showed a hypoactivation of V5 area, superior parietal lobe, occipito-parietal cortex and premotor cortices, but a greater activation in inferior parietal lobule and activated additional areas. This abnormal visual profile of AD supports a pathophysiological basis for the visuospatial disorientation.

More recently, Li et al. (2015) conducted a meta-analysis study examining brain network dysfunction in MCI and AD along task-based fMRI studies, supporting studies that investigated the brain network dysfunction from the system level (including visual functional areas). The meta-analytic results revealed that: i) MCI patients showed hypoactivation in default, frontoparietal, and visual networks relative to healthy controls; ii) AD-related hypoactivation mainly located in visual, default, and ventral attention networks relative to healthy controls; and both MCI-related and AD-related hyperactivation fell in frontoparietal, ventral attention, default, and somatomotor networks relative to healthy controls.

Vannini et al. (2008) investigated task demand-dependent signal changes in mild AD patients, using an approach that modelled the dependency of the blood oxygenation level-dependent (BOLD) signal on the subject's reaction time. Along with controls, AD patients showed overlapping neural networks engaged in angle discrimination, including the occipito-parietal and frontal regions. Moreover, they also demonstrated, in several network regions, a significantly weaker and sometimes no BOLD signal due to increased task demand; and a general task demand-independent increase of activation in right middle temporal gyrus. The authors suggest that this finding may indicate an attempt to compensate for dysfunctional areas in the dorsal visual pathway, in AD pathology. Accordingly, a three-year prospective study of the same authors (Vannini, Almkvist, Dierks, Lehmann, & Wahlund, 2007) aimed to investigate the functioning of brain regions in the visuospatial networks responsible for preclinical symptoms in AD using event-related fMRI. Again, an angle discrimination task with varying task demands was used, not yielding any performance differences. However, a network of bilateral activations in the dorsal pathway showed increased linearly

activity, with increasing task demand, in all subjects. Increased parietal activation in progressing MCI was suggested to reflect a reduced "neuronal efficacy" due to accumulating AD pathology and to be predictive of future clinical decline in MCI patients.

Another study focused not so much on performance but more on activation patterns and their correlations with morphometric measures (Teipel et al., 2007). This showed that during face matching tasks, fusiform activation is positively correlated with cortical grey matter density of brain areas belonging to the ventral visual stream and negatively correlated with grey matter density of brain areas belonging to the dorsal visual stream. It further reported that these effects were more pronounced in MCI patients than in controls (Teipel et al., 2007). In this type of task there were no statistical differences found, in performance or activation, between groups (Bokde et al., 2006). MCI showed to affect functional connectivity from the right middle fusiform gyrus to the visual areas and medial frontal areas. A higher linear correlation in the MCI group, in the parietal lobe, might indicate the initial appearance of compensatory processes (Bokde et al., 2006).

Additionally, the study of Rombouts et al. (2005) focused on altered resting state networks in MCI in AD during a visual task. Deactivation was found in the default mode network involving the anterior frontal, precuneus, and posterior cingulate cortex. MCI patients showed less deactivation than controls, but more than AD subjects. The default mode network response in the anterior frontal cortex significantly distinguished MCI from both controls (in the medial frontal) and AD subjects (in the anterior cingulate cortex). The response in the precuneus could only distinguish between patients and controls, not between MCI and AD. The study showed early changes in MCI in the posterior cingulate cortex and precuneus.

As posited by Werheid and Clare (2007), neuroimaging has revealed face perception requires a complex interplay of highly specialized visual areas located in the occipito-temporal cortex which interact with a widely distributed system of cortical areas subserving other cognitive operations. This helps explain why progress is slow and strongly dependent on unravelling cognitive operations.

Teipel et al. (2007) showed that, during face matching tasks, fusiform activation is positively correlated with cortical grey matter density of brain areas belonging to the

ventral visual stream and negatively correlated with grey matter density of brain areas belonging to the dorsal visual stream and that these effects are more pronounced in MCI patients than in controls.

Activation changes were compared by means of BOLD signal functional magnetic resonance imaging in the visual system between MCI and healthy control subjects (Bokde et al., 2008). The findings of this study showed that there were no areas of increased activation in the control group compared with the MCI group. Patterns of activation also reflected some differences since the control group selectively activated the ventral and dorsal pathways during face and location matching tasks, respectively.

Graewe et al. (2013) showed that an increased representation of low-level stimulus aspects may impair face perception in MCI, as elevated depth sensitivity was present in left FFA/OFA (occipital face area). Discriminant function analysis using face and depth sensitivity indices in FFA/OFA classified MCI and healthy elderly with 88.2% accuracy. Potentially related findings include altered activation patterns in dorsal–ventral stream integration regions and attention related networks of MCI patients. Their results highlight aberrant visual and additional potentially compensatory processes that identify dispositions of preclinical AD.

Yamasaki et al. (2012), in a ERPs and fMRI review study, concluded that visual impairments in patients with AD and MCI are mainly caused by dysfunction in higher-level parallel visual pathways. In particular, a deficit in ventro-dorsal stream function related to optic flow perception is responsible for the earliest and most prominent visual symptoms in MCI.

More recently, Krajcovicova et al. (2014) studied the changes in connectivity of the posterior node of the default mode network (DMN) using fMRI, in AD patients. Results showed that while in controls the task-induced connectivity decreases between the posterior cingulate and middle temporal and occipital visual cortices – implying a successful involvement of the ventral visual pathway during the visual processing; in AD, the involvement of the areas engaged in the ventral visual pathway was observed only in a small volume of the right middle temporal gyrus. Additional connectivity decreases in AD were present between the posterior cingulate and superior temporal gyrus when switching from baseline to task condition, thus reflecting deficits and compensatory mechanisms within the large scale brain networks in this population.

Brewer and Barton (2014) used fMRI to compare the visual field map (VFM) organization and population receptive fields (pRFs) between young adults and healthy ageing subjects. Healthy ageing subjects did not show major VFM organizational deficits, but had reduced surface area and increased pRF sizes. Later, the authors demonstrated the feasibility and first characterization of these measurements in two patients with mild AD, which reveal potential changes in the visual cortex as part of the pathophysiology of AD by showing more irregularities in the organization of the posterior VFMs.

The aforementioned studies focused on demonstrating that functional connectivity can be an effective marker for the detection of changes in brain function in MCI subjects, regardless of performance differences.

Nuclear imaging [Single-photon emission computed tomography (SPECT), fluorodeoxyglucose-Positron emission tomography (FDG-PET), and Pittsburgh compound B-Positron emission tomography (PiB-PET)]

Although imaging approaches are now trying to address visual performance, a link with clear cut impairment is still lacking.

SPECT was clinically used to characterize the ageing process. Regarding its use for visual research purposes, it has scarcely been used to probe structure-function attentional mechanisms in AD. Buck et al. (1997) showed the ability of AD patients to shift attention between spatial locations and between objects, and the brain regions involved in these cognitive tasks using SPECT imaging. In AD patients, hypoperfusion in the right superior parietal lobe was correlated with shifts of attention between different spatial locations, while hypoperfusion in the left inferior parietal lobe was correlated with shifts of attention between different objects. These results support the specialized role of the right and left parietal regions in the spatial and object mechanisms of attention shifting respectively, and suggest that the cognitive profile associated with AD includes attentional impairments in both spatial and object-based levels.

van Rhijn et al. (2004) investigated the relationships between intermediate visual processes involving object and space perception and regional brain activity using FDG-PET and SPECT, in a group of AD patients. Their results showed significant region

specific correlations between unfamiliar face matching and cerebral activity in the left occipito-temporal region and middle/inferior temporal regions bilaterally. Letter-word identification was significantly correlated with brain activity in the angular gyri and occipital association cortices bilaterally, as well as a broad region of activation in the left hemisphere temporal, parietal and occipital lobes. Moreover, a significant correlation was found between ratings of performance of instrumental activities of daily living and brain activity in occipito-temporal and middle/inferior temporal regions, proving that the neuropathological distribution typical of AD corresponds to impairments in specific aspects of intermediate visual perceptual processing, and is related to the impairment on daily living skills of these patients.

Pietrini et al. (1996) also used FDG-PET to study two groups of AD patients: one with visual disturbances at onset and the other without them, comprising measures of regional cerebral glucose metabolic rates. Their aim was to investigate whether specific cortical networks associated with visual processes were preferentially affected in the subgroup with visual disturbances, and determine the clinical implications of such abnormalities. The results revealed that the two groups of patients showed reduced glucose metabolism in parietal and in middle and superior temporal regions, when compared to controls. The AD subgroup without visual disturbances also showed reductions in inferior temporal, frontal, and limbic structures, as is typical of this disease. In contrast, the subgroup with visual symptoms had larger metabolic deficits in the parietal and occipital cortices (including the primary visual cortex), with a relative sparing of inferior temporal, frontal and limbic regions. These results showed that AD patients with visual symptoms had significantly greater visuospatial deficits, and less severe memory impairments, than patients with no visual disturbances. The authors concluded that AD patients with visuospatial deficits have a distinctive regional distribution of cerebral metabolic impairment which is related to a specific cognitive impairment, thus distinguishable from patients with typical AD disturbance. Fujimori et al. (2000) showed that visuospatial disturbance was related to bilateral parietal metabolism, and that visuoperceptual disturbance was related to right temporo-parietal metabolism in patients with mild-to-moderate AD, in a FDG-PET experience within tasks of visuospatial recognition. Mielke et al. (1995) also found an

involvement of the secondary visual cortex in the pathological changes in AD, in a FDG-PET study.

These findings imply that regional disparities in brain dysfunction can occur in AD, with differential involvement of cortical structures resulting in distinctive clinical subgroups.

The neuropathological findings characteristic of AD, including neurofibrillary tangles (NFT) and neuritic plaques (NP), are also present in the visual cortical areas, especially in the visual association areas (Hof & Bouras, 1991). Armstrong (1996) suggested that pathological differences between cuneal and lingual gyri could contribute to the reported visual field defects in some AD patients, due to differences in density of NP and NFT in these areas. Butter et al. (1996) findings also proved that patients with AD, who have prominent visual symptoms, have accentuated histologic and metabolic abnormalities in the occipito-parietal regions known to process visual-spatial information.

The Pittsburgh Compound-B (PIB) ligand for PET (PiB-PET) imaging is one of the molecules that are improving the ability to differentiate AD from other neurodegenerative dementias. This compound and others have allowed for the delineation of maps of deposition of amyloid which will allow us to answer several questions but also raised several conundrums. If this distribution map of amyloid plaques should be used to differential diagnosis between AD and normal ageing, how can we reconcile them with the differences obtained with the other methods (Huddleston & Small, 2005)? Future in vivo studies should improve this scenario, because so far the number of case studies is relatively small. Moreover, not all conclusions agree with information from post-mortem studies (Klunk et al., 2004; Shoghi-Jadid et al., 2002). PET studies during activation indicate the brain's reserve capacity to respond to functional tasks. Since metabolism in AD patients during activation is more severely impaired than at rest, PET studies during (visual) functional tests could help in the selection of patients with a potential to benefit from therapeutic intervention (Kessler, Herholz, Grond, & Heiss, 1991).

In recent years, many studies have been proposed with the goal of developing substances which bind to amyloid plaques. These are meant to allow visualizing and locating plaques in vivo by PiB-PET (Jack et al., 2008). According to a study by

Ikonomovic et al. (2012), the above mentioned radiotracer PIB is considered one of the most valuable markers. In fact this marker that binds with high affinity to Aβ and seems to be one of the most relevant PET methods for in vivo evaluation of AD (Ikonomovic et al., 2012). Ishibashi et al. (2014) quantified the Aβ deposition in the striatum and several cortical regions, in patients with AD, through a PiB-PET study. These authors confirmed that there were ventral > dorsal, and anterior > posterior gradients of Aβ deposition in patients with AD, and provided the first evidence of a robust correlation between Aβ deposition levels in the ventral striatum and the medial part of the orbitofrontal area.

Other biomarkers of great utility, such as FDG-PET were used in addition to the PIB-PET in several studies, aiming to unveil the link between amyloid deposition and abnormal metabolism. Though some of the apparent discrepancies that were identified between studies may be explained by distinct binding affinities, the mismatches remain nevertheless puzzling: (i) Shoghi-Jadid et al. (2002), in their studies, used the radioligand [18F]FDDNP that binds to both amyloid plaques and neurofibrillary tangles. Main deposits were found in the medial-temporal lobe; nevertheless this was not in accordance with metabolic defects that were observed in lateral-temporal lobe using FDG-PET; (ii) Klunk et al. (2004) used the PiB-PET which selectively binds to only amyloid plaques and observed a large binding pattern in frontal lobe but the major metabolic defects were observed in parietal lobe.

One of the main interim conclusions has been that amyloid plaques deposits do not necessarily predict brain dysfunctions observed in AD (Huddleston & Small, 2005). One of the possible explanations to this divergence between cognitive and metabolic deficits and radioligand binding on patients may be that soluble amyloid oligomers are toxic but deposits may actually be innocuous per se or even protective by constituting an inert compartment (Engler et al., 2006; Mintun et al., 2006).

It is important to note that there is no definite consensus on the best neuroimaging technique to calculate the gradual conversion of MCI in AD. Yuan et al. (2009) concluded that FDG-PET showed better predictive capacity than SPECT or structural MRI techniques.

Posterior cortical Atrophy (ACP) – a visual variant of AD

Up to now we have focused on studies related to the typical AD (Dubois et al., 2010, 2014) or amnestic presentation (McKhann et al., 2011). Nevertheless, since we are focusing on the visual deficits of AD, it is imperative to refer that the recent criteria for AD comprise atypical forms of AD that include the posterior cortical atrophy (PCA; Dubois et al. 2010, 2014), or in the words of McKhann et al. (2011) - the visuospatial presentation of AD. Latter clinical criteria include: deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia, and deficits in other cognitive domains. In this section, we only wanted to take a brief overview on PCA's concept and not review research studies on this pathology. For a recent literature review see Beh et al. (2015); Borruat (2013).

