UNIVERSIDADE DE LISBOA
FACULDADE DE MEDICINA DE LISBOA

NEUROPSYCHOLOGICAL PREDICTORS OF THE OUTCOME IN NON-DEMENTED SUBJECTS WITH COGNITIVE COMPLAINTS

Dina Lúcia Gomes da Silva

Tese de doutoramento orientada por:
Senhor Professor Doutor Alexandre de Mendonça
Tese de doutoramento co-orientada por:
Senhora Professora Doutora Manuela Guerreiro

Doutoramento em CIÊNCIAS BIOMÉDICAS
Especialidade em NEUROCIÊNCIAS

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stat dubius tremulusque senex semperque malorum
credulus, et stultus quae facit ipse timet,
laudat praeteritos, praesentes despicit annos,
(…)
multa licet nolis referens eademque revolvens
horret et alloquium conspuit ipse suum.

Maximianus

PUBLICATIONS

Scientific results from the present thesis were submitted to peer-reviewed publication in the following original articles:

- Silva D, Lunet N, Guerreiro M, de Mendonça A. Neuropsychological assessment and progression to dementia: systematic review and meta-analysis (manuscript in preparation).

- Maroco J, Silva D, Rodrigues A, Guerreiro M, Santana I, de Mendonça A. Data mining methods in the prediction of Dementia: A real-data comparison of the accuracy, sensitivity and specificity of linear discriminant analysis, logistic regression, neural networks, support vector machines, classification trees and random forests. *BMC Res Notes* 2011 Aug 17; 4: 299.

- Silva D, Guerreiro M, Maroco J, Santana I, Rodrigues A, Marques JB, de Mendonça A. Comparison of Four Verbal Memory Tests for the Diagnosis and Predictive Value of Mild Cognitive Impairment. *Dement Geriatr Cogn Disord Extra* 2012; 2: 120-131.

- Silva D, Guerreiro M, Maroco J, Cardoso S, Santana I, Rodrigues A, de Mendonça A. Prediction of long-term (5 years) conversion to dementia using neuropsychological tests. (Manuscript submitted).

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Abbreviations

2-[fluorine-18]-fluoro-2-deoxy-d-glucose – ^{18}F-FDG
Addenbrookes Cognitive Examination – ACE
Age-associated memory impairment – AAMI
Aging-associated cognitive decline – AACD
Alzheimer's disease – AD
Alzheimer's Disease Neuroimaging Initiative – ADNI
American Psychological Association – APA
Amyloid precursor protein – APP
Analysis of Variance – ANOVA
Apolipoprotein E gene – APOE
Area Under Curve – AUC
Battery of Lisbon for the Assessment of Dementia – BLAD
Beta-amyloid protein – Aβ
Blessed Dementia Rating Scale – BDRS
California Verbal Learning Test – CVLT
Cambridge Cognition Examination – CAMCOG
Cerebrospinal fluid – CSF
Chi-squared Automatic Interaction Detector – CHAID
Classification and Regression Tree – CART
Classification trees – CTrees
Clinical Dementia Rating scale **–** CDR
Cognitive Complaints Cohort – CCC
Computed tomography – CT
Confidence Interval – CI
Diagnosis of dementia due to Alzheimer's disease – NIA-AA
Diagnostic and Statistical Manual of Mental Disorders (4th Ed., Text Revision) – DSM-IV-TR
Digit Symbol – DS
Free and Cued Selective Reminding Test – FCSRT
Fundação para a Ciência e a Tecnologia – FCT
Geriatric Depression Scale – GDS
Hazard Ratio – HR
International Psychogeriatric Association – IPA
International Statistical Classification of Diseases and Related Health Problems – ICD-10
Linear Discriminant Analysis – LDA
List A total number of words correctly recalled on the five learning trials of CVLT – Atot
Logical Memory – LM
Logistic Regression – LR
Long-delayed free recall of CVLT – LDFR
Magnetic resonance imaging – MRI
Mild Cognitive Impairment – MCI
Mini-Mental State Examination – MMSE
Montreal Cognitive Assessment – MoCA
Multilayer Perceptron – MLP
National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders – NINCDS–ADRDA
Neural Networks – NN

Particular specie of Beta-amyloid protein with 42 amino acids long – $A\beta_{1-42}$
Pittsburgh compound B – PiB
Positron emission tomography – PET
Predictive Analytics Software – PASW
Presenilin 1 – PSEN1
Presenilin 2 – PSEN2
Quadratic Discriminant Analysis – QDA
Quick Unbiased Efficient Statistical Tree – QUEST
Radial Basis Function – RBF
Random forests – RF
Receiver operating characteristic curves – ROC
Relative Risk – RR
Standard Deviation – SD
Statistical Package for Social Sciences – SPSS
Story Recall Test – SRT
Support Vector Machines – SVM
Toulouse-Piéron Test – TP
Trail Making Test (part A and part B) – TMT
Verbal Paired-Associate Learning – VPAL
Wechsler Memory Scale – WMS
World Health Organization – WHO

SUMMARY

Nowadays, life expectancy has increased and gradually the prevalence of neurodegenerative disorders in the aging population began to represent a major public health problem. Alzheimer's disease (AD) is the most common dementia and affects millions of older adults. Despite recent advances in the knowledge of AD biomarkers of pathophysiological processes, clearly the phenotype remains aetiologically heterogeneous. Understanding the clinical phenotype variation contingent to the neuropathological progression is crucial to provide intervention in the earliest phases of neurodegeneration. Newly research biomarkers have been proposed for early diagnosis of AD, however cognitive impairment remains a prominent and early feature of AD. Neuropsychological markers could offer a relatively inexpensive and noninvasive indicator of future progression to dementia because biological markers are expensive, some of them only available at few specialized centers, and, in the case of lumbar puncture, invasive. Therefore, it would not be reasonable to offer the newer and expensive biomarker techniques to all patients with cognitive complaints. Importantly, new treatments of disease modification approach require the selection of those patients with higher risk of conversion to dementia. Thus, the main goal of the present thesis was to improve the predictive value of neuropsychological measures to future conversion to dementia of patients presenting with cognitive complaints who do not fulfil the dementia criteria. Four steps were conducted in order to reach that main goal:

1. º Original published articles reporting values of sensitivity, specificity and effect sizes for neuropsychological tests to predict conversion to dementia in patients at risk of future cognitive decline were analysed in a systematic review of literature. Twenty-four studies published in the last 20 years were selected. Neuropsychological tests administered vary considerably among studies, yet the battery of tests applied generally assessed verbal memory performances, and many included also cognitive areas such as executive functions, attention and language. Methodological constrains limited the ability to provide reasonable predictive values; some studies have reported rather disparate global sensitivity and specificity rates for the neuropsychological tests to predict conversion to dementia. Conversely, other studies reported high and balanced sensitivity/specificity ratios (≥80%), mainly for verbal episodic memory tests, however the follow-up period of those studies was generally short (≈2 years). Certainly, it would be important to achieve a consensus according to the more feasible and accurate neuropsychological tests to administer for the assessment of patients at risk of conversion to dementia. On the other hand, cohort studies with longer follow-up periods would be important to propose neuropsychological tests with higher predictive accuracy and clinical relevance regarding conversion to dementia.

2. º Newer statistical classification methods derived from data mining and machine learning methods were applied to improve accuracy, sensitivity and specificity of predictors obtained from neuropsychological testing. Data used to perform the comparison of classification methods was extracted from a cohort study (CCC – Cognitive Complaints Cohort) with 775 elderly non-demented patients with cognitive complaints referred for neuropsychological evaluation. Seven non-parametric classifiers derived from data mining methods (Multilayer Perceptrons Neural Networks, Radial Basis Function Neural Networks, Support Vector Machines, CART, CHAID and QUEST Classification Trees and Random Forests) were compared to three traditional classifiers (Linear Discriminant Analysis, Quadratic Discriminant Analysis and Logistic Regression) in terms of overall classification accuracy, specificity, sensitivity, Area under the ROC curve and Press'Q. Model predictors were 10 neuropsychological tests currently used in the diagnosis of dementia. Comparison of classifiers highlighted three methods more adequate to study the predictive value of neuropsychological tests in longitudinal clinical cohort studies. Support Vector Machines demonstrated the larger overall classification accuracy (Median (Me) = 0.76) and area under the ROC (Me =0.90). However, this method showed high specificity (Me = 1.0) but very low sensitivity (Me = 0.3). Random Forests ranked second in overall accuracy (Me = 0.73) with high area under the ROC (Me = 0.73), specificity (Me = 0.73) and sensitivity (Me = 0.64). Linear Discriminant Analysis also showed acceptable overall accuracy (Me = 0.66), with acceptable area under the ROC (Me = 0.72), specificity (Me = 0.66) and sensitivity (Me = 0.64). Results indicated the innovative data mining method of Random Forests, along with more traditional methods, namely the Linear Discriminant Analysis, should be the option in cohort studies of neuropsychological predictors of future dementia.

3. º Verbal memory is one of the first cognitive areas to decline, therefore, the predictive value of Mild Cognitive Impairment (MCI) for the conversion to dementia when using four different verbal memory tests (Logical Memory, LM; California Verbal Learning Test, CVLT; Verbal Paired-Associate Learning, VPAL; and Digit Span, DS) was analysed. Participants were consecutive patients with subjective cognitive complaints who performed a comprehensive neuropsychological evaluation and were not demented, observed in a memory clinic setting. At baseline, 272 patients from CCC reporting subjective cognitive complaints and not demented were included. During the follow-up time (3.0±1.9 years), 58 patients converted to dementia, and 214 did not. Statistically significant differences between the converters and non-converters were present in LM, VPAL and CVLT. A multivariate Cox regression analysis combining the 4 memory tests revealed that only the CVLT test remained significant as predictor of conversion to dementia. Non-demented patients with cognitive complaints diagnosed as MCI according to abnormal (< 1.5 SD) learning in the CVLT test had 3.6 higher risk of becoming demented in the follow-up. As so, the verbal memory

assessment using the CVLT should be preferred in the diagnostic criteria of MCI for a more accurate prediction of conversion to dementia.

4. º The predictive value for future conversion to dementia of a comprehensive neuropsychological battery applied to a cohort of nondemented patients followed-up for 5 years was presented. Two hundred and fifty subjects were selected from CCC having cognitive complaints, assessment with a comprehensive neuropsychological battery, and follow-up of at least 5 years (if patients have not converted to dementia earlier). During the follow-up period (2.6±1.8 years for converters and 6.1±2.1 for non converters), 162 patients (64.8%) progressed to dementia (mostly Alzheimer's disease), and 88 (35.2%) did not. A Linear Discriminant Analysis (LDA) model constituted by Digit Span backward, Semantic Fluency, Logical Memory (immediate recall) and Forgetting Index significantly discriminated converters from non-converters (λ Wilks=0.64; $\chi 2(4)=81.95$; $p<0.001$; RCanonical=0.60). Logical Memory (immediate recall) was the strongest predictor with a standardized canonical discriminant function coefficient of 0.70. The LDA classificatory model showed good sensitivity, specificity and accuracy values (78.8%, 79.9% and 78.6%, respectively) of the neuropsychological tests to predict long-term conversion to dementia. Results showed that it is possible to predict, on the basis of the initial clinical and neuropsychological evaluation, namely with routine tests from a comprehensive neuropsychological battery, whether non-demented patients with cognitive complaints will probably convert to dementia, or remain stable. This prediction is obtained with very good accuracy values (≈80%), similar to those reported for the newly research biomarkers, and at a reasonably long and clinically relevant term (5 years).

Conclusion:

Cognitive impairment is a prominent and early feature of AD, thus neuropsychological markers could offer a relatively inexpensive and non-invasive indicator of future progression to dementia. The present thesis shows that neuropsychological tests have good long-term predictive values for future conversion to dementia in non-demented patients with cognitive complaints. Nowadays, clinicians have to reconcile assistance to a large number of patients with cognitive complaints, novel expensive diagnostic techniques, promising disease-modifying treatments, and marked financial constraints. Therefore, it is crucial to assess as early as possible if patients have a low probability of progression to dementia, in which case a regular follow-up and general preventive measures might be indicated, or a high probability of progression to dementia, so that complex ancillary examinations and new disease-modifying treatments might be proposed.