PCA is an insidiously progressive dementia characterized by prominent disorders of higher visual processing as a result of an atrophy of the occipital and occipito-parietal regions of the brain. Benson et al. (1988) introduced the term PCA in 1988 to describe five patients with a progressive dementia, whose first symptoms were apraxia, alexia and visual agnosia. These patients usually have visual complaints, due to deficits in complex visual processing. This condition most commonly begins in the 50s or 60s with equal gender involvement, and a course of about 6-12 years (Cronin-Golomb, 2004). PCA patients have normal visual acuity but mild-to-moderate constriction of the peripheral visual fields; contrast sensitivity for low spatial frequencies can be severely impaired (as can be found for AD patients). These patients probably have deficits in depth perception similar to those seen in typical AD, and show an impairment in global as opposed to local processing (Cronin-Golomb, 2004) – simultanagnosia.

Visuospatial deficits such as Bálint's Syndrome (BS) are among the most common manifestations of PCA. This syndrome described by Rezso Bálint "is caused by bilateral lesions of the occipito-parietal junction that rendered its victims functionally blind" (Rafal, 2001). PCA patients can show: inability to copy or trace drawings ("constructional apraxia"); difficulty in visual integration of whole scenes ("ventral simultanagnosia") and detection of two or more stimuli simultaneously ("dorsal simultanagnosia") (Benson et al., 1988). This last condition leads patients to have their attention fixed on a single object or detail in the scene and neglect all the other objects – they perceive each object at a time (Rafal, 2001). Dorsal simultanagnosia is part of the triad of BS along with inability to look towards a stimulus by visual guidance

(oculomotor apraxia); and inability to reach for a stimulus by visual guidance (optic ataxia) (Cronin-Golomb, 2004).

Subjects with PCA may present dorsal simultanagnosia as an initial manifestation, but can manifest other isolated symptoms of BS during the course of the disease (Cronin-Golomb, 2004). These patients can also have deficits in visuospatial attention resulting in right or left visual field extinction, hemi-inattention, or hemispatial neglect. PCA is related with other visuospatial disturbances such as: general difficulty with spatial localization, environmental disorientation, dressing apraxia, and disturbed spatial cognition (determining the orientation or axes of non-upright objects) (Cronin-Golomb, 2004).

PCA patients can also show perceptual visual symptoms, as progressive visual agnosia, with impaired visual recognition, in the presence of intact tactile recognition. This condition is usually of the apperceptive type, given the presence of difficulty with figure-ground discrimination, vulnerability to ambient illumination, visual synthesis, fragmented or degraded stimuli, and matching and copying shapes. Colour perception can also be altered in PCA in the forms of hemiachromatopsia, colour anomia, or colour agnosia. Problems as prosopagnosia, or recognition of familiar faces, are less common in PCA probably due to sparing of the more anterior, inferior temporal lobes (Cronin-Golomb, 2004).

PCA subjects often complain of difficulties in reading or writing. Alexia that is disproportionate in comparison to other language problems is the most common disturbance in PCA. In addition to “pure alexia” (alexia without agraphia), visual disturbances such as simultanagnosia can play a role in producing alexia and in particular, letter-by-letter reading (Cronin-Golomb, 2004).

PCA have two major types of asymmetric variants: i) BS - if it comprises the dorsal “where” (occipito-parietal) visual pathway, thus resulting in spatial perception impairment; and ii) visual agnosia and impairment in object perception – if the ventral “what” (occipito-temporal) visual pathway is involved. This segregation of deficits into dorsal and ventral streams is not precise, and some patients have a mixture of disturbances from both. It is worth to note that PCA may affect one hemisphere more than the other. A great involvement of the left hemisphere can result in a progressive visual agnosia, Gerstmann’s syndrome (linguistic agraphia, acalculia, right-left

disorientation, and finger agnosia), right hemiachromatopsia, and pure alexia without agraphia. A predominant involvement of the right hemisphere can result in left visual hemi-neglect, oculomotor apraxia, dressing apraxia, alexia for music, and spatial agraphia (Cronin-Golomb, 2004).

PCA differs in several ways from typical clinical AD. PCA patients usually have a younger age of onset than those with typical AD. In PCA, memory and language are quite preserved until later in the course of the disease (Goethals & Santens, 2001), due to a relative sparing of the mesio-temporal region on this condition. In contrast, patients with typical AD have complex visual deficits later in the course of the disease, in contrast with PCA where a massive deposition of neurofibrillary tangles and neuritic plaques may occur in primary visual and visual association areas. PCA patients have also more insight for their illness and more depression, consistent with sparing of the frontal lobe (Cronin-Golomb, 2004). These patients showed hypometabolism in primary and extrastriate visual areas and in parietal and superior temporal cortical areas, relative to healthy aged controls; and hypometabolism in visual association areas, relative to amnestic AD subjects (Bokde et al., 2001), proving the selective involvement of the visual areas on this specific condition.

PCA is most commonly, but not exclusively, an atypical/non-amnestic form of AD. It corresponds to the “visual variant” of AD due to the neuropathology in primary visual and visual association areas (Cronin-Golomb, 2004).

General outline and aims of Chapter II

The main purpose of Chapter II of the current thesis was to investigate the visuospatial processing of AD and MCI pathologies and to further explore it as a potential new biomarker.

As previously reported, there is a lack of visual function studies in MCI when compared with the amount of research in AD. Some studies report an involvement of high-level visual functions, showing visual search/attentional impairment in MCI (Mapstone et al. 2003; Tales et al. 2005). Nevertheless, other functions may still be preserved in this condition (Rizzo et al. 2000). Despite the lack of cure or prevention for AD at the present moment, medication for modifying or slowing down the progression of the

disease is currently being developed, making biomarkers for early detection of true preclinical AD a major concern and priority. Given MCI's potential conversion predicting value, it is important to study visual function at its stage.

Moreover, Cronin-Golomb et al. (1995) suggested that visual dysfunction is a "significant predictor of cognitive dysfunction in AD" and "may have a strong functional impact on cognitive domains". This idea is corroborated by recent evidence indicating that sensory and motor changes may precede the cognitive symptoms of AD (visual system included) (Albers et al., 2015).

Behavioural studies through the use of psychophysical techniques are among the majority of references reported. But it is noteworthy that, in the recent years, the role of neuroimaging in the understanding of disease mechanisms in AD is becoming increasingly recognized. Neuroimaging has the potential to provide novel biomarkers, in addition to psychophysical and neurophysiological measures and to confirm the involvement of specific brain regions while performing visual paradigms.

Study 8, *Specific dorsal and ventral visual stream deficits in Mild Cognitive Impairment and Alzheimer's disease*, explored both the dorsal and ventral processings in AD and MCI. The inclusion of tasks requiring low-level visual engagement, as well as more high-level motion coherence detection paradigms, aimed at highlighting the visual dorsal stream dysfunction of AD and exploring the performance of MCI patients. An additional goal was to correlate the performance across the visual tasks with the cognitive results.

In Study 9 our main goal was to identify the structural correlates of the results observed in Study 8 and in Graewe et al. (2013) where deficits in complex face and object recognition in MCI patients were found. We wanted to explore the contribution of both ventral and dorsal visual areas as a putative biomarker of AD symptomatology. Our approach included a behavioral experimental paradigm with 3D SFM defined faces and objects and morphometric analysis including the computation of cortical thickness maps and hippocampal volumetry using MRI, in MCI.

At the end of this chapter, we present a discussion emphasising the main results of this studies, and thus reflecting on their main limitations, as well as the implications of including new protocols that quantify visual dysfunction in monitoring the disease progression in MCI and AD.

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STUDY 8

Specific dorsal and ventral visual stream deficits in Mild Cognitive Impairment and Alzheimer's disease

Adapted from: **Lemos, R.**, Figueiredo, P. M., Santana, I., Simões, M. R. & Castelo-Branco, M. (2012). Specific dorsal and ventral visual stream deficits in Mild Cognitive Impairment and Alzheimer's Disease. *Journal of Alzheimers Disease*; 28(4):885-896. doi: 10.3233/JAD-2011-110719.

Abstract

The nature of visual impairments in Alzheimer's disease (AD) and their relation with other cognitive deficits remains highly debated. We asked whether independent visual deficits are present in AD and amnestic forms of Mild Cognitive Impairment (MCI) in the absence of other comorbidities by performing a hierarchical analysis of low-level and high-level visual function in MCI and AD. Since parietal structures are a frequent pathophysiological target in AD and sub-serve 3D vision driven by motion cues, we hypothesized that the parietal visual dorsal stream function is predominantly affected in these conditions. We used a novel 3D task combining three critical variables to challenge parietal function: 3D *motion coherence* of objects of unknown *orientation*, with constrained *temporal integration* of these cues. Groups of amnestic MCI (N=20), AD (N=19) and matched controls (N=20) were studied. Low-level visual function was assessed using psychophysical contrast sensitivity tests probing the magnocellular, parvocellular and koniocellular pathways. We probed visual ventral stream function using the Benton Face recognition task.

We have found hierarchical visual impairment in AD, independently of neuropsychological deficits, in particular in the novel parietal 3D task, which was selectively affected in MCI. Integration of local motion cues into 3D objects was specifically and most strongly impaired in AD and MCI, especially when 3D motion was unpredictable, with variable orientation and short-lived in space and time.

In sum, specific early dorsal stream visual impairment occurs independently of ventral stream, low-level visual and neuropsychological deficits, in amnestic types of MCI and AD.

Introduction

Alzheimer's disease (AD) is the most common type of dementia and its pathophysiology may start years before the clinical onset, leading to the concept of preclinical AD (Albert et al., 2011; Dubois et al., 2007, 2010). This entity is separable from the clinical definition of Mild Cognitive Impairment (MCI; Petersen et al., 1999) and is operationally defined based on biomarkers such as CSF amyloid or elevated tracer retention on PET amyloid imaging. MCI is characterized by a greater cognitive impairment than that expected for age and education level but not into an extent to qualify patients as demented (Petersen et al., 1999). In AD it is however hard to find a solid link between the appearance of any specific biomarker and the subsequent emergence of clinical symptoms, and a substantial amount of work is still needed to validate and standardize the criteria that use biomarkers (Albert et al., 2011). In this study we have therefore focused on established AD and MCI.

AD is known to involve visual pathways, but the nature of its effects on vision in relation to functional pathways and disease stage still remains elusive (for a review see Duffy (2009). This point is of outstanding importance give that multimodal imaging studies have shown that dorsal stream parietal regions involved in 3D object processing (Mendes et al., 2005; Orban, 2011; Verhoef, Vogels, & Janssen, 2010) seem to be an early target of disease pathology in terms of cortical thinning (Ewers et al., 2011); amyloid binding (Apostolova et al., 2010; Chételat et al., 2010; Tosun, Schuff, Mathis, Jagust, & Weiner, 2011) and impaired metabolism (FDG-PET; Herholz, 2011; Morbelli et al., 2010).

Most previous functional studies do not separate visual processing across specific features and pathways from other cognitive processes. A notable exception is a study (Rizzo, Anderson, & Nawrot, 2000) in participants with AD which suggested static visual acuity, stereoacuity, dynamic visual acuity or motion direction discrimination are preserved or less affected in AD, in comparison with static spatial contrast sensitivity (CS), visual attention, shape-from-motion, color, visuospatial construction and visual memory. In any case, these studies on visual cognition have focused on established AD and not MCI. In addition to the described dorsal stream deficits (Rizzo et al., 2000) and attentional impairments (Tales, Muir, Bayer, & Snowden, 2002; Tales, Haworth,

Nelson, Snowden, & Wilcock, 2005), ventral stream (object recognition) deficits have also been reported, using the Benton Facial Recognition Test and the Overlapping figures task (Mosimann et al., 2004). A recent fMRI study examined visual processing in MCI (Bokde et al., 2008) but did not find any differences in task performance, in spite of the observed differences in activation patterns.

An event-related fMRI three-year prospective study (Vannini, Almkvist, Dierks, Lehmann, & Wahlund, 2007) investigated the function of brain regions in the visuospatial networks underlying preclinical symptoms in AD but no performance differences were found using an angle discrimination task. Nevertheless, increased parietal activation in progressing MCI has been suggested to reflect a reduced "neuronal efficacy" (a still controversial concept) due to accumulating AD pathology and to be predictive of future clinical decline. In line with this reasoning, another study (Teipel et al., 2007) showed that during face matching tasks, fusiform gyrus activation is positively correlated with cortical grey matter density of brain areas belonging to the ventral visual stream and negatively correlated with grey matter density of brain areas belonging to the dorsal visual stream, and that these effects are more pronounced in MCI patients than in controls. In this type of task there were no statistical differences found in task performance or activation between groups (Bokde et al., 2006). These studies are important because they pinpoint the occurrence of functional and structural changes in regions of the cerebral cortex (fusiform and in particular parietal) involved in the perception of 3D objects (Whitwell et al., 2007), but do not directly address differences in performance levels across clinical populations. Similar findings have been uncovered by electro-encephalography (EEG) measures, such as defined by a source image study that found three different neural patterns in aged individuals (Haupt, González-Hernández, & Scherbaum, 2008). Still other studies (Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005) have focused on altered resting state networks in MCI in AD. However, in spite of the value of pattern recognition based neuroimaging strategies, direct approaches that focus on psychophysical performance are needed. Here we chose to analyze low and high level visual performance in MCI and AD, with an emphasis on dorsal stream (parietal) performance in 3D vision tasks.