RESUMO

A esperança média de vida tem vindo a aumentar e consequentemente, de modo gradual, também a prevalência de doenças neurodegenerativas, representando actualmente na população mais envelhecida um alarmante problema de saúde pública. A doença de Alzheimer é a forma mais comum de demência e afecta milhões de indivíduos adultos. Recentemente tem sido possível alcançar avanços significativos na compreensão e no conhecimento sobre os biomarcadores que traduzem os processos patofisiológicos associados à doença de Alzheimer, no entanto, é importante salientar que o fenótipo manifestado pode ainda ser de etiologia heterogénea. Compreender melhor a variação das expressões de fenótipo contigentes ao processo neuropatológico é essencial para uma identificação e intervenção mais precoce no processo neurodegenerativo. Recentemente foram propostos novos biomarcadores, ainda limitados ao âmbito da investigação, com o propósito de realizar mais cedo o diagnóstico de doença de Alzheimer. Não obstante o seu potencial, será de referir que a presença de significativas alterações cognitivas continua a ser um elemento de diagnóstico incontornável e um indicador precoce da doença de Alzheimer. Os marcadores neuropsicológicos poderão oferecer indicadores de uma futura progressão para demência que serão economicamente mais acessíveis e clinicamente menos invasivos do que a realização dos métodos necessários aos marcadores biológicos, que além de serem mais dispendiosos, apenas se encontram disponíveis em alguns centros médicos especializados e serão em alguns casos métodos invasivos (e.g., recolha de líquido cefalorraquidiano através de punção lombar). Por conseguinte, não será razoável assumir que se irá disponibilizar a todos os indivíduos com manifestas queixas subjectivas de alterações cognitivas os recentes biomarcadores, por requerem técnicas dispendiosas e/ou invasivas. Por outro lado, é importante referir que a abordagem em presente desenvolvimento para tratar a doença incidindo na modificação dos seus factores causais requer uma selecção inicial do maior número possível de indivíduos para os quais o risco de progressão para demência seja significativo. Assim sendo, o objectivo central da presente tese foi o de melhorar o valor preditivo das medidas neuropsicológicas para a determinação de uma futura progressão para demência de indivíduos com queixa de alterações cognitivas que contudo não preenchem ainda os critérios para o diagnóstico de demência. De modo a concretizar o objectivo central, quatro estudos foram desenvolvidos:

1.º - Uma revisão sistemática da literatura foi realizada com base em estudos originais publicados sobre o valor preditivo da avaliação neuropsicológica de uma futura progressão para demência, apresentando para tal os valores de sensibilidade, especificidade e magnitude do efeito para cada uma das provas neuropsicológicas. A selecção dos artigos permitiu a identificação de 24 artigos publicados nos últimos 20 anos. Os testes neuropsicológicos aplicados mudavam consideravelmente consoante o estudo em questão, contudo verificava-se

que no conjunto de estudos era consistente a aplicação de provas de avaliação da memória verbal, mas também de avaliação de funções executivas, capacidade de atenção e linguagem. A presença de limitações metodológicas condicionou a potencialidade de apresentar valores preditivos razoáveis em alguns estudos, além disso, noutros estudos os valores de sensibilidade e especificidade apresentados para as provas neuropsicológicas enquanto preditoras de futura progressão para demência eram consideravelmente díspares. No entanto será importante salientar que também foi possível identificar em parte dos estudos descritos a presença de valores muito positivos e de razões equilibradas entre sensibilidade e especificidade (≥80%), principalmente para provas de avaliação da memória verbal episódica, contudo os tempos de seguimento eram na sua maioria curtos (aproximadamente 2 anos). Com certeza que seria relevante encontrar um consenso que pudesse futuramente guiar uma escolha viável e precisa das provas neuropsicológicas a aplicar para melhor predizer uma futura progressão para demência. Por outro lado, a existência de estudos de coorte longitudinais com períodos de seguimento mais alargados seria essencial para melhorar a precisão dos valores preditivos da avaliação neuropsicológica, tornando-se estes clinicamente mais relevantes no que respeita a uma futura progressão para demência.

2.º Os novos métodos de classificação estatística associados a técnicas de Prospecção de dados (em inglês *data mining*) e Sistemas de Aprendizagem (em inglês *machine learning*) foram aplicados com o intuito de melhorar a precisão, sensibilidade e especificidade dos preditores obtidos pela avaliação neuropsicológica. Para a comparação dos métodos classificatórios recorreu-se à base de dados CCC (CCC – *Cognitive Complaints Cohort*) que era constituída na altura por 775 casos de pacientes idosos não-dementes com queixas de alterações cognitivas e que foram referenciados para realizarem uma avaliação neuropsicológica. A comparação dos métodos estatísticos realizou-se entre 7 classificadores não-paramétricos provenientes de métodos de Prospecção de dados (Redes Neuronais com Perceptrões Multicamada; Redes Neuronais com Funções de Base Radial; Máquinas de Vectores de Suporte; CART; CHAID; Árvores de Classificação QUEST e Árvores de Classificação Aleatória) que foram comparados com três classificadores tradicionais (Análise Discriminante Linear; Análise Discriminante Quadrática, e Regressão Logística) em termos de precisão classificatória, especificidade, sensibilidade, área abaixo da curva ROC e Press'Q. O modelo para a predição consistia em 10 testes neuropsicológicos utilizados recorrentemente para o diagnóstico de demência. A comparação de classificadores identificou três métodos como os mais adequados para testar o valor preditivo dos testes neuropsicológicos em estudos longitudinais de coortes clínicas. As Máquinas de Vectores de Suporte demonstraram valores mais elevados de precisão classificatória (Mediana (Me)= 0,76) e de área abaixo da curva ROC (Me= 0,90). De salientar que, no que respeita à especificidade, este método revelou um valor elevado (Me= 1,0), contudo o valor de sensibilidade era consideravelmente baixo (Me= 0,30). As Florestas Aleatórias foram o segundo método com melhores resultados em termos

de precisão (Me= 0,73), área abaixo da curva ROC (Me= 0,73), especificidade (Me= 0,73) e sensibilidade (Me= 0,64). A Análise Discriminante Linear demonstrou igualmente valores razoáveis de precisão (Me= 0,66), área abaixo da curva ROC (Me= 0,72), especificidade (Me= 0,66) e sensibilidade (Me= 0,64). Os resultados apresentados indicam que os melhores métodos classificatórios para analisar os preditores neuropsicológicos de futura progressão para demência correspondem às Florestas Aleatórias no âmbito dos mais inovadores métodos de Prospecção de dados e à Análise Discriminante Linear, enquanto método de eleição de entre os mais tradicionais para classificação de dados.

3.º A memória verbal é considerada uma das primeiras áreas cognitivas a manifestar declínio nos casos de Doença de Alzheimer. Por conseguinte, o valor preditivo de progressão para demência (Doença de Alzheimer) associado ao Defeito Cognitivo Ligeiro (DCL) foi analisado contemplando para o diagnóstico de DCL quatro testes diferentes de avaliação da memória verbal (Memória Lógica (LM); Teste de Aprendizagem Verbal de Califórnia (CVLT); Aprendizagem Verbal Associativa com Pares de Palavras (VPAL); e, Memória de Dígitos (DS)). Para o estudo foi seleccionada uma amostra consecutiva de pacientes com queixas de alterações cognitivas que em consequência das mesmas foram referenciados para realizar uma avaliação neuropsicológica pormenorizada numa clínica de memória, mas que não preenchiam ainda os critérios para o diagnóstico de demência. Uma amostra inicial de 272 pacientes com queixas cognitivas e não-dementes foram seleccionados da coorte CCC para o presente estudo. No decurso do período de seguimento (3,0±1,9 anos) ocorreu a conversão para demência em 58 pacientes, enquanto 214 permaneceram cognitivamente estáveis. Nas provas de LM, VPAL e CVLT verificaram-se diferenças estatisticamente significativas entre o grupo que converteu e o que não converteu. Através de uma análise de Regressão Multivariada de COX com um modelo constituído pelas quatro provas de memória verbal demonstrou-se que apenas a prova CVLT mantém a significância enquanto preditor de futura conversão para demência. Assim sendo, pacientes que não se encontram dementes mas que manifestam queixas de alterações cognitivas, com o diagnóstico de DCL recorrendo à pontuação na prova CVLT, se apresentarem defeito nesta prova (< 1,5 desvios-padrão abaixo da média de referência) têm um risco acrescido de evoluir para demência dentro do período de seguimento. Consequentemente, uma avaliação neuropsicológica incluindo a prova CVLT deve ser contemplada para os critérios de diagnóstico de DCL de modo a predizer com maior precisão uma futura conversão para demência.

4.º Uma coorte constituída por 250 indivíduos (seleccionados da base de dados CCC) com queixas cognitivas mas sem critérios de demência e com seguimento clínico superior a 5 anos (com excepção para os casos que evoluíram para demência antes dos 5 anos) foi analisada com vista à determinação do valor preditivo dos testes neuropsicológicos a longo prazo. Durante o período de seguimento (2,6±1,8 anos para os indivíduos que evoluíram para

demência e 6,1±2,1 anos para os que permaneceram estáveis a nível cognitivo) 162 indivíduos (64,8%) apresentaram os critérios para o diagnóstico de demência (principalmente para Doença de Alzheimer), enquanto que 88 (35,2%) permaneceram estáveis. Foi possível discriminar entre os indivíduos que progrediram para demência e os que permaneceram estáveis através de um modelo de Análise Discriminante Linear (ADL) com os resultados iniciais da avaliação nas provas: Memória de Dígitos inversa, Fluência Semântica, Memória Lógica (evocação imediata), e o Índice de Esquecimento da Memória Lógica (λ Wilks= 0,64; χ^2 (4)= 81,95; p< 0,001; RCanonical= 0,60). O preditor neuropsicológico mais robusto, com coeficiente estandardizado da função discriminante (canónica) de 0,70, foi a prova de Memória Lógica (evocação imediata). O modelo classificatório da ADL demonstrou valores muito positivos para a sensibilidade, especificidade e precisão classificatória (78,8%, 79,9% e 78,6%, respectivamente), dos testes neuropsicológicos para predizer uma futura progressão para demência a longo prazo. Os resultados apresentados evidenciam a possibilidade de predizer, com base numa avaliação inicial, clínica e neuropsicológica, com uma bateria de provas cognitivas aplicada na rotina clínica, se o indivíduo que apresenta queixas cognitivas irá evoluir para demência ou permanecer estável nos próximos anos. Será de salientar que o valor preditivo foi obtido com uma precisão bastante aceitável (≈ 80%), na ordem dos valores obtidos para os biomarcadores mais recentes, e no âmbito de um período de seguimento consideravelmente longo e portanto clinicamente relevante (5 anos).

Conclusão:

O declínio cognitivo constitui um sintoma inicial e crucial para o diagnóstico de Doença de Alzheimer, e por conseguinte, a avaliação neuropsicológica poderá permitir a identificação de alterações cognitivas associadas a uma futura progressão para demência a um custo relativamente acessível e sem sujeição do indivíduo a métodos de diagnóstico mais invasivos. A presente tese de doutoramento demonstra que a avaliação neuropsicológica poderá oferecer valores preditivos significativos no que respeita a uma futura conversão para demência num grupo de indivíduos com queixas cognitivas. Nos nossos dias, os profissionais que trabalham na área da geriatria, principalmente os neurologistas e psiquiatras, têm de dar assistência e tomar decisões a respeito de um número considerável de indivíduos que surgem diariamente com queixas cognitivas. Isto ocorre numa altura em que se começam a integrar meios complementares de diagnóstico mais inovadores e dispendiosos, assim como ensaios clínicos com potenciais tratamentos dirigidos às causas da demência, mas num contexto socio-económico onde as restrições financeiras se encontram bem patentes. Assim sendo, urge avaliar no momento presente o risco de progressão para demência o mais precocemente possível, de modo a identificar se existe uma probabilidade baixa de futura conversão para demência, caso em que um acompanhamento regular e manutenção das medidas de prevenção serão os procedimentos mais adequados, ou se pelo contrário existe um risco elevado, caso em que será mais adequando propor a realização dos meios complementares de diagnóstico

mais inovadores e dispendiosos, assim como referenciar o indivíduo para iniciar os tratamentos dirigidos aos mecanismos causadores, assim que os mesmos estiverem clinicamente bem estabelecidos.

Illustration dating from the 1500s and published at the *Guild Book of the Barber-Surgeons of York* portraying the four temperaments, top-down left-right, melancholic, sanguine, choleric, and phlegmatic, respectively. The phlegmatic humour denoting apathy or sluggishness was back then associated with old age. Printed by permission of The British Library (R97/1263). Source: Berchtold and Cotman, 1998.

PART I – INTRODUCTION

1.1 Dementia before Alzheimer's Disease

The word dementia comes from the Latin *dēmēns* based on the words *de* ("down from, concerning") and *mēns* ("mind") and had the meaning: *out of one's mind*. The medical connotation associated to the word was only established by the early eighteenth century, however the concern given to age-related cognitive decline dates back to the antiquity. Earliest references to age-related mental deficiency in the 7th century BC were attributed to the Greek physician Pythagoras. Back then, not only Pythagoras but also Hippocrates, Plato, Aristotle and Galen seemed to believe that the aging process was a life phase of expected degeneration and inevitable age-related cognitive decline. Some have attributed the semantic mutation of the word "senile" to the concept of aging, since the term "senile" was no longer perceived as only meaning "advance age" but have become to denote a "demented phase" in life. However, the Roman philosopher Cicero was perspicacious enough to observe that the aging process with cognitive and/or behaviour deterioration occurred only in some elderly people, the ones that Cicero called "weak in will" (Berchtold and Cotman, 1998). Around the end of second century AD another insightful differentiation on dementia conditions was suggested by Aretheus of Cappadocia who described acute disorders as reversible and chronic disorders (for instance dementia) as an irreversible affectation of higher cognitive functions (Boller and Forbes, 1998). Clearly, ancient thinkers, like the Latin elegiac poet Maximianus, were sharp enough to observe and describe the key cognitive deficits and typical behavioural manifestations in old demented subjects. Notwithstanding these poignant perspectives, the classification of dementing disorders (see Table 1.1) remained confusing until the late nineteenth and twenty centuries. From the ancient Greek and Roman periods to the 19th century no major evolution occurred in the conceptualization of the aging process. The next important step was taken with the meticulous work of Pinel and Esquirol in the 19th century. By presenting a systematic description of mental disorders, it was possible to identify subtle differences that set apart senile dementia from other mental diseases, and that way the concept became more concrete (Román, 1999). Pinel distinguished four broad groups of mental disorders: melancholy, mania, dementia, and mental retardation. Esquirol (one of the most outstanding students of Pinel) gave continuity to Pinel's work through the identification of subtypes and categories of mental disorders that became the pillars of modern classification of

mental diseases (Cipriani *et al.*, 2011). Until the proposal of the anatomo-clinical model by the nineteenth century alienists, dementia was considered no more than an inevitable consequence of normal aging process.