This hierarchical approach is justified by the notion that the retinocortical magnocellular pathway (sensitive to local motion and with high CS) represents the main projection to the visual dorsal stream, where motion integration takes place (Castelo-Branco et al., 2002, 2006, 2007). The parvocellular pathway is, on the contrary, contrast and motion insensitive, and responds to spatial detail (Silva et al., 2005) (its neurons behaving as high resolution channels, sensitive to high spatial frequencies). Importantly, it is essential to compare performance across multiple low and high-level tasks and understand their interdependence. Magnocellular impairment occurs in other neurodegenerative disorders such as Parkinson disease, and does not necessarily predict high-level motion integration deficits (Castelo-Branco et al., 2009; Silva et al., 2005). It is important to understand how these deficits in MCI and AD relate to intermediate (motion detection, speed and direction discrimination) and high-level motion processing (requiring global integration of coherent motion cues). We used a simple 3D visual task that required integration of motion cues (3D motion coherence task). Direction of motion was unpredictable and time constraints were either present or absent (Mendes et al., 2005).

In our study, we have therefore explored tasks requiring low-level visual engagement, as well as more high-level motion coherence detection paradigms (Mendes et al., 2005). Based on previous studies in other models of dorsal stream function (Castelo-Branco et al., 2007, 2009; Mendes et al., 2005), we designed a novel 3D task made to target dorsal stream (parietal) brain functions involved in AD pathology. Subjects just had to detect the presence of a "sphere" and task comprehension could be objectively controlled for in every subject by verifying that the shape of curve of the psychophysical response staircase moved monotonically to a threshold value. The "sphere" could be integrated from "signal" dots moving with its surfaces. "Noise" dots (not belonging to the surface) were also present. The percentage of signal dots (coherence level) varied between 0 and 100%.

In sum, the main goal was to highlight visual dorsal stream dysfunction in established AD and MCI by forcing participants to extract 3D *motion coherence* of objects of unknown *orientation*, with constrained *temporal integration* of these cues. An additional goal was to establish a correlation between performance across tasks

recruiting different levels and streams of visual analysis, and clinical/neuropsychological stage.

Methods

Participants

Both MCI (n=20) and AD (n=19) patients were recruited from the Neurology Department of Coimbra University Hospital. The clinical evaluation was performed by one of the authors (I.S.) and the diagnosis was established following Petersen's classification criteria for MCI (Petersen, 2004) and NINCDS-ADRDA (McKhann et al., 1984) criteria for AD. MCI patients included in this study were of the amnestic type and the diagnosis was made in accordance with published criteria (Albert et al., 2011; Petersen, 2004; Petersen et al., 1999) and taking into account the use of imaging biomarkers to exclude other comorbidities (Albert et al., 2011). We have focused on patients with amnestic single domain MCI (at high risk for AD) and excluded patients with amnestic multidomain MCI. Controls underwent the same evaluation to exclude MCI, as well as ophthalmological assessment concerning exclusion criteria for visual conditions (Castelo-Branco, Faria, Forjaz, Kozak, & Azevedo, 2004).

Diagnostic investigation included a standard clinical evaluation, an extensive cognitive and staging assessment, laboratory tests and imaging studies. Standard laboratory tests (including apolipoprotein E (ApoE) allele genotyping, imaging studies (CT or MRI) and SPECT were always performed in both patient groups. For genotyping, DNA was isolated from whole blood using a commercial kit (Roche Diagnostics GmbH, Manheim, Germany), as described by the manufacturer. ApoE genotype was determined by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP) assay. A comprehensive diagnostic battery was administered, including: 1) Cognitive instruments as the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) Portuguese version (cut off scores were adjusted for education level according to (Guerreiro et al., 2008: 3 cut offs for 3 education levels), the Alzheimer Disease Assessment Scale-Cognitive [ADAS-Cog; Mohs, Rosen, & Davis, 1983) Portuguese version (Guerreiro, Fonseca, Barreto, & Garcia, 2008)] and a comprehensive neuropsychological battery with normative data for the Portuguese

population (BLAD; Guerreiro, 1998) exploring memory (Wechsler Memory Scale subtests) and other cognitive domains; 2) The Clinical Dementia Rating (CDR; Garrett et al., 2008; Morris, 1993) was used for global staging.

MCI patients were identified as follows: 1) A subjective complaint of memory decline (reported by the subject or an informant); 2) An objective memory impairment (considered when scores on standard Wechsler memory tests were 1.5 standard deviation below age/education adjusted norms); 3) Normal general cognition suggested by normal scores in the MMSE and ADAS-Cog using the Portuguese cut off scores (Guerreiro, Fonseca, et al., 2008; Guerreiro, Silva, et al., 2008); 4) Largely normal daily life activities; 5) Absence of dementia, indicated by a CDR rating of 0.5; and 6) Exclusion of co-morbidities using imaging methods. The patients of the MCI group were previously characterized in two previous studies from our group (Baldeiras et al., 2008, 2010) the first concerning oxidative damage, and the second being a follow-up study of progression to AD. In this last study, within the group showing conversion to dementia (within two years), 6 subjects were part of the present study and 4 were ApoE-ε4 allele carriers.

Control subjects (n=20) were recruited among the patients' spouses, age-matched hospital or university staff, or their relatives, all participants belonging to the local community, without any neurological or psychiatric relevant condition. All control subjects had normal MMSE scores (mean 28.9), absence of memory impairment and normal daily life activities. All subjects from the 3 groups were submitted to the same experimental research protocol.

Informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of the ethics committee of the Faculty of Medicine of Coimbra. All subjects underwent full ophthalmologic examination that consisted of best-corrected visual acuity (VA; Snellen chart), slit lamp examination of anterior chamber, IOP measurement (Goldman applanation tonometer), angle and fundus examination (Goldman lens), cataract grading by the Lens Opacities Classification System II (LOCS) and the assessment of subjective visual complaints.

As exclusion criteria we considered neurological/psychiatric conditions other than MCI and AD; CT or MRI demonstration of significant vascular burden (Román et al., 1993)

(large cortico-subcortical infarct; subcortical white matter lesions superior to 25%; uni or bilateral thalamic lacune; lacune in head of caudate nucleus; more than 2 lacunes); diabetes, glaucoma, visual acuity < 0.6 , high ammetropy (sphere dpt > 4 and cylinder dpt > 2), untreated cataract requiring surgery, ocular motor paralysis, congenital amblyopia or hereditary colour blindness of retinal origin and other ophthalmological diseases.

The three groups were matched for age [F(2,56)=1.800, *p*=0.143] and education levels [F(2,56)=0.225, *p*=0.79]. The education level was not significantly correlated with sensory performance.

Demographic and clinical characteristics of the population are shown in Table 8.1.

Procedure

- Neuropsychological assessment

To study overall cognitive functioning of the three groups, we used an extensive neuropsychological test battery. The general cognitive function/verbal intelligence was measured with the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 2008). Verbal memory was assessed with the Portuguese version of the Rey Auditory Verbal Learning Test (RAVLT; Cavaco et al., 2008), and visual memory was measured by the Benton Visual Retention Test (BVRT; Benton, Hamsher, & Spreen, 1994). The Digit Span (Forward and Backward recall versions) and the Digit Symbol of the WAIS-III (Wechsler, 2008) were also tested. Face perception was assessed by the Benton Facial Recognition Test (Benton et al., 1994). Handedness was defined by using a translated version of the Edinburgh Handedness Inventory (Oldfield, 1971).

- Psychophysical assessment of visual function

All participants performed chromatic and achromatic CS testing under monocular conditions (using the dominant eye as a pseudorandom choice criterion), in centre (5 degrees) and peripheral (5 to 10 and 10 to 20 degrees) visual locations. Stimuli were displayed on a 21 inch monitor (GDM-F520; Sony, Tokyo, Japan) that was gamma-corrected.

Hierarchical approach to study the magnocellular and dorsal stream processing's.

1) Assessment of low-level (magnocellular) performance:

Here we used a very simple contrast detection task, using stimulus characteristics that are suited to activate the magnocellular pathway. This pathway is motion and CS and feeds to the visual dorsal pathway.

CS measurements were therefore applied using stimuli with high temporal and low spatial frequency. We have applied CS multiple interleaved staircase test strategies, where stimuli were patches of 0.25 cpd (cycle per degree) of vertically oriented sinusoidal gratings, undergoing 25 Hz counterphase flicker, that are best suited to assess the magnocellular system (Castelo-Branco et al., 2006; Silva et al., 2005; 2008). Standard voltage–luminance curves were measured for each phosphor with software and hardware (including a Minolta colorimeter) provided by CRS (Cambridge Research Systems, Rochester, UK), which ensured gamma correction. Mean background luminance was 61.7 cd/m^2.

2) Parvocellular/Koniocellular pathways:

The parvocellular pathway is sensitive to specific modulations of red-green color contrast whereas the koniocellular pathway is modulated by chromatic modulations in the blue-yellow axis. Our psychophysical strategy did therefore rely on these types of manipulation.

We have probed the parvo and koniocellular pathways using a computer controlled psychophysical method taken from the Cambridge Color Test [Cambridge Research Systems (CRS), Rochester, UK] (Castelo-Branco et al., 2004). This technique uses a luminance noise strategy that forces the subject to rely exclusively on color cues to identify the position of a gap in a Landolt-like C-shaped ring. Implementation and calibration procedures were performed with software and hardware provided by CRS (Minolta colorimeter; calibration software and CRS/VSG 2/5 graphics card, with 15-bit contrast resolution per pixel). All participants viewed with refraction corrected for viewing distance a screen with a pattern of circles of various sizes and luminance with superimposed chromatic contrast defining the C-ring. The monocular viewing conditions were such that of all areas it was the macular area of the retina that the patients had to use to perform chromatic comparisons. Given the subjects' average age, and to exclude confounding factors such as motor errors, the experimenter recorded subjects' oral responses using a 4-button response box. To further emphasize accuracy versus speed in the measurement of psychophysical responses, subjects were

instructed that they had up to 20 seconds to report their decision. The subject had to indicate one out of four possible gap positions (bottom, top, left and right) of the Landolt C stimulus. Luminance and size variation of stimulus patches forced the subject to use specific color cues, since he/she could not use spatial or luminance cues to infer the embedded shape. These patches were randomly assigned six different luminance noise levels (8 to 18 cd/m^2 in steps of two units). A minimum excursion of 0.002 units in CIE 1976 u' v' color space was then superimposed on such noise levels, to define the chromatic shape.

The chromaticity of the Landolt C shape was adjusted according to a staircase procedure (see below). Quantitative adjustment in terms of modulation of chromatic contrast allowed for isolation of cone or color-opponent specific responses in CIE 1976 (u' v' color space). Chromatic performance along the classical cone axes (protan, deutan and tritan) were explored with algorithms implementing three independent random staircases, from the Trivector version of the test, which ensured unbiased measurement of thresholds across the three main chromatic axes.

Hierarchical approach to the study of integrative dorsal stream's processing.

1) Assessment of high-level 3D structure-from-motion (SFM) performance:

The choice of the task was made to target functions from dorsal stream brain regions (posterior parietal) involved in AD pathology and sub-serving 3D vision. Given the nature of the clinical populations we designed a very simple task where subjects just need to report the presence of a "ball or sphere". This task is very easy to perform because the "sphere" becomes very noticeable, with a strong 3D percept, once stimuli are above threshold. Comprehension and performance can objectively be controlled by analysing the shape of the curve of the psychophysical staircase (if the subjects understand the task, the staircase converges in a monotonic way to asymptotic threshold levels). This represents a great methodological advance because one can reliably control for correct task performance using objective criteria. We also had a familiarization session prior to the formal test and made sure that all subjects understood the task. This was then verified by analysis of the psychophysical staircase.

Motion stimuli were generated using Vision-WorksTM for Windows (Vision Research Graphics, Wisconsin, USA) in a Trinitron GDM-F520 monitor. Viewing distance was 56

cm. Pixel size was 0.056 degree^2 and dot size was 3*2 pixels. Dot density was 3 dots/degree^2. Background luminance was ~0 cd/m^2 and one pixel had approximately 18 cd/m^2. In all experiments, a two-alternative forced-choice staircase method (temporal) was used (with 12 reversals, 6 practice and 6 experimental). Steps were 0.01 log units in size. Durations of fixed stimulus presentations were of 200 ms in the main test, after which a grey background appeared, and was present until the subject responded and the next trial commenced. In an additional control task stimuli were present until the behavioural response.

Visual thresholds were measured in terms of motion coherence of spherical surfaces. The stimulus consisted of dots placed on the surface of a rotating sphere 3-in diameter revolving around an imaginary axis, whose angle varied in a pseudo-random way. Speed of revolution was purposefully slow (20 rpm). The sphere alternated within one aperture with a stimulus consisting of 100% noise dots that moved at 2 degrees/s. Subjects had to report the presence or absence of a rotating sphere.

Statistical analysis

Statistical analysis was performed with the STATVIEW and SPSS software packages (SAS, Cary, NC and SPSS, Inc., Chicago, IL, respectively). We have used ANOVA after verifying statistical assumptions using the Kolmogorov-Smirnov normality check and Levene homogeneity tests. Pearson correlation analysis between visual low (magno/parvo), high level (dorsal/ventral) parameters of visual function and neuropsychological measures was also performed.

Results

Neuropsychological evaluation

Concerning demographic variables (Table 8.1), ANOVA showed neither group effects concerning age nor education.