Table 1.1 – Different designations for dementia since antiquity and attributed causes.

Nosologic entities corresponding to "dementia"*	Causes of dementia according to Esquirol*
Alienation	Menstrual disorders
Amentia	Sequelae of delivery
Anoea (extinction of the imagination and judgment)	Head injuries
Dotage or 'second childhood'	Progression of age
Fatuitas (silliness)	Ataxic fever
Foolishness	Hemorrhoids surgery
Idiocy	Mania and monomania
Imbecility	Paralysis
Insanity	Apoplexy
Lethargy	Syphilis
Morosis	Mercury abuse
Organic brain syndrome	Dietary excesses
Phrenesis	Wine abuse
Senile dementia	Masturbation
Senile psychosis	Unhappy love
Senility	Fears
Simplicity	Unfulfilled ambitions
Stupidity	Poverty
	Domestic problems

*See source for further references: Boller and Forbes, 1998

1.2 Alzheimer's Disease

In the 1890s, Alois Alzheimer and Otto Binswanger described the arteriosclerotic brain atrophy frequently accompanied by stroke as a necessary precursory event for the development of senile brain atrophy and senile dementia (Forstl and Howard, 1991). Alois Alzheimer put together the clinical and pathologic changes associated nowadays with Alzheimer's disease during the lecture in the Meeting of the Psychiatrists of South West Germany, in 1906. The worldwide known Auguste D. case described a woman with unusually marked dementia symptoms before the 50 years, whose brain in post-mortem examination

had marked neurofibrillary tangle pathology, neuronal degeneration and widespread amyloid plaques. After retrieving the original clinical files written by Alois Alzheimer, it was possible to access the description of Auguste D. behaviour and cognitive capacities documented in his daily notes, revealing memory deficits, disorientation and extensive cognitive impairment (Maurer, Volk and Gerbaldo, 1997). Notwithstading the clinical symptomatology, Alzheimer's eminent colleague and so called founder of modern scientific psychiatry, Emil Kraepelin, was reluctant to consider that dementia at the age of 50 was the same as the oldest dementia cases. This neurodegenerative disorder, later on called Alzheimer's disease (AD), was considered by that time as a truly unique disease which main clinical and pathological concept essentially remained until nowadays. Currently, it is known that Alzheimer's disease can be of familial/genetic or sporadic type. The familial form is rare and usually early-onset, occurring in people with 30 to 60 years old and it is caused by changes in three well-known inherited genes, amyloid precursor protein (APP), presenilin 1 and presenilin 2. Most people with Alzheimer's disease have the sporadic form, which usually develops after the age of 60. Different genetic and environmental abnormalities can contribute to the brain damage in AD. The consensual pathophysiological cascade involves synaptic dysfunction in vulnerable areas, mitochondrial damage, local inflammatory reaction, oxidative stress and excitotoxicity, leading to the formation of neurofibrillary tangles, amyloid accumulation and ultimately neuronal loss (Poirier, Danik and Blass, 2001). Although the definite diagnosis still relies on the presence of clinical and neuropathological findings, several criteria for the clinical diagnosis of dementia have been used, like those from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR; American Psychiatric Association, 2000; see Annex, Table 5.2, page 83), and the International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organisation, 1992; see Annex, Table 5.2, page 83). Perhaps the most common for over 25 years have been the NINCDS-ADRDA criteria (see Annex, Table 5.2, page 83; McKhann *et al.*, 1984; Dubois *et al.*, 2007). As mentioned in detail below, the NINCDS-ADRDA criteria, first published in 1984, were recently revised to take into account the presence of the most recently recognized biomarkers associated to the AD neurodegenerative process. Revision of AD criteria sought to identify the earliest detectable phase of neurodegeneration and recently a stage of "preclinical AD" has also been identified as a period where biomarkers like brain amyloid deposition and cerebrospinal fluid tau and amyloid can be detected *in vivo* (McKhann *et al.*, 2010).

1.3 Alzheimer's Disease before dementia

Many histopathological studies in Alzheimer's disease revealed that neuronal damage caused by the pathophysiological cascade mentioned above (Poirier, Danik and Blass, 2001) starts at particular regions of the brain, namely the hippocampal formation and the enthorinal cortex, and spreads through the brain as the disease advances. At first the neurodegenerative process entails no discernible symptoms, and is afterwards reflected by progressive clinical manifestations. The National Institute on Aging and the Alzheimer's Association Workgroup tried to reflect this concept by proposing to stage AD from the early pre-clinical process. The first stage is described as asymptomatic cerebral amyloidosis (altered β-amyloid by positron emission tomography (PET) or in the cerebrospinal fluid (CSF)), the second stage is characterized as asymptomatic amyloidosis plus markers of neurodegeneration (as revealed by magnetic resonance imaging (MRI), ^{18}F-FDG (2-Fluoro-2-deoxy-D-glucose) PET and altered tau/phospho-tau ratio in the CSF), and stage 3 combines markers of amyloidosis and of neurodegeneration plus subtle cognitive and behavioral decline (Sperling *et al.*, 2011). Thus, the term degenerative process within the spectrum of AD nowadays covers different early phases of AD-related pathology: histopathological data without clinical and biomarker data; altered biomarkers without clinical signs; and the presence of only early or advanced stages of mental deterioration and cognitive impairment. The core clinical features for diagnosis are based on a careful clinical history and examination, combined with cognitive assessment, neuroimaging exams and laboratory tests (Ferrer, 2012). The concept of Alzheimer´s disease as a disorder that begins ahead of the first symptoms, and certainly much before full-blown dementia, thus relies on the recent development of biomarkers. Biomarkers of AD can be signs of molecular or structural pathology or indicators of clinical status. This differentiation reflects the upstream (alterations that can occur in a prodromal asymptomatic phase) and downstream (symptomatic phase) continuum of the disease process. The biomarkers have been extensively studied, namely cerebrospinal fluid biomarkers, $A\beta_{1-42}$, total tau protein and hyperphosphorylated tau protein (Csernansky *et al.*, 2002; Simonsen *et al.*, 2007; Mattsson *et al.*, 2009; Snider *et al.*, 2009; Tapiola *et al.*, 2009; Mulder *et al.*, 2010); inherited pathogenic mutations (amyloid precursor protein, presenilin 1, and presenilin 2) (Growdon, 1999; Finckh *et al.*, 2005; Devi *et al.*, 2000; Poorkaj *et al.*, 2001; Tedde *et al.*, 2003; Lleó *et al.*, 2004; Kumar-Singh *et al.*, 2006; Theuns *et al.*, 2006; Ringman *et al.*,