Table 8.1. Demographic and Clinical characteristics of the population

	Controls (n=20)	MCI (n=20)	AD (n=19)
Gender (m:f)	10:10	10:10	7:12
Age (years)	67.6 (8.7)	69.9 (8.1)	73.1 (8.9)
Education Level (years)	9.7 (6)	8.8 (5.3)	8.5 (5.7)
MMSE (score)	28.9 (1.1)	27.8 (2.1)	22.4 (3.3)
CDR (score)	--	0.5 (0.0)	1.0 (0.0)
ApoE ε4 carrier, n(%)	--	9 (45)	9 (47)

Abbreviations: MCI = Mild Cognitive Impairment
AD = Alzheimer's disease
MMSE = Mini-Mental State Examination
CDR = Clinical Dementia Rating
Note: Data are expressed as mean (SEM) except for the ApoE carrier state.

For neuropsychological performance, we found main effects for Digit Symbol [F(2,56)=10.8, *p*<.001]; Backward Digit Span [F(2,56)=5, *p*=.01]; Vocabulary subtest of the WAIS-III [F(2,56)=7.6, *p*=.001]; BVRT [F(2,56)=20, p<.001] and RAVLT. Except for the expected deterioration observed in MCI for RAVLT measures, post hoc (Dunnett) analysis showed that these differences were mainly due to the deterioration observed in AD patients (post hoc *t* comparisons with the control group: Digit Symbol, *p*<.001; Backward Digit Span, *p*=.01; Vocabulary, *p*<.001; BVRT, *p*<.001). MCI participants showed a performance pattern in these tasks that did not significantly differ from controls except in RAVLT, as expected. Concerning memory performance, we did indeed observe the expected pattern of amnestic deterioration as indexed by performance differences in the RAVLT (total trials 1-5, recall and recognition measures) depicted in Table 8.1 (F(2,56)=11.4, *p*<.001, total trials 1-5 RAVLT; F(2,56)=40.6, *p*<.001, recall RAVLT; F(2,56)=39.2, *p*<.001, recognition RAVLT). In all these memory measures, the two pathological groups were impaired (post hoc Dunnett: Total trials 1-5, Controls *versus* AD: *p*<.001; Recall Controls *versus* MCI: *p*<.05; and Recognition, Controls vs. MCI: *p*<.01).

Table 8.2. Neuropsychological data

	Controls (n=20)	MCI (n=20)	AD (n=19)	*F*	Between-group comparisons
Handedness (R:L)	19:1	20:0	19:0	NA	NA
Vocabulary – WAIS-III (raw score)	44.2 (3.2)	36.5 (2.9)	27.6 (2.7)	7.6	p =.001*
RAVLT (total trials 1-5)	43.4 (1.8)	36.5 (2.3)	20.9 (1.8)	11.4	p <.001[†]
RAVLT (Recall)	10.0 (0.6)	6.6 (0.8)	1.3 (0.6)	40.6	p <.001[‡]
RAVLT (Recognition)	29.3 (0.3)	26.5 (0.7)	21.2 (0.9)	39.2	p <.001[‡]
BVRT (total correct)	4.6 (0.3)	4.4 (0.3)	1.9 (0.3)	20.0	p <.001*
BVRT (errors)	8.9 (0.6)	10.5 (1.0)	17.6 (0.9)	30.6	p <.001*
Digit Span – WAIS-III (forward)	7.2 (0.4)	7.3 (0.4)	6.6 (0.4)	0.6	*NS*
Digit Span – WAIS-III (backward)	4.8 (0.4)	4.7 (0.4)	3.3 (0.3)	5.0	p =.01[§]
Digit Span – WAIS-III (total)	12.0 (0.7)	11.9 (0.6)	9.9 (0.7)	2.9	*NS*
Digit Symbol – WAIS-III (raw score)	30.4 (3.5)	22.8 (2.1)	13.0 (1.9)	10.8	p <.001*

Abbreviations: WAIS-III = Wechsler Adult Intelligence Scale-Third edition.
RAVLT = Rey Auditory Verbal Learning Test.
BVRT = Benton Visual Retention Test
Note: Data are expressed as mean (SEM).
Post hoc Dunnett tests compared Controls vs. MCI, Controls vs. AD, MCI vs. AD, and significant group differences are reported:
* Controls vs. AD: p <.001.
[†] Controls vs. MCI: p <.05; Controls vs. AD: p <.001; MCI vs. AD: p <.001.
[‡] Controls vs. MCI: p <.01; Controls vs. AD: p <.001; MCI vs. AD: p <.001.
[§] Controls vs. AD: p <.05.
NA = not applicable.
NS = not significant (p >.05).

Low-level visual magno and parvocellular function in central and peripheral visual field

- Functional evaluation of the magnocellular pathway (sensitive to local motion and with high CS):

Central visual performance was preserved in all groups, in contrast to peripheral visual field performance (main effects: F(2,56) >7 for all peripheral regions: p<.001 for nasal, temporal and inferior regions, p<.002 for superior regions. Post hoc comparisons were all significant for the AD group (p<.001, for all tests). Interestingly, the MCI group showed a specific pattern of impairment in the temporal region (Figure 8.1, p=.04, post hoc Dunnett *t* test).

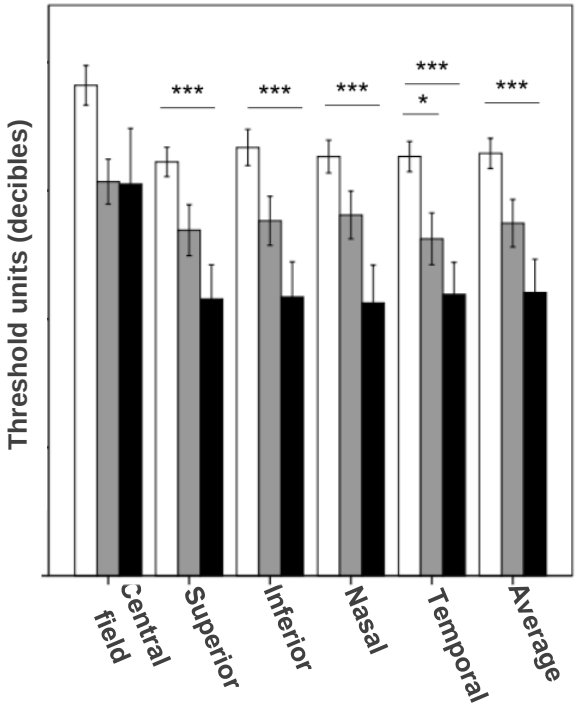

Figure 8.1 Performance of the magnocellular system (sensitive to local motion and contrast) across the visual field is preserved in central vision for both clinical groups, impaired in all peripheral regions in AD (black), and notably, already significantly impaired in the peripheral temporal region in MCI (grey) when compared to controls (white). This region is known to vulnerable to early damage in some neurophthalmological diseases.

Error bars depict standard error of the mean (SEM). The dependent measure is CS measured in decibel units.
*p <.05; ***p <.001.

- Functional evaluation of the parvocellular and koniocellular pathways (sensitive to chromatic contrast along the red-green and blue yellow axes, respectively):

We isolated the function of parvocellular and koniocellular pathways by means of imposed colour modulation across specific contrast axes. We found a main group effect of CS loss across tritan (blue cone), protan (red cone) and deutan (green cone) pathways (F(2,56) = 7.6; 4.9; and 7.68, respectively with p=.001; .01 and .001, respectively). Post hoc analyses confirmed that these effects stemmed from the differences observed between the AD and the control group (p=.001; .01 and .001, respectively, in post hoc t tests). In sum, both parvocellular (red-green) and koniocellular (blue-yellow) pathways show significant impairment in AD, no significant changes being observed in MCI (Figure 8.2).

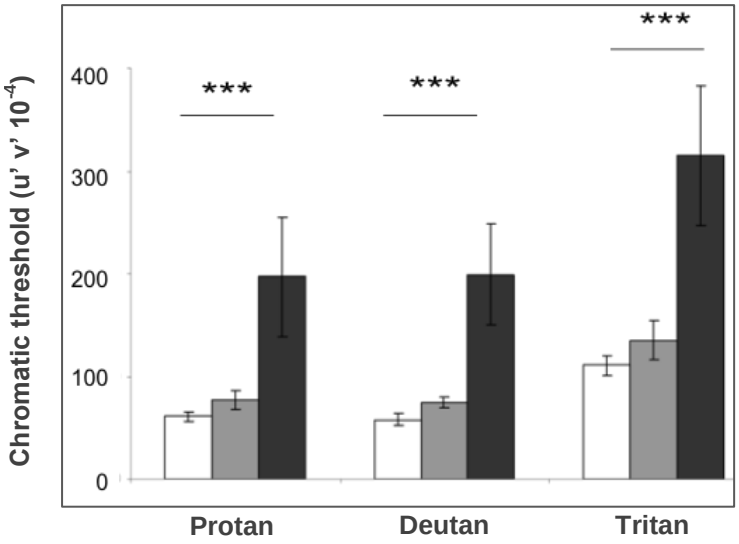

Figure 8.2 Both parvocellular (red-green) and koniocellular (blue-yellow) pathways show significant impairment in AD (black), no significant changes being observed in MCI (grey) when compared to controls (white).

Error bars depict standard error of the mean (SEM). The dependent measure is color excursion units measured in CIE u' v'color space units (enabling measures of chromatic contrast).

***p <.001.

<u>High-level visual function in the dorsal parietal (3D object perception from motion cues) and ventral streams (static 2D object perception)</u>

We assessed object recognition, as an index of ventral stream function by means of the Benton Face Recognition Test. We observed again a main group effect ($F(2,56)=13.5$; $p<.001$) which was again solely explained by the difference between the AD group and the control group (Dunnett test, $p<.001$). This finding is further illustrated in Figure 8.3, which suggests that face discrimination recognition performance is significantly impaired only in the AD group.

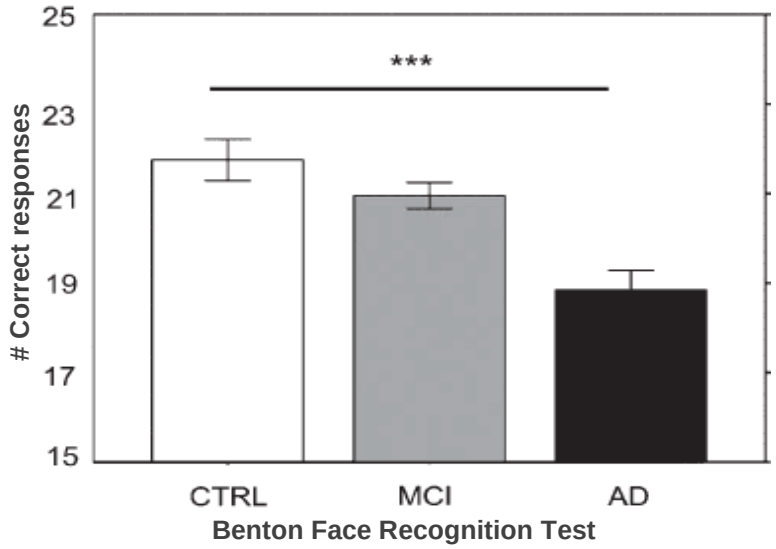

Figure 8.3 Visual ventral stream performance in AD and MCI. Face discrimination recognition performance (as measured with the Benton Face Recognition Test) is significantly impaired only in AD.

Error bars depict standard error of the mean (SEM). The dependent measure is number of correct responses.

***p <.001.

Concerning dorsal stream function, we have used the novel 3D visual task (Figure 8.4). To increase the dorsal stream demands of the task, the 3D spheres had a random axis of rotation, which forced discrimination of signal *versus* noise across multiple possible orientations. This rendered the task quite difficult especially for the 200 ms temporal presentation time condition. In an additional control condition, the participant was exposed to no limited stimulus presentation, rendering the task free of temporal integration constraints. Under both conditions (short and unlimited temporal presentation) a main effect of group was observed ($F(2,56) = 26.3$ and 10, respectively, $p<.001$ for both conditions). Post hoc analysis showed that this effect was significant for the MCI group only in the temporally constrained integration condition ($p=.035$ for the comparison between MCI and control participants, $p<.001$ for the comparison between AD and control participants, post hoc *t* tests). Time is therefore a critical variable in the performance of this 3D task. In sum, the ability to detect simple 3D spheres with unpredictable axis of rotation and immersed in noise (variable 3D structure-from-motion task) is significantly impaired in AD and even MCI subjects (Figure 8.4). Interestingly, ROC analysis of this novel measure showed a significant discriminatory power of the AUC (area under the curve measure) in AD (AUC=0.96,

p<.001, with sensitivity reaching 90% for a specificity above 95%). In MCI discriminatory power was also significant (AUC=0.7, *p*<.05, with sensitivity reaching 70% for a specificity above 65%). The novel 3D task was the most discriminative in terms of identifying visual dysfunction (as measured by the ROC based AUC) in AD (AUC = 96%, as compared to 78% in magnocellular measures, and 87% in parvocellular measures).

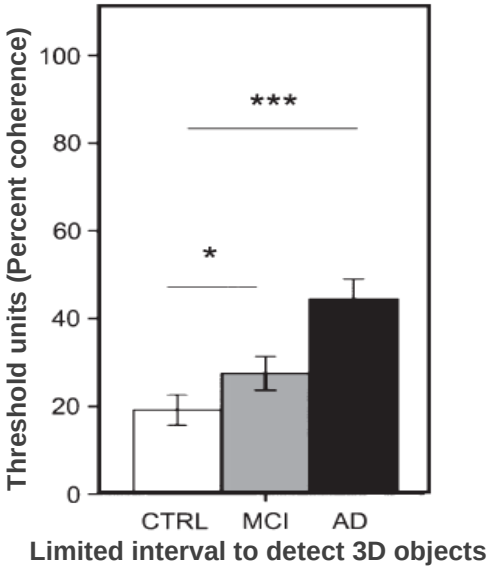

Figure 8.4 Visual dorsal stream performance in AD and MCI, using a novel 3D task. The ability to detect moving 3D spheres with unpredictable axis of rotation, during a fixed temporal exposure (200 ms) and immersed in motion noise (variable 3D structure from motion task) is significantly impaired in MCI and AD.

Error bars depict standard error of the mean (SEM). The dependent measure is % coherence (percentage of signal dots that are necessary for the subject to report the presence of a sphere).

**p* <.05; ****p* <.001.

<u>Correlation analysis between visual low (magno/parvo), high-level (dorsal/ventral) parameters of visual function, and neuropsychological measures.</u>

- Control Group

Visual function measures were found to be uncorrelated between performance measures testing low and high-levels of processing, as expected from the stimulus construction approach, which attempted isolation of distinct functional mechanisms (magno, konio, parvocellular, high level 3D vision and high level cognitive functions). Accordingly, correlations between high level (3D perception), low level magnocellular, parvocellular and neuropsychological measures (Vocabulary, MMSE, Digit Span and Digit Symbol, RAVLT) were absent.

- AD

Concerning the AD group, no significant correlations were observed between magnocellular and dorsal stream 3D motion integration measures. Surprisingly, parvocellular function was significantly correlated with 3D motion coherence performance when temporal integration was constrained (*p* (corrected) <.05 for the green cone pathway, *r*=0.53) suggesting concomitant pathophysiology.

Interestingly, both SFM (structure from motion 3D tasks, with or without in time constraints) share a relatively low amount of variance (25% percent in this group), which is consistent with the observation that visual temporal integration is strongly impaired in AD.

Correlations between high level (3D perception) and neuropsychological measures (RAVLT, Vocabulary, MMSE, Digit Span and Digit Symbol) were not significant except for the MMSE measure (*r*=- 0.74, *p*<.05). Low level magnocellular and parvocellular visual measures were not significantly correlated with neuropsychological measures.

- MCI

The MCI group showed a correlation pattern that was more similar to the AD group than to controls, with parvocellular measures showing correlations with SFM (3D structure from motion) performance at both temporal presentation schemes (in particular for the red pathway, *p* (corrected) <.05 , *r*=0.60). Interestingly, temporal field magnocellular measures also showed significant correlations with SFM performance in particular for the short presentation condition (*p* (corrected) <.05, *r* = -0.56). The negative correlation is due to the fact that higher SFM scores correspond to worse performance and high achromatic CS scores in magnocellular tasks correspond to better performance. Correlations between high level (3D perception), low level magnocellular, parvocellular visual measures and neuropsychological measures were not significant, showing that other cognitive factors were not influencing task performance.

Discussion

Our results provide evidence for early dysfunction of dorsal stream (parietal) pathways processing 3D motion information relevant to object perception in MCI and AD, by

using objective psychophysical tests of achromatic CS, colour perception, 3D structure from motion and face perception. The specific pattern of impairment found in our patient samples suggests that occipital and parietal networks involved in 3D perception are dominantly affected in the course of disease, in relation to early visual magno, parvo and koniocelullar pathways.

The 3D task was made to target functions from dorsal stream brain regions (posterior parietal) involved in AD pathology and sub-serving 3D vision. The task was very easy to perform because the subjects just had to detect the presence of a "sphere" and comprehension and performance could be objectively analysed by the shape of curve of the psychophysical response staircase (moving asymptotically to a threshold value).

This type of impairment in 3D visual perception was found to be selectively present in MCI as opposed to magno/parvocellular impairment (related to local motion and spatial resolution processing, respectively) and high level visual processing deficits based on the ventral stream (related to static 2D object processing). The visual deficit in 3D processing was also dominant in AD. We were able in this way to show that high-level integration of local motion cues into 3D objects was impaired in MCI and AD, especially when 3D motion was unpredictable and short lived. This independent impairment was not explained by other neuropsychological deficits, as revealed by correlation analysis, and was significantly discriminatory of AD and MCI groups, as revealed by ROC analysis.

Although it is already known that high level object perception is impaired in AD (Duffy, 2009), studies focusing on sensitive and specific paradigms that can unravel pathway specific impairment in this condition and MCI are still lacking. The combination of three critical variables that are relevant for dorsal stream function: 3D motion coherence (*%* signal versus noise motion cues), requiring motion cue integration, discrimination of 3D orientation of objects, and temporal integration of these cues, was relevant in this respect. This is because we have probed the ability to integrate motion signals from noise signals (which percentage varied) to perceive 3D rotating spheres with unpredictable orientation. Performance under noisy conditions may be important in real life conditions as well as in biomarker search. To increase the dorsal stream demands of the task, these spheres had indeed a random axis of rotation, which forced discrimination of signal *versus* noise across multiple possible integration

axes. Interestingly, we also found evidence that available time is critical in perceptual integration in this condition.

Previous studies have shown impaired space-motion perception in late stages of Parkinson's disease (accompanied with dementia) (Mosimann et al., 2004), and our study extends its logic and design by exploring motion perception in a hierarchical manner (separating local from global motion perception), in MCI and AD. Furthermore, we have explicitly correlated motion integration skills with magnocellular function. Impairment of more basic detection of local displacement had been reported previously in Parkinson's disease, but the low *versus* high-level correlation with magno/dorsal stream dysfunction was not explicitly attempted (Silva et al., 2008). Our correlation analysis shows the expected absence of association across measures of low and high level visual function in normal subjects. Remarkably significant correlations between visual function measures were observed in both patient groups, suggesting an ongoing pathophysiological process that commonly affected multiple pathways. Notably, these correlations were not observed with neuropsychological measures, showing that psychophysical measures were genuinely independent.

Interestingly, we found a magnocellular pattern of loss in the supero-temporal visual field in MCI. This pattern of early damage in some is in agreement with the known physiological lower functional reserve of this region (Silva et al., 2008, 2010) and features a vulnerability that is also observed in other visual disorders (Castelo-Branco et al., 2002; Maia-Lopes et al., 2008; Mendes et al., 2005).

Concerning MCI patients it appears that parietal (dorsal visual) function, as measured by the novel 3D task, is probably affected earlier than occipital (early visual) cortex and infero-temporal (ventral visual) functions. In AD patients, this task was the most discriminative in terms of identifying visual dysfunction (as measured by the ROC based AUC measure). However, we also find that CS impairments are more salient in visual peripheral representations (in AD and to a smaller extent in MCI) suggesting a novel dissociation pattern between central (foveal) and peripheral loss patterns in these conditions. This dissociative profile is consistent with our previous findings concerning physiological integration of signals in central and peripheral processing (Kozak & Castelo-Branco, 2009; Ribeiro & Castelo-Branco, 2010). In any case, the demonstration that low signal to noise strength in space and time have a strong impact

on performance, generalizes to high level domains the notion that enhanced stimulus strength may improve visual cognition in aging and AD (Cronin-Golomb, Gilmore, Neargarder, Morrison, & Laudate, 2007).

One limitation of our study is however that we could not address preclinical/prodromal AD, as operationally defined using biomarker criteria (Albert et al., 2011). Future studies should address this issue.

We conclude that impaired dorsal stream (parietal) integration of 3D moving objects in short time windows occurs independently of ventral visual stream and neuropsychological deficits in amnestic types of MCI and AD. These deficits can be detected with high sensitivity both in MCI, and particularly in AD, using the reported novel 3D task, which allows separation between low and high level visual and other cognitive deficits.

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STUDY 9

Dorsal-ventral integration in the recognition of 3D SFM objects in mild cognitive impairment: a structure-function correlational study

Adapted from: **Lemos, R.**, Santana, I., Caetano, G., Bernardino, I., Morais, R., Farivar, R., & Castelo-Branco, M. (2015). 3D face recognition in Mild Cognitive Impairment: a psychophysical and structural MR study. *(submitted to publication)*

Abstract

Mild Cognitive Impairment (MCI) has been associated with a high risk of conversion to Alzheimer's disease (AD). In addition to memory complaints, impairments in the visuo-spatial domain have been reported in this condition. We have previously shown that deficits in perceiving structure-from-motion (SFM) objects are reflected in functional reorganization of brain activity within the visual ventral stream. Here we aimed to identify structural correlates of psychophysical face recognition performance in amnestic MCI patients (n=30 *versus* n=25 controls). This study was therefore motivated by evidence from recent studies showing that a combination of visual information across dorsal and ventral visual streams may be needed for the perception of 3D SFM objects.

In our experimental paradigm participants had to discriminate 3D SFM objects (faces) from 3D SFM meaningless (scrambled) shapes. Morphometric analysis established biological evidence for impairment in MCI as demonstrated by reduction of left hippocampal volume. We found association between cortical thickness and face recognition performance, comprising occipital lobe and visual ventral stream fusiform regions (overlapping the known location of face fusiform area) in the right hemisphere, in MCI.

We conclude that impairment of 3D visual integration already exists at an early stage of MCI which also involves the visual ventral stream and contributes to face recognition deficits in biologically identified prodromal AD. The specificity of such observed structure-function correlation for faces suggests a special role of this processing pathway in health and disease.

Introduction

The clinical interest in predicting progression of cognitive impairment to dementia (particularly Alzheimer's disease – AD) has led to the definition of a transition period between normal cognitive function and dementia. This period has been defined using various clinical syndromal terms such as mild cognitive impairment (MCI; Petersen et al., 1999), prodromal AD (Dubois et al., 2007, 2010) and "MCI due to AD"(Albert et al., 2011).

In addition to the expected objective memory deficit, other brain systems may be altered in the preclinical (pre-dementia) phases of AD, including visual function. Distinct forms of visual impairment have been extensively reported in AD, ranging from contrast sensitivity and color perception deficits to impairments in higher-order visual functions, including object and face perception and visual attention, as well as visual memory and learning (Butter, Trobe, Foster, & Berent, 1996; Duffy, Tetewsky, & O'Brien, 2000; Rizzo, Anderson, & Nawrot, 2000).

In a previous study, we found a selective deficit regarding integration of local motion cues into 3D objects (structure-from-motion – SFM – stimulus) in a MCI group (Lemos, Figueiredo, Santana, Simões, & Castelo-Branco, 2012). The perception of SFM stimulus requires the integration of the local motion cues to extract the 3 D global configuration. Accordingly, the neural correlates of SFM perception involve the integration of two main visual cortical pathways: the ventral stream underlying the recognition of object shape properties and the dorsal pathway involved in spatial vision and motion perception (Farivar, Blanke, & Chaudhuri, 2009; Konen & Kastner, 2008).

Early evidence from primate studies reported strong tuning in MT for motion gradient selective neurons (Xiao, Marcar, Raiguel, & Orban, 1997), suggesting that the center-surround structure may support 3-D slant and curvature perception. Mysore, Vogels, Raiguel, Todd, & Orban (2010) showed the selectivity of FST neurons for stimuli depicting specific shapes, coding motion-defined 3D shape fragments and underscoring the central role of FST in processing 3D SFM.

Interestingly, the neural substrates of SFM perception in MCI patients were found to predominantly relate to aberrant patterns of activation in FFA/OFA in the presence of

normal recruitment of motion selective areas (MT), suggesting the activation pattern within the ventral visual stream as a putative biomarker for MCI (Graewe et al., 2013). The study of visuospatial perception in the MCI group using an experimental paradigm requiring dorsal and ventral processing may be important to clarify the role of these two visual pathways in the prediction of AD and better understand its pathophysiology, besides medial temporal lobe areas already known to be affected in this disorder (Jacobs et al., 2015; McKee et al., 2006; Villain, Chételat, Desgranges, & Eustache, 2010; Villain, Fouquet, et al., 2010).

Psychophysical evidence corroborates this need, by indicating that the ventral visual pathway is more affected in full blown AD (Cronin-Golomb, 2004; Rizzo et al., 2000). Dorsal visual deficits have nevertheless also been documented in AD (A. L. W. Bokde et al., 2010; Kavcic, Vaughn, & Duffy, 2011; Lemos et al., 2012). Previous functional Magnetic Resonance Imaging (fMRI) studies suggested that reorganization may occur in both streams (Bokde et al., 2006; Prvulovic et al., 2002; Teipel et al., 2007; Vannini, Almkvist, Dierks, Lehmann, & Wahlund, 2007; Yamasaki, Muranaka, Kaseda, Mimori, & Tobimatsu, 2012).

The main goal of this study was to identify the structural correlates of the previously observed (Graewe et al., 2013; Lemos et al., 2012) deficits in complex face and object recognition, in MCI patients, and explore the contribution of both ventral and dorsal visual areas as putative biomarker of AD symptomatology.

Our approach included a behavioral experimental paradigm with 3D SFM defined faces and objects and morphometric analysis including the computation of cortical thickness (CT) maps and hippocampal volumetry using Magnetic Resonance Imaging (MRI).

Methods

Participants

MCI patients (n=30) were recruited from the Neurology Department of the Coimbra University Hospital. Diagnosis was reached through gold standard neurological and neuropsychological assessment following published classification criteria for MCI (Albert et al., 2011; Petersen, 2004). All patients were of the amnestic MCI type (at high risk for AD). Diagnostic investigation included a standard clinical evaluation, a

staging assessment as well as laboratory tests including apolipoprotein E (ApoE) allele genotyping and imaging studies (MRI, and SPECT/CT).