2012); the topographic pattern of atrophy measured by neuroimaging techniques (computed tomography (CT)/MRI); cerebral metabolism/perfusion studied by functional neuroimaging (PET with ^{18}F FDG/ PET with Pittsburgh compound B (PiB)/ functional MRI) (Johnson *et al.*, 2012b; Whitwell *et al.*, 2012; Klunk, 2011; Herholz *et al.*, 2011; Sabuncu *et al.*, 2011; Dickerson, 2010; Pedrosa *et al.*, 2010; Svedberg *et al.*, 2009; Mintun *et al.*, 2006; Neugroschl and Davis, 2002); and evidence of cognitive decline (neuropsychological assessment) (Wagner *et al.*, 2012; Llano *et al.*, 2011; Razani *et al.*, 2011; Jungwirth *et al.*, 2009; Nordlund *et al.*, 2008; Hussain, 2007; Rozzini *et al.*, 2007; Tabert *et al.*, 2006; Lehrner *et al.*, 2005; Rapp and Reischies, 2005; Scheurich *et al.*, 2005; Tierney *et al.*, 2005; Perry and Hodges, 2000; Albert, 1996; Claman and Radebaugh, 1991; Haxby *et al.*, 1990). The upstream and downstream markers might represent factors of cause or consequence of the disease process, consequently appearing at different stages of neurodegeneration (See Figure 1.1).

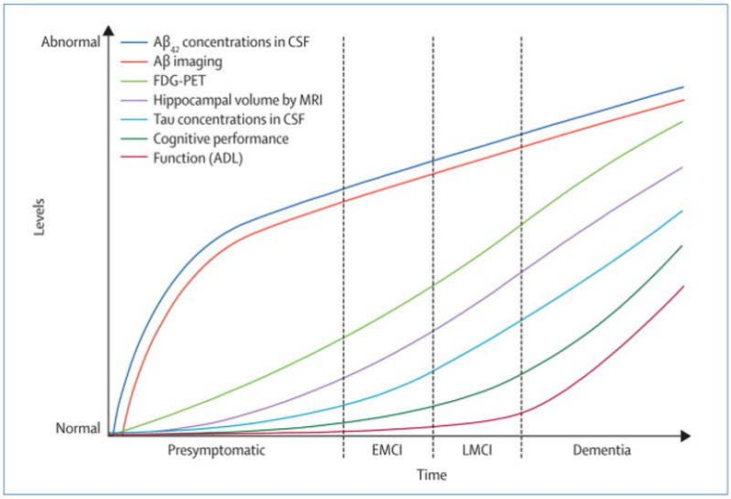

Figure 1.1 - Hypothetical progression of pathological and clinical events that lead to Alzheimer's disease. ADL=activities of daily living. EMCI=early MCI. FDG-PET=18F-fluorodeoxyglucose PET. LMCI=late MCI. Source: Petersen, 2010.

One of the most extensively studied molecular biomarker is amyloid beta-protein (Aβ). Aβ is produced mainly in the nerve cells of the brain and secreted about 12 hours later into the cerebrospinal fluid (CSF), then excreted through the blood–brain barrier 24 hours later into bloodstream (Aβ clearance), and finally degraded in the reticuloendothelial system (Bateman *et al.*, 2009). The particular species of Aβ 42 amino acids long ($A\beta_{1-42}$) is the most amyloidogenic form of the peptide and forms insoluble aggregates, which start to deposit and

accumulate extracellulary as plaques in the brain. Apparently, $A\beta_{1-42}$ levels are decreased in the CSF of AD patients due to the deterioration of physiologic Aβ clearance into the CSF (Kawarabayashi *et al.*, 2001). CSF $A\beta_{1-42}$ concentrations are decreased by about 50% in patients with AD dementia or mild cognitive impairment, compared with age-matched controls (Hulstaert *et al.*, 1999). This decrease has been associated with enhanced deposition of $A\beta_{1-42}$ in the brain (Fagan *et al.*, 2007). The main component related to intraneuronal changes in AD patients is the microtubule-associated tau protein. This protein is expressed in neurons, normally acts to stabilize microtubules in the cell cytoskeleton, and is normally regulated by phosphorylation. When hyperphosphorylated tau accumulates as paired helical filaments it can aggregate inside the nerve cell bodies into deposits known as neurofibrillary tangles (Spillantini *et al.*, 1990). In AD patients, tau protein is present in this hyperphosphorylated form. Tau protein was quantified in the CSF under the hypothesis that it is released extracellularly as a result of the neurodegenerative process. The methods initially analyzed all forms of tau, regardless of their phosphorylation status, but hyperphosphorylated tau protein (p-tau) has shown more potential as a biomarker. CSF total tau is increased on average by approximately two to three times in AD, whereas some phosphorylated tau species can be increased by one or two times when compared to control levels (Blennow *et al.*, 1995, 2001; Andreasen *et al.*, 2001; Buerger *et al.*, 2002; Buerger *et al.*, 2005; Bouwman *et al.*, 2009; Lewczuk *et al.*, 2008). Notwithstanding the established potential as biomarker of disease, CSF tau levels differentiate more accurately between AD patients and controls for ages below 70 years old (Bürger née Buch *et al.*, 1999). In comparison to tau protein and other biomarkers, CSF $A\beta_{1-42}$ concentrations have shown to be the most sensitive and informative single AD biomarker both in the Alzheimer's disease Neuroimaging Initiative (ADNI) cohort and the ADNI-independent autopsy confirmed cohort, reaching a sensibility of 96.4% and a specificity of 76.9% (Shaw *et al.*, 2009). However, the values reported correspond to a follow-up of 12 months in patients that where in an advanced phase of the disease and not in a prodromal phase of neurodegeneration where the detection should be most useful. For the ADNI cohort of mild cognitive impairment patients that converted to AD, an incidence of AD-like CSF profile was observed in only 86.5% of patients (Shaw *et al.*, 2009). To predict accurately the future conversion to dementia, biomarkers assessment should be made in cohort studies with longer follow-up periods, because otherwise the risk of false negatives is considerable. An example is the ADNI cohort study on the use of