The neuropsychological evaluation included a comprehensive diagnostic battery: 1) Cognitive instruments as the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) Portuguese version (Guerreiro, Silva, et al., 2008), the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog; Mohs, Rosen, & Davis, 1983) Portuguese version (Guerreiro, Fonseca, Barreto, & Garcia, 2008), and a comprehensive neuropsychological battery with normative data for the Portuguese population (BLAD; Guerreiro, 1998) exploring memory (Wechsler Memory Scale sub-tests) and other cognitive domains; 2) The Clinical Dementia Rating (CDR; Morris, 1993) Portuguese version (Garrett et al., 2008) was used for global staging.

The inclusion criteria for MCI were those proposed by Petersen for MCI (Petersen, 2004; Petersen et al., 2001) and were operationalized as follows: 1) A subjective complaint of memory decline (reported by the subject or an informant); 2) An objective memory impairment (considered when scores on standard Wechsler memory tests were 1.5 standard deviation below age/education adjusted norms) with or without deficits in other cognitive domains; 3) Normal general cognition suggested by normal scores in the MMSE and ADAS-Cog using the Portuguese cut off scores (Guerreiro, Fonseca, et al., 2008; Guerreiro, Silva, et al., 2008); 4) Largely normal daily life activities; 5) Absence of dementia, indicated by a CDR rating of 0.5 (Morris, 1993).

Patients were excluded if they had other psychiatric or neurological conditions than MCI; CT or MRI demonstration of significant vascular burden (Román et al., 1993) (large cortico-subcortical infarction; extensive subcortical white matter lesions superior to 25%; uni or bilateral thalamic lacunae; lacunae in head of caudate nucleus; more than 2 lacunae).

Control subjects (n=25) were recruited among the patients' spouses, age-matched hospital or university staff, or their relatives; with no relevant history of neurological or psychiatric conditions. All control subjects had normal MMSE scores (mean 29.3), absence of cognitive complaints and were independently functioning members of the community.

All participants had no history of abnormal ophthalmological conditions and had normal or corrected-to-normal vision.

Informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, with the approval of our local ethics committee.

The two groups were matched for age [*t* (53) =-1.149, *p*=.256], education levels [*t* (53) =.841, *p*<.404], and gender [χ^2 (2) =.039, *p*=.843]. As expected MCI patients performed poorly on the MMSE [*t* (53) =2.479, *p*<.016]. Demographical and clinical characteristics of the population are shown in Table 9.1.

Table 9.1 Demographical and clinical characteristics of the population.

	Control subjects (n=25)	MCI (n=30)
Gender (m:f)	11:14	14:16
Age (years)	63.4 (1.7)	66.1 (1.5)
Education Level (years)	8.5 (0.7)	7.5 (0.8)
MMSE (score)	29.3 (0.2)	28.5 (0.3)*
CDR (score)	--	0.5 (0.0)
ApoE ε4 carrier, n(%)[1]	--	11 (36.7)

Note:
MCI – Mild Cognitive Impairment
MMSE – Mini-Mental State Examination
CDR = Clinical Dementia Rating
Data are expressed as mean (SEM)
*p<.05
[1]DNA was isolated from whole blood using a commercial kit (Roche Diagnostics GmbH, Manheim, Germany), as described by the manufacturer. ApoE genotype was determined by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP) assay.

Stimuli

The paradigm used in this study is based on the study of Graewe et al. (2013), nevertheless, only the intermediate duration condition (160 ms) was used as it was the only one capable of discriminating MCI patients from healthy elderly controls. Videos of 3D SFM defined faces (for details see Farivar et al., 2009), scrambled faces, chairs and scrambled chairs were used as stimuli. The face stimulus consisted of one laser-scanned facial surface taken from the Max-Planck Face Database (Troje & Bülthoff, 1996). The surfaces were rendered a volumetric texture map to ensure uniform texture density – a process analogous to carving a surface out of a stone block. Shadows and shading were removed from the rendering. The faces were rendered against a similarly textured random-dot background. During the animation, the face

rotated from -22.5 degrees to 22.5 degrees, centered at the frontal plan, in one cycle (Figure 9.1a). The chair stimulus was obtained from a chair model database and was rendered in exactly the same manner as the face stimulus. Scrambled versions of the two stimuli were constructed by cutting the rendered whole object (face or chair) videos on the horizontal plane into ten blocks and scrambling their local curvatures/positions. The resulting scrambled stimuli share many of the low-level features of the original videos and are recognized as unfamiliar objects. It is important to note that these motion-defined objects are only visible when the animation is playing; otherwise participants are not able to interpret the SFM cues in order to extract a vivid three-dimensional percept, as desired.

Procedure

Participants were individually tested in a quiet and darkened room. They were seated in a comfortable chair at a distance of 50 cm from the computer screen. The stimuli, subtending ~13º horizontally and ~10º vertically, were presented in the center of a 33,8 cm x 27,1 cm dark computer screen (1280 x 1024 pixels) using the software package Presentation (Neurobehavioral systems).

Participants had to discriminate 3D SFM objects (faces and chairs) from 3D SFM meaningless objects (scrambled faces and scrambled chairs) on videos of 160ms duration. The investigator recorded subjects' verbal responses using a 2-button response box to exclude confounding factors such as motor errors. On both Face and Chair tasks, depth was manipulated with the purpose of increasing the task complexity and unpredictability at variable 3D levels (full, intermediate and flat) (Figure 9.1b). 10 trials per parameter value were included, in a total of 120 trials (Figure 9.1c). Before performing the experimental tasks, all participants underwent a demonstration and a practice phase. In the demonstration phase, the stimuli included in both Face and Chair tasks were shown in order to allow the participants to become familiar with the objects that they would be asked to recognize afterwards. The practice phase was applied before each experimental task and included 18 trials in which the different conditions were randomly presented. The practice phase was repeated whenever the participant did not understand the instructions.

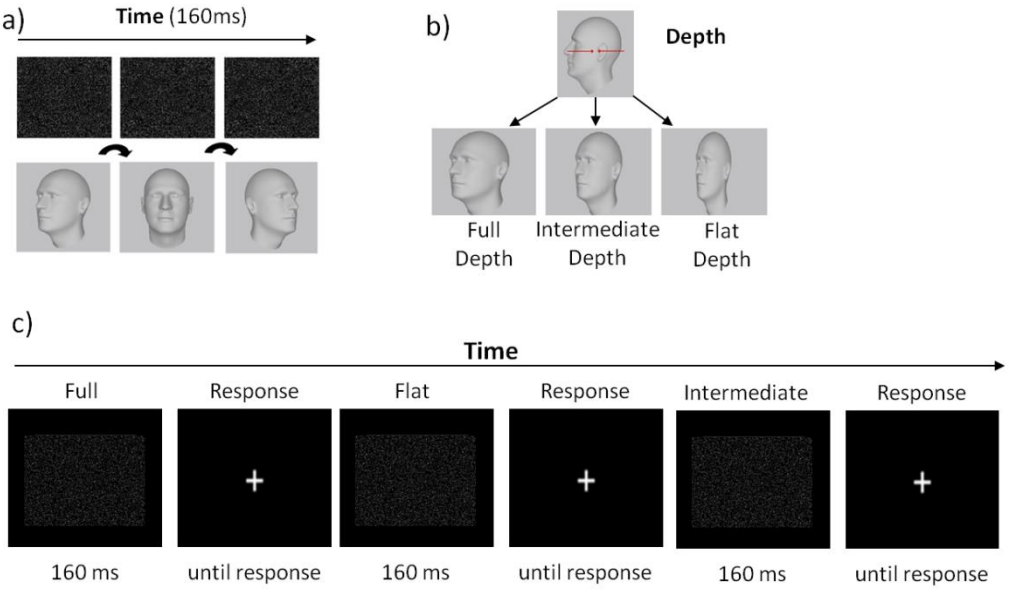

Figure 9.1 – Stimuli and paradigm (adapted from Graewe et al., 2013): a) SFM faces and chairs rotated from left to right in one cycle and were shown during 160 ms. Object perception is rendered possible by integration of the moving dot pattern, the object being physically absent when the rotation/motion is absent; b) The depth modulation resulted in SFM stimulus conditions with variable depth levels parameterized in terms of anterior-posterior range; c) Stimuli were presented randomly at one of the three depth levels, separated by a fixation period during which the participants had unlimited time for response.

Note: The images of the heads just illustrate the structure in the SFM stimuli (because they are physically absent and not visible in static images) and do not represent the exact percept constructed during the movies' presentation.

Image (MRI) acquisition

Participants underwent Magnetic Resonance Imaging (MRI) scanning on a 3T Siemens Magnetom Trio scanner (Erlangen, Germany), using a 12-channel birdcage head coil. All participants belong to a local MRI cohort database, comprising a total of 108 MCI and 76 controls, from which 30 MCI and 18 controls participated in the psychophysics experiment described in the above section.

1 (and often 2) high-resolution 3D T1-weighted magnetization-prepared rapid gradient echo (MP-RAGE) scans were collected per participant, with parameters defined on the basis of guidelines from the Alzheimer's Disease Network Initiative (Jack et al., 2008): FOV=256, 160 slices, voxel resolution 1 x 1 x 1 mm3, TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, 9° flip angle, bandwidth 240Hz/px, acceleration factor of 2 with 24 reference lines in the phase encoding direction. Acquisition parameters were optimized for increased great-white matter image contrast, while minimizing acquisition time.

- Image Analysis Procedures

Measurement of cortical thickness and volumes in individual participants

The structural MRI scans were processed using the FreeSurfer 5.0.0 software package (http://surfer.nmr.mgh.harvard.edu), using methods that are fully automated and extensively described (Dale, Fischl, & Sereno, 1999; Desikan et al., 2006; Fischl & Dale, 2000; Fischl, Sereno, & Dale, 1999; Fischl et al., 2004; Fischl et al., 2002; Han et al., 2006). Each MPRAGE MRI acquisition image was visually inspected for abnormalities unrelated to the underlying pathology, such as movement artifacts or concomitant pathologies. When available, two MRI acquisitions for each participant were motion corrected, averaged and normalized for intensity inhomogeneities, resulting on a single image with increased contrast-to-noise ratio. The resulting volume was used to locate the grey/white matter boundary, then used as a starting the point to define the grey/CSF boundary across the entire cortical mantle. For each participant, cortical thickness was estimated at each point of the cortical mantle by finding the shortest distance from the white matter surface to the grey matter surface (and vice-versa) and averaging those two values (Fischl & Dale, 2000). The neocortex was parcellated onto 32 gyral-based regions-of-interest (ROI) (Fischl et al., 2004; Fischl et al., 2002) in each hemisphere, and in addition non-neocortical ROIs, such as hippocampus, were defined on the basis of automated procedures (Desikan et al., 2006).

For each participant, the accuracy of the grey and white matter surfaces and of each individual ROI was carefully inspected by a trained neuroradiologist. When necessary, manual editing and corrections were applied, precluding skull stripping, white matter, control points, and removing inclusion of dura matter in grey matter surface (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/).

Registration and group cortical thickness maps

For each participant, the white matter surface was morphed to an average spherical surface folding pattern representation – this is performed one hemisphere at a time – from which surface maps of cortical thickness were generated, at each vertex of the cortical mantle (Fischl et al., 1999). Smoothing of the data on the cortical tessellation was performed with a 2D surface-based Gaussian kernel of ≈20 mm full width half maximum.

Statistical analysis

Statistical analysis was performed with the SPSS statistical software package, version 19.0 (SPSS, Inc., Chicago, IL) with parametric and non-parametric tests corrected for multiple comparisons, when applicable. Results with $p<.05$ were considered statistically significant.

- Psychophysics

For the statistical analysis of the behavioral data a d' (dprime) performance measure was computed for face and chair detection for each participant [d' = Z(hit rate) - Z(false alarm rate)]. A hit was considered when the subject recognized correctly the stimulus, whereas a false alarm was considered for conditions when the subject reported face/chair detection in the presence of a scrambled stimulus. Independent t-tests were performed for comparison between the two groups.

- Imaging

Hippocampal volumes

Two non-neocortical ROIs (left and right hemisphere hippocampus) were used in this study, with the purpose of assessing differences between MCI and control groups, in regions known to be pivotal in AD pathology. Volume measures were normalized for differences in estimated total intracranial volume (eTIV) through a ratio procedure.

Group differences were assessed two-fold (Wilcoxon-Mann-Whitney, Bonferroni corrected): within the local MRI cohort database, and within the study sub-sample with structural MR images.

Cortical thickness and vertex-based correlational analysis

Analysis was performed using the cortical thickness maps obtained through spherical mapping and smoothing. A vertex-by-vertex analysis was carried out using a general linear model, with cortical thickness as the dependent variable and group as the independent variable. Age interaction effects were scrutinized for, and the number of structural MR images was introduced as a nuisance factor. Corrections for multiple comparisons were applied using false discovery rate (FDR) at a .05 significance level.

Correlational analysis was performed, on a vertex-by-vertex basis, regressing cortical thickness against behavioral performance measures (dprime), and Nuisance factors

were taken into account, with the inclusion of participants' age and the number of structural images per participant.

Results

Psychophysics

We found significant group differences for face recognition performance (t (53) = 2.503, p=.015). Interestingly, performance differences were also found for the chairs category (t (53) = 2.491, p=.016), albeit at a higher performance level.