neuropsychological, brain imaging, and CSF neurochemical biomarkers for conversion to dementia during a follow-up of approximately 2 years that reported a predictive accuracy for conversion to dementia of only 64% (Ewers *et al.*, 2012). Longer follow-up periods would not only elucidate the specificity of biomarkers but also increase the understanding of biomarkers contribution along the disease process. The "biomarker cascade model" (Jack *et al.*, 2010a; see Figure 1.1) proposed that specific Aβ biomarkers foretold the development of dementia due to Alzheimer's disease, whereas time-to-dementia would be predicted by measures of neurodegeneration severity, such as atrophy in MRI. Abnormal Aβ processing is a central feature of Alzheimer's pathology and a core biomarker for neurodegeneration associated with brain injury, atrophy and subsequent cognitive decline (van Rossum *et al.*, 2012). However, CSF level of $A\beta_{1-42}$ does not predict time-to-dementia because there appears to be a plateau early in the course of the disease that remains stable afterwards (Ingelsson *et al.*, 2004; Jack *et al.*, 2010a,b; van Rossum *et al.*, 2012).

Historically, neuroimaging techniques have been used to exclude potentially surgically treatable causes of cognitive decline, however nowadays these techniques provide priceless information about Alzheimer's disease preclinical phase revealing characteristic patterns (signatures) of structural and functional cerebral alterations.

Magnetic resonance (MR) imaging with high spatial resolution allows visualization of subtle anatomic changes and thus can help to detect brain atrophy (with T1-weighted volumetric sequences) at the initial stages of the disease. The medial temporal lobe, specially the hippocampus, is known to be affected at the earliest stages of AD (Braak and Braak, 1995) and assessment of atrophy has revealed an accurate predictive value for AD. Visual assessment differentiates mild AD from normal aging with sensitivity and specificity of about 85% (Scheltens *et al.*, 1992; Duara *et al.*, 2008; Burton *et al.*, 2009). Identifying individuals with mild cognitive complaints who will progress to AD in the near future from those who will not is more difficult, and medial temporal atrophy on MRI only predicts progression with sensitivity of approximately 50%-70% and specificity around 70% during a follow-up time of 3 years (Korf *et al.*, 2004; DeCarli *et al.*, 2007).

Longitudinal MRI studies of individuals who were initially asymptomatic but who have subsequently developed AD revealed that rates of hippocampal atrophy increase gradually 5 years before diagnosis, and hippocampal volumes were already reduced by about 10% 3 years before receiving a diagnosis of dementia due to AD (Johnson *et al.*, 2012). Although

volumetric measurements of the volumes of the temporal lobe and hippocampal formation have demonstrated that both volumes decreased with age for AD patients and elderly controls, the hippocampal formation volume accurately differentiates AD patients from cognitively normal elderly individuals, thus being considered a biomarker with relevant potential (Jack *et al.*, 1992). In addition to the hippocampal volumetry, the volumetric measurement of the entorhinal cortex is valuable in distinguishing patients with AD from elderly controls. In the discriminant function analysis, volumetry of the entorhinal cortex yielded a specificity of 94% with a sensitivity of 90%. No essential difference was found in the discriminative power of entorhinal and hippocampal volumetry (Juottonen *et al.*, 1999). Notwithstanding the remarkable value of hippocampal volumetry to differentiate AD patients and elderly controls, the accuracy obtained for patients in the prodromal phases of AD is usually much lower, ranging from 60% to 74% (Convit *et al.*, 1997; de Santi *et al.*, 2001; Du *et al.*, 2001; Pennanen *et al.*, 2004). Moreover, most volumetric studies previously relied on manual segmentation, which is time-consuming and requires specific training and is thus not suitable to clinical practice. Gerardin and colleagues (2009) presented a study using multidimensional classification of hippocampal shape features done automatically to overcome that difficulty however, predictive results clearly require confirmation in longitudinal studies with larger samples of individuals.

Several PET tracers are available to assess molecular aspects of Alzheimer's pathophysiological process *in vivo*. ^{18}F-FDG is a glucose analogue and, as such, its uptake is strongly associated with neuronal function. Pittsburgh compound B (^{11}C-PiB) is used in PET scans to image beta-amyloid plaques in neuronal tissue, and it is well known that AD patients show significantly higher retention of this compound in brain cortical areas (Klunk *et al.*, 2004; Buckner *et al.*, 2005; Rowe *et al.*, 2007). Although the hippocampus is a structure of acknowledged importance to assess the prodromal phase of AD, the early amyloid burden apears to spare or is difficult to detect in the hippocampus; therefore ^{11}C-PiB is unlikely to replace the need for other imaging techniques on hippocampal formation structures (Schuff and Zhu, 2007).

More recent studies, addressing the question whether these amyloid traces *in vivo* changed longitudinally in patients with AD, revealed that increased cortical ^{11}C-PiB binding was seen earlier in mild cognitive impairment patients and decreased ^{18}F-FDG uptake only occurred in AD patients (Ossenkoppele *et al.*, 2012). At early stages of the disease, accumulation of Aβ is

an ongoing event while no or only minor metabolic changes occur. As the clinical course of AD progresses, the amyloid curve flattens and evident generalized glucose hypometabolism arises (Jack *et al.*, 2010a). Therefore, an earlier detection of neurodegenerative process would be preferable using ^{11}C-PiB scan. According to twin studies, Alzheimer-like β-amyloid plaque pathology is influenced by genetic but also environmental/acquired factors that modulate the relationship between brain amyloidosis and neurodegeneration and its clinical expression as cognitive impairment (Scheinin *et al.*, 2011). Notwithstanding, PiB is an ^{11}C labelled compound with a short half-life that can only be used at academic medical centers equipped with with a cyclotron, which hampers the widespread use for diagnostic purposes. Besides, the extent to which amyloid retention changes over time is not clearly established (Sojkova *et al.*, 2011). Moreover, cognitively normal elderly individuals can also present beta-amyloid (Aβ) deposition and although a slight ^{11}C-PiB elevation might have a biological relevance (Mormino *et al.*, 2009, 2012), endeavors are needed to determine whether ambiguously elevated ^{11}C-PiB values represent a biologically meaningful signal. A recent review raised the question whether Aβ would be cause or consequence of Alzheimer's disease symptoms because a decreased brain synaptic/metabolic activity, independent of etiology, could lead to cognitive decline and indirectly to Aβ deposition (Struble *et al.*, 2010).