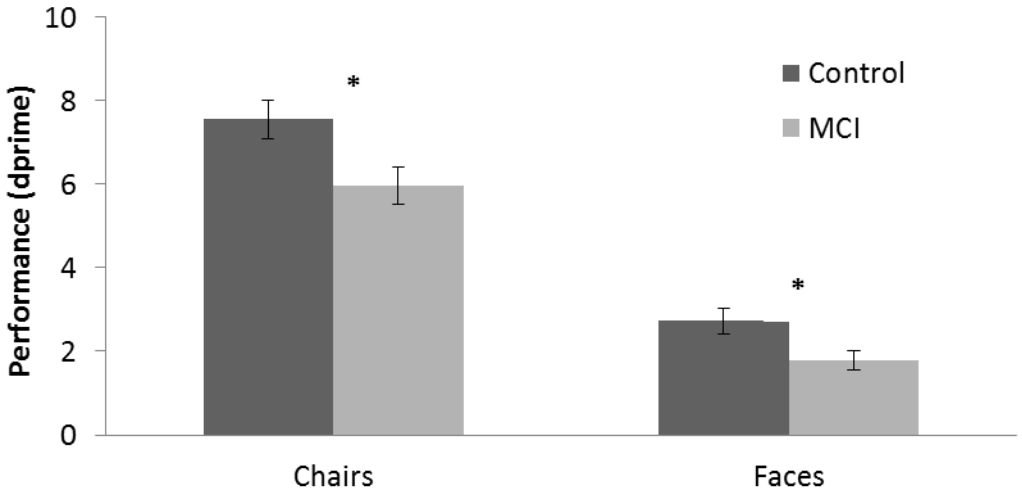

Figure 9.2 – Performance (as assessed by dprime measures) for the global Face and Chair Conditions. Stimulus duration: 160 ms.

Hippocampal volumetry and cortical thickness and vertex-based correlational analysis

- Hippocampal volumes were decreased bilaterally in the MCI study group, in particular in the left hemisphere (p<.01):

Significant differences in the hippocampal volume were found in both the local cohort and the study sub-sample. In the former, hippocampal volumes were decreased bilaterally in the MCI group (Wilcoxon Mann-Whitney, p<.001, Bonferroni corrected), whereas in the latter, decreased volume was significant in the left hemisphere (Wilcoxon Mann-Whitney, p<.01, Bonferroni Corrected).

At the level of cortical thickness analysis, we found that these measures were matched across the study group structural MR scans. Significant correlations between cortical thickness and behavioral measures were detected and can be found depicted in Figure

9.3 (with correction for multiple comparisons). Positive associations of cortical thickness and the face recognition performance (as assessed by dprime values), for the right hemisphere (in line with the known right hemispheric lateralization for face recognition), were identified in the MCI group, comprising occipital lobe (BA18) and fusiform (BA37) regions [(Table 9.2, showing a region overlapping FFA as identified by Graewe et al. (2013)] involved in visual face processing. No significant correlations applied for the chairs condition.

Table 9.2 – Cortical areas showing positive correlations between thickness and psychophysical dprime scores in the MCI group in the face integration condition that differentiates between groups.

	BA	Hemisphere	Area	*p* value	Talairach Coordinates
Occipital Lobe	BA18	R	1676	.000012	26, -96, -2
Fusiform	BA37	R	309	.000069	41, -53, -7

Note: BA – Broadmann area; Area – Cluster surface area in mm^2.
p values are reported at the vertex maxima for each cluster, and respective Talairach coordinates were estimated on basis of non-linear MNI to Talairach transformation (white matter surface). The fusiform cluster overlaps the previously described Face Fusiform Area region (Graewe et al., 2013).

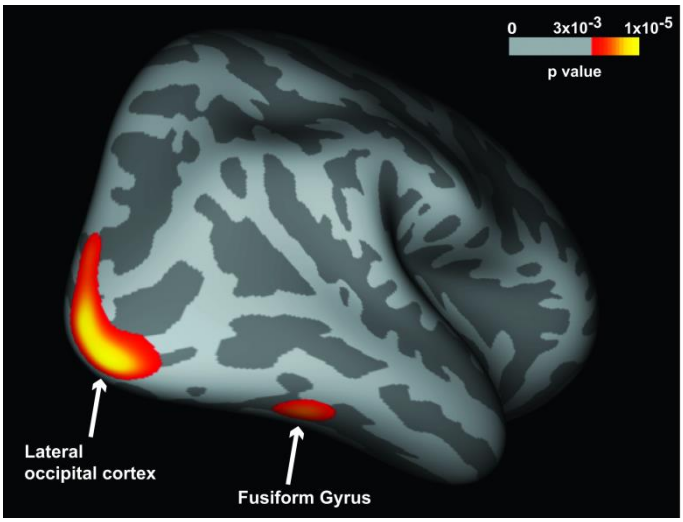

Figure 9.3 – Statistical results rendered on an inflated grey matter surface.
Note: The cortical areas in which thickness correlates positively with dprime scores (see Table 9.2) are depicted. The color scale represents the *p* values as depicted for significant correlations (corrected for multiple comparisons: FDR significance level at .05).

Discussion

Here we investigated the role of visual integration of three-dimensional SFM face objects, in MCI. Our paradigm requires visual integration across features with an important role for the visual ventral stream (Farivar et al., 2009; Graewe et al., 2013).

Behavioral results confirmed that high level integration in visual face recognition is impaired in MCI, thereby extending previous results on coherence thresholds of simple spherical objects (Lemos et al., 2012). Temporal requirements for visual integration were chosen (160 ms) to impose a performance challenge. This work supports the idea that either dorsal or ventral stream impairment will cause poor performance on this task. In other words, we found an association of task performance with the ventral stream integrity, which may support different aspects of the task than does the dorsal stream.

It is known that integration of information from dorsal and ventral visual streams is crucial to recognize 3D SFM stimuli. The present results suggest that the ventral pathway represents an important role, specifically for face stimuli, as suggested by structure-function correlation analysis. Indeed, the patients with larger fusiform cortical thickness had more preserved recognition performance, but only for faces and not chairs. These results do not dispute the notion that the dorsal stream is also affected as suggested by the work of Rizzo et al. (2000) on motion perception and our own previous psychophysical and studies (Graewe et al., 2013; Lemos et al., 2012). Nevertheless, the results from the present study do not exclude the involvement of an impaired dorsal stream in the recognition of 3D SFM faces in MCI patients.

The main finding of this study is the observed specificity of structural functional correlations for faces. This suggests that different circuits and biomarkers may track face rather than chair recognition, even though chair recognition is also impaired. Another novelty of our study is the report of visual structure-function correlations at the early stage of MCI, as the majority of imaging studies on AD-related pathology have documented structural/functional changes of regions related with the memory impairment, such as the hippocampus and related structures in the medial temporal lobe (Albert et al., 2011; Dubois et al., 2007, 2014; Sperling, 2011; Teipel et al., 2013). Nonetheless, previous studies have suggested that visual responses are modified in MCI and AD (Bokde et al., 2006; Mentis et al., 1996; Prvulovic et al., 2002; Teipel et al., 2007; Vannini et al., 2007; Yamasaki et al., 2012). However it has remained difficult to establish a direct correlation with performance.

In our study we found that behavioral performance is significantly correlated with cortical thickness. Accordingly, after controlling for different nuisance factors, we

found significantly positive correlations with face recognition condition and thickness in both the occipital lobe (BA18), and the ventral fusiform (BA37) areas on the right hemisphere, in the MCI group. These correlations were found in the condition that was previously reported (Graewe et al., 2013) to better discriminate MCI patients from healthy elderly and corroborated in the present study. Some psychophysical studies had indicated that the ventral visual pathway is more affected in AD spectrum (Cronin-Golomb, 2004; Rizzo et al., 2000) although, as stated above, this does not exclude afferent dorsal stream deficits (Bokde et al., 2010; Kavcic et al., 2011; Lemos et al., 2012). The lack of cortical differences in the control group, as function of face recognition performance, suggest a disease specific mechanism.

Our results confirm the tenet that the fusiform gyrus (BA37), comprising the fusiform face area, may be critically affected in distinct stages of the natural history of AD (Bokde et al., 2006; Graewe et al., 2013; Teipel et al., 2007). Furthermore, our findings do suggest that the right BA37 is more closely associated with performance changes which is also consistent with the notion of lateralization of face-selective responses in right hemisphere (for a review, see Cabeza & Nyberg, 2000). Moreover, the findings from the present work corroborate the previous findings of Graewe et al. (2013) on the decreased sensitivity for faces in the right FFA, in MCI patients. The fusiform region identified in this study overlaps the FFA region described in that study. The involvement of extrastriate visual cortex may help explain the early visual deficits in AD-related pathology found by other groups (Risacher et al., 2013; Rizzo et al., 2000; Rose et al., 2006).

We propose that both dorsal, and ventral, processing are required in the visual integration task used in this study. This is consistent with previous studies (James, Humphrey, Gati, Menon, & Goodale, 2002; Klaver et al., 2008; Konen & Kastner, 2008; Orban, Sunaert, Todd, Van Hecke, & Marchal, 1999). The decreased thickness present in MCI patients is not explained by atrophy as no differences in the same regions were found between patients and controls. This may suggest that our observations may be related to compensatory mechanisms.

Our study also suggests new ways of studying complex object recognition (in particular face processing) and its neural correlates in pathological ageing. Dynamic aspects of a visual scene provide important cues for object segregation and identification, and 3D

SFM paradigms are particularly relevant in this context. Dynamic cues are highly informative of an object's shape and may be capable of driving complex recognition processes in the absence of other shape cues. The visual integration ability needed to achieve holistic perception of the whole 3D shape from local information seems to be impaired in MCI patients, and to also require the ventral pathway. Our results suggest the existence of a ventral pathway that provides the substrate for information re-routing and reorganization in the presence of dorsal stream vulnerability.

In sum, we found evidence for a strong correlation between recognition of complex 3D moving faces and integrity in extrastriate and a fusiform region overlapping FFA in MCI.

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This discussion briefly analyses the main results achieved during Studies 8 and 9. It is divided into the following topics: *Description of Chapter II* (*Dorsal pathway*, *Ventral pathway, and Dorsal-ventral integration in the AD spectrum disorders); Highlights and limitations of the two studies; Future outlook; and Conclusions*.

Description of Chapter II

In the current chapter we explored the visuospatial processing in MCI and AD patients. AD pathology is known to involve the visual pathways, leading to impairments in several visual functions. In particular, the dorsal and ventral pathways were considered throughout the performance of these pathological groups in psychophysical tasks (research papers either published or submitted for publication). Accordingly, visual function studies associated with these two pathways allow inferring about the functioning of the temporal and parietal lobes areas, known to be involved in AD spectrum disorders. In the visual cortex, the lateral geniculate nucleus (LGN) has shown to be affected in AD patients: neuropathological findings have been reported in both the magno and the parvocellular layers of the LGN with the latter showing a higher number of senile plaques (Gilmore, Morrison, & Groth, 2004). As we reported earlier, there is already a great amount of research considering the visual function in AD pathology; nevertheless, the same does not apply for studies in MCI and is almost circumscribed to research about high-level visual functions (visual search or attention). We presume that this may be due to its more recent categorization as a diagnostic entity. We tried to lift the veil on this scarcity by deepening our research into MCI, mainly due to its diagnostic conversion predicting value and also to the imperative need of finding new AD biomarkers.

This discussion chapter was organized under the following topics: *Dorsal pathway in the AD spectrum disorders*, *Ventral pathway in the AD spectrum disorders*, *Dorsal-ventral integration in the AD spectrum disorders*, *Highlights and limitations*, *Future outlook*, and *Conclusions*.

Dorsal pathway in the AD spectrum disorders

The dorsal (or magnocellular, or *where*) pathway is involved in object spatial location functions (Ungerleider & Mishkin, 1982) such as: spatial vision, motion perception,

direction integration, and speed discrimination. Nonetheless, Goodale & Milner (1992) argued that the key function of the dorsal stream is to mediate visually guided motor movements; this notion has been supported by studies of patients with parietal lesions whose difficulty is to form objects appropriate grasp size and orientation, in the presence of a preserved ability to describe the spatial location of these objects.

Undoubtedly is the network of brain regions involved in this pathway spanning from the occipital lobe to parietal regions (Ungerleider & Mishkin, 1982). In fact, a hierarchical approach is justified by the notion that this retinocortical magnocellular pathway flows forward from the primary visual cortex to the visual dorsal stream (where motion integration takes place) (Castelo-Branco et al., 2002).

Contrast sensitivity (CS), as a low-level function of the dorsal stream, is the most studied task in the AD spectrum (Cronin-Golomb, 2004) and, while the majority of researchers found it to be impaired (Lemos, Patrício, & Castelo-Branco, 2015), few researchers proved it as a spared visual function in this condition (Rizzo & Nawrot, 1998; Schlotterer, Moscovitch, & Crapper-Mclachlan, 1984). CS reflects the “minimum amount of contrast that an observer needs to resolve a stimulus of a given size”(Cronin-Golomb et al., 2000), which is probably relevant concerning deficits in daily function activities in elderly people. The deficits in CS shown by AD patients are often described as the visual image being viewed through a filter and it is called the “Alzheimer filter”; moreover, this impaired CS at low facial frequencies contributes to the poor face discrimination observed in AD patients (Cronin-Golomb et al., 2000).

Another commonly reported visuospatial deficit in AD patients is the spatial disorientation that consequently led patients to get lost even in familiar surroundings. The involvement of occipito-parietal regions includes the radial patterns of visual motion that create optic flow and guide movements through the environment by showing one's direction of self-movement. Tetewsky and Duffy (1999) proved that the ability to see radial patterns of optic flow is impaired in AD, interfering with their use of visual information to guide self-movement and maintain spatial orientation and leading to visuospatial disorientation. In general, deficits in global motion perception have been commonly reported in AD patients, with more noticeable evidence for impairment in higher level motion tests (Lemos, Patrício, et al., 2015). Concerning MCI,

Mapstone, Steffenella, and Duffy (2003) reported a subdivided pattern of performance among this group: while some have significant visual perceptual deficits along with memory impairment, others have isolated memory impairment with no visual perceptual deficits. This finding led the authors to suggest a visuospatial variant of MCI.

In Study 8 (Lemos, Figueiredo, Santana, Simões, & Castelo-Branco, 2012) we explored the magnocellular processing both at low and high-level performances in MCI and AD patients. For the former we comprised a very simple CS detection task, using stimuli with high temporal and low spatial frequencies in order to activate the magnocellular pathway; in the latter a task of 3D motion coherence objects of unknown orientation with constrained temporal integration of cues was included. Our results enabled us to corroborate the AD CS impairment in the peripheral visual fields, in spite of a preserved central visual performance, and to show a specific pattern of impairment only in the peripheral-temporal region in the MCI group. Concerning the high-level 3D SFM performance, an impaired cue combination of 3D orientation and motion of simple objects in short time windows proved specific early dorsal stream impairment both in AD and MCI groups.

The deterioration of magnocellular processing is quite important in understanding the behavior of AD spectrum disorder patients. Firstly, a reduced sensitivity may adversely affect routine perceptual activities that depend on low spatial frequencies, such as face and object recognition; secondly a deficit in perceiving moving objects leads to problems in visuospatial disorientation.

Ventral pathway in the AD spectrum disorders

The ventral visual-processing stream (or parvocellular, or *what*) identifies objects from their visual features (Ungerleider & Mishkin, 1982). This pathway, through a network of projections from the striate cortex to the inferotemporal cortex, plays the major role in the perceptual identification of objects (Goodale & Milner, 1992).

The parvocellular pathway is, contrariwise to the magnocellular stream, contrast and motion insensitive, and responds to spatial detail (Silva et al., 2005) with its neurons behaving as high resolution channels, sensitive to high spatial frequencies.

At an initial level of an object's registration one must attend to its local features, such as colour. Ventral visual perceptual processing in AD patients have mostly focused on early levels of visual perception, such as colour vision, although not necessarily implying that higher levels of perception are impaired in AD (Tippett, 2004). Isolating the stages of ventral visual processing at an intermediate and/or high-level in (typical) AD is a demanding task due to semantic and lexical (naming), or memory deficits that may bias the object recognition (that is also expected to be compromised), leading to an ambiguous underlying cause of impairment: language, memory or visual processing (Tippett, Blackwood, & Farah, 2003; Tippett, 2004)?

In Study 8 (Lemos, Figueiredo, Santana, Simões, & Castelo-Branco, 2012) we investigated the parvocellular pathway through a computer controlled psychophysical colour perception task. Our results proved a significant impairment in AD's parvocellular pathways in the presence of a spared colour perception in MCI subjects. Colour discrimination deficits among AD patients have been extensively reported (Lemos, Patrício, et al., 2015) either on clinical tests or psychophysical assessments, principally along the tritan (blue-yellow) colour axis (Rocco, 2004). Nevertheless, Wijk et al. (2002) argued in favour of a preserved colour perception ability in AD pathology. In respect to MCI performance relative to colour discrimination, we believe that our Study 8 was the first reporting a lack of deficits in colour vision in this pathological group.

At a higher-level of ventral visual processing is the object recognition, including face perception, both reported as being impaired in AD (Kurylo, 2004; Lemos, Patrício, et al., 2015). In Study 8 (Lemos, Figueiredo, Santana, Simões, & Castelo-Branco, 2012) we explored face recognition, as an index of ventral stream function, both in AD and MCI groups, by means of the Benton Face Recognition Test (BFRT). We observed a pattern of face discrimination recognition impairment specifically on the AD group. Cronin-Golomb et al. (2000) found AD subjects to be impaired at discriminating medium or large faces in the BFRT, but with a normal discrimination of small faces. The authors conclude that impaired CS at low facial frequencies contributes to the poor face discrimination of AD. Thus, by reducing the size of face stimuli, the perception of the low facial frequency content improves, thereby improving face discrimination in AD.

The development of recent research techniques such as the functional MRI (fMRI) endorsed the study of face perception independently of other cognitive deficits, by allowing the achievement of patterns of cerebral areas activation during face matching tasks (Lemos, Patrício, et al., 2015). These studies enabled a deepened understanding of face-specific cerebral regions both in AD patients, but also in MCI subjects.

Dorsal-ventral integration in the AD spectrum disorders

Despite the concomitant involvement of the dorsal and ventral stream in order to completely perceive a detailed moving scene, it is known that the parvocellular must contribute substantially to the magnocellular pathway in motion processing capabilities (Gilmore et al., 2004). This notion is supported by the importance of the local cues to extract the global configuration. Accordingly, the neural correlates of motion perception involve the integration of the ventral stream underlying the recognition of object shape properties and the dorsal pathway involved in spatial vision and motion perception (Farivar, 2009; Konen & Kastner, 2008; Milner & Goodale, 2008).

In AD, the majority of studies reporting deficits in coherent motion perception use stimuli that drive the magno channel more actively than the parvocellular (Gilmore et al., 2004). Yet, if this coherent motion threshold impairment in AD is attributable to an interaction deficit or even a sole parvo deficit, opposite results should be found (Gilmore et al., 2004). Furthermore, the neural substrates of 3D motion perception in MCI patients were found to predominantly relate to aberrant patterns of activation in face and object perception (FFA/OFA) areas in the presence of normal recruitment of motion selective areas, suggesting the activation pattern within the ventral visual stream as a putative biomarker for this pre-dementia stage (Graewe et al., 2013). Previous functional imaging reports also suggest that reorganization may occur in both streams in AD spectrum disorders (Lemos, Patrício, et al., 2015).

Among all the reported visual deficits present in AD are object recognition, including disrupted facial recognition, and impaired recognition of familiar objects (Lemos, Patrício, et al., 2015)**.** This impaired object recognition is attributable to an abnormal organization of the visual scene where an improper use of discrete visual elements is

present, either in segregating and identifying coherent objects, or in simultaneously processing multiple elements to interpret the image (Kurylo, 2004).

With these notions, we moved forward to Study 9 (Lemos, Santana, et al., 2015) in order to study the visuospatial perception in MCI using an experimental paradigm that required both dorsal and ventral processing. Our rationale was the clarification of these two visual pathways' role and understanding its pathophysiology as a putative biomarker of AD symptomatology. For this, we included a behavioral experimental paradigm with 3D SFM defined faces and objects and morphometric analysis including the computation of cortical thickness (CT) maps and hippocampal volumetry using MRI. Our results confirmed that high level integration in visual face recognition is impaired in MCI, thereby extending the results on coherence thresholds of simple spherical objects from Study 8 (Lemos et al., 2012). Moreover, the ventral pathway represented an important role, specifically for face stimuli, as suggested by structure-function correlation analysis: patients with larger fusiform CT had more preserved recognition performance for faces; positive correlations between face recognition condition and thickness either in the right occipital lobe and the right ventral fusiform areas were found. These findings corroborated our previous functional outcomes (Graewe et al. 2013) on the decreased sensitivity for faces in the right fusiform face area (FFA) in MCI patients, as the fusiform region identified in Study 9 overlaps the FFA region described before. The visual integration ability needed to achieve holistic perception of the whole 3D shape from local information was found to require the involvement of the ventral pathway, and was impaired in MCI patients. These results suggest that the ventral pathway provides the substrate for information re-routing and reorganization in the presence of dorsal stream vulnerability in MCI.

Highlights and Limitations

We understand that we were able to explore the visual function deficits in AD spectrum disorders. The structure and function of the visual cortex was studied as an innovative field for the early diagnosis, by exploring the interaction between dorsal and ventral streams in MCI patients; additionaly, we suggest these as alternative tools in MCI/AD assessment.

As reported in part I of the current thesis, the pathological groups were recruited at the Neurology Department of the Coimbra University Hospital, where the most recent and sophisticated supplementary means of clinical diagnosis are available, therefore enabling an accurate differential diagnosis. Additionally, the experiments reported in this section were developed and run in the Visual Neuroscience Laboratory of the Institute of Biomedical Research in Light and Image from the Faculty of Medicine of the University of Coimbra, which is a research reference center not only in visual studies but also in clinical neuroscience.

Our main guidelines for the control groups' selection were taking into consideration the demographical aspects of the pathological groups and also making sure that these subjects had no history of neurological, psychiatric, or ophthalmological relevant conditions, neither significant motor or auditory deficits which could influence their performance.

All subjects performed a comprehensive neuropsychological assessment at baseline in order to define the cognitive profile of impairment and the diagnosis of the pathological groups, and to assure the lack of cognitive impairment among the control subjects; in Study 8 the cognitive results were found not to be correlated with visual performance among all the groups.

Study 9 was developed in order to test whether three-dimensional SFM cues were sufficient to drive complex object recognition in MCI patients, therefore complementing the achievements of Study 8 where 3D motion integration was specifically impaired, thus indicating that parietal function may become affected early in the course of the disease. While Study 8 comprised a behavioral psychophysical task used both MCI and AD patients, in Study 9 we moved forward and included data from structural imaging that was correlated with results from a different visual experimental paradigm.

One main limitation of the two studies is the relatively small groups' size, even though it is in line with the majority of studies in this area (Lemos, Patrício, et al., 2015). Accounting for this limitation is the strict criteria of exclusively including subjects with no ophthalmological diseases so that our results would only been explained in terms of

cortical vision performance; moreover, in Study 8 all subjects underwent full ophthalmologic examination.

The MCI groups included in both studies were of the amnestic type, due to their higher risk of conversion to AD. This circumstance discourages the inclusion of other subtypes of MCI, and consequently the results obtained in our studies should not be generalized to all MCI subtypes.

The main objectives of both studies were addressed through the use of psychophysical research experiments to assess the cortical vision function. Despite the neuropsychological examination, data of ApoE genotype (presence of ε4 allele) among the pathological groups was included in both studies, and in Study 9 morphometric analysis established biological evidence for impairment in MCI as demonstrated by reduction of left hippocampal volume. Nonetheless, we are aware that these results should be corroborated with AD clinical biomarkers in order to address preclinical/prodromal AD as defined by specific diagnosis criteria.

Future Outlook

We think that results from visual function studies should be further explored in MCI patients that have AD clinical biomarkers and may be considered as preclinical/prodromal AD. As such, cortical vision tasks may possibly be seen as alternative tools in the AD spectrum assessment.

Among the AD spectrum disorders in general, and relative to the visual dysfunction in particular, it is mandatory to refer the extreme point of impairment as is the posterior cortical atrophy (PCA; Dubois et al., 2010, 2014), or the visuospatial presentation of AD (McKhann et al., 2011), that is an insidiously progressive dementia characterized by prominent disorders of higher visual processing as a result of an atrophy of the occipital and occipito-parietal regions of the brain. We think that analyzing the performance of this atypical form of AD in the same, or similar, psychophysical visual tasks would enhance a complete understanding of the visual function in AD spectrum disorders.

Conclusions

AD patients, caregivers, and health professionals are liable to misinterpret the visual disabilities as cognitive problems, leading to undiagnosed visual deficits. With the work presented in the current thesis, we believe to have contributed to this topic and to have further explored and confirmed the existence of AD visual deficits as early as in the MCI stage not only through behavioral psychophysical results, but also in terms of neural correlates. By suggesting visual assessment as an additional diagnostic tool, we consider that future interventions can be designed to compensate for visual problems in AD spectrum disorders, such as increasing signal strength through the use of higher contrast or larger stimuli.

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CONCLUDING REMARKS

Concluding Remarks

The work presented in this thesis allowed us to confirm the usefulness of the FCSRT as a valid and accurate memory test in the objective characterization of the amnestic syndrome associated with AD, thus corroborating the suggestion of the IWG-1 and 2 criteria. By adapting and validating the FCSRT, we also contributed to the increase of Portuguese-adapted neuropsychological instruments' availability and to introduce a different paradigm of verbal memory evaluation in this context in our country.

Furthermore, we corroborated the existence of deficits among the two visual pathways on AD patients and showed specific impairments on motion perception and integration in the MCI. We went further in the understanding of the important and specific role of the ventral pathway for face stimuli on structure-function correlation analysis, suggesting that the ventral pathway provides the substrate for information re-routing and reorganization in the presence of dorsal stream vulnerability in MCI. These findings improve our knowledge of the visual deficits in AD spectrum disorders, as early as in the MCI stage, and allow us both to suggest the assessment of visual functions as an additional diagnostic tool for AD spectrum disorders and to consider that future interventions can be designed to compensate for visual problems in these pathologies, such as using higher contrast or larger stimuli.

List of Publications

Baldeiras, I., Santana, I., Garrucho, M. H., Pascoal, R., Lemos, R., Santiago, B., & Oliveira, C. (2012). CSF biomarkers for the early diagnosis of Alzheimer's disease in a routine clinical setting – the first Portuguese study. *Sinapse*, *12*(2), 14–22.

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Curriculum Vitae

Raquel Lemos Oliveira was born on October 13, 1980 in Braga, Portugal. In 1997, she concluded her secondary school education at Escola Secundária Carlos Amarante in Braga, after which she studied Psychology at the Faculty of Psychology and Educational Sciences of the University of Coimbra, graduating in 2003. Her internship was completed at the Neurology Department of the Hospitais da Universidade de Coimbra, under the supervision of Professors Isabel Santana and Mário Rodrigues Simões. She worked as a clinical psychologist at Hospital de São João de Deus – Barcelos, from 2005 to 2006. After working as a research assistant in neuropsychology for five years, first in the Instituto de Imagem Biomédica e Ciências da Vida, (Faculty of Medicine, University of Coimbra), and then in the Neurology Department of the Hospitais da Universidade de Coimbra. In 2008, she started her PhD in Neuropsychology under the supervision of Professor Isabel Santana and the co-supervision of Professors Mário Rodrigues Simões and Miguel Castelo-Branco, for which in 2011 she received a scholarship from the Fundação para a Ciência e Tecnologia – Portugal.