1.4 Cognitive markers of Alzheimer's disease

Cognitive symptoms have been crucial not only to the diagnosis of Alzheimer's disease but also to staging the neurodegenerative progression (Flicker *et al.* 1984; Vitaliano *et al.*, 1984; Cummings and Benson, 1986; Storandt and Hill, 1989; Storandt, 1991). Moreover, cognitive markers were for long proposed to detected future converters to dementia, and may constitute a particularly feasible and accessible way to reveal the subjects at risk (Small *et al.*, 1997; Stern *et al.*, 1994).

A lot of recent knowledge about the initial cognitive decline in patients with AD actually came from many studies performed in patients with Mild Cognitive impairment (MCI), developed as a clinical entity linking healthy aging and dementia. The diagnosis of MCI actually relies on the finding of specific alterations in cognitive tests. Petersen and colleagues (1999) defined MCI as a condition characterized by subjective cognitive complaints, objective memory deficit, normal general cognitive performance and maintained activities of daily living (see Annex, Table 5.1, page 82). Thereafter, criteria were revised by Portet and

colleagues (2006) and slight changes were introduced to improve the identification of patients at high risk of progression to dementia and establish the prognosis more accurately. According to this revision, the diagnosis should rely on clinical impression and not on memory performance solely, the cognitive complaints gained an important prognostic role, some repercussions on complex day-to-day activities might occur due to cognitive impairment and, finally, a decline in cognitive function should be detected. The syndrome subtype may be recognised as early as the initial evaluation and would correspond to amnestic MCI, involving predominant impairment of the memory domain; non-amnestic MCI, characterised by slight impairment of multiple cognitive domains (multiple-domain MCI); or impairment of a cognitive domain other than of memory (single-domain MCI) (Petersen, 1998; Portet *et al.*, 2006).

Later on, the MCI criteria were revised for research purposes and newly biomarkers were incorporated to assiste the estimation of the likelihood of conversion to dementia. Albert and colleagues (2011; see Annex, Table 5.1, page 82) revised criteria proposed that high likelihood was present if a positive Aβ biomarker and a positive biomarker of neuronal injury were detected; intermediate likelihood if a positive Aβ biomarker was present whenever neuronal injury biomarkers were not tested, or otherwise, if there is a positive biomarker of neuronal injury but Aβ biomarkers were not tested. So, if the subject met the core clinical criteria for MCI and in addition had positive biomarkers for both Aβ and neuronal injury, this would provides the highest level of certainty that over time the individual will progress to AD dementia.

We can certainly acknowledge that MCI represents a relevant clinical concept, and longitudinal studies in patients with MCI have shed light on changes associated with the development of AD. In large epidemiological studies performed in subjects above 65 years old, about 5% have Alzheimer's disease (Lobo *et al.*, 2000), and as much as 16% suffer from MCI (Artero *et al.*, 2006). The term MCI assumes that some type of cognitive continuum exists between normality and Alzheimer's disease, the main cause of dementia (Jelic, Kivipelto and Winblad, 2006; Portet *et al.*, 2006), since it corresponds to a condition likely to progress to Alzheimer's disease (AD) at an accelerated rate with well-established reports of conversion in a clinical setting of about 80% in 6 years (Petersen *et al.*, 2001b; Portet *et al.*, 2006). Patients suffering from AD at a prodromal stage have been, mostly, clinically

classified as amnestic mild cognitive impairment (MCI) (Petersen *et al.*, 1999; Dubois and Albert, 2004), but not all patients with amnestic MCI will develop AD. The consideration of different cognitive and functional factors for MCI diagnosis is important to better predict future conversion in dementia (Saxton *et al.*, 2009). A decline in episodic memory, confirmed by neuropsychological tests, has been the hallmark to identify a prodromal phase of AD and establish the diagnosis (Dubois *et al.*, 2007; Albert *et al.*, 2011), however cognitive changes may be observed 3 to 4 years before the diagnosis of MCI (Howieson *et al.*, 2008). The MCI condition may not have the same evolution for all patients, however amnestic MCI (aMCI) with consistent memory loss preferentially progresses to AD (Petersen *et al.*, 2001a). Patients categorized as having aMCI have roughly 8.6-fold higher odds of developing AD than patients without evident memory impairment on neuropsychological testing. Since MCI is a heterogeneous entity and different pathological processes may contribute to the cognitive impairment, it is reasonable to expect different trajectories of cognitive decline among people with MCI and heterogeneous outcomes (Xie, Mayo and Kosk, 2011). Cognitive domains can be affected differently in MCI subtypes and, although episodic memory has been pointed out as the core deficit observed early in the course of the disease, multi-domain MCI patients convert at a higher rate to dementia (Tabert *et al.*, 2006; Mitchell *et al.*, 2009; Peraita, García-Herranz and Díaz-Mardomingo, 2011). From what is known from the pathological progression of Alzheimer's disease, we could expect that impairment in several cognitive areas might relate to a more advanced neurodegeneration stage.

On the other hand, the MCI concept has some important limitations. Since it represents a phase of cognitive decline between normality and dementia, it is a clinical description of a stage rather than a disease itself (Gauthier *et al.*, 2006). Heterogeneity of MCI entity also requires more careful consideration, regarding not only the MCI subtype but also the criteria by which it is diagnosed, as well as the neuropsychological tests used and the cutoff selected, all of which can interfere with the predictive accuracy of MCI (Ritchie and Tuokko, 2010; Trittschuh *et al.*, 2011; Silva *et al.*, 2012). Some patients with MCI remain intriguingly stable for a very long period of time and it is not certain if they will eventually progress to dementia (Petersen *et al.*, 2001a,b). Clearly, the MCI diagnosis is not sufficient or a necessary condition for progression to dementia (Nunes *et al.*, 2010). Moreover, 10–20% of persons meeting criteria for MCI at a particular time will not progress to dementia (Petersen, 2003), and some may even revert to normal levels, at least in community-based studies (Ritchie, 2004).

Although the probability of patients without objective memory decline to develop AD is small, some patients convert to AD (Lehrner *et al.*, 2005). More longitudinal studies are needed to assess the way in which cognitive impairments develop during the MCI phase. Recently, need to identify markers of progression, independently of MCI diagnosis, in the subjects more prone to progress to AD dementia was emphasised (Tian *et al.*, 2003; Powell *et al.*, 2006; Andersson *et al.*, 2008; Craig-Schapiro, Fagan and Holtzman, 2009; Jungwirth *et al.*, 2009; Leow *et al.*, 2009; Lekeu *et al.*, 2010).

Cognitive deficits may appear many years before the clinical diagnosis of AD, almost 7 years before it is possible to detect deficits on verbal memory. However, the magnitude of these deficits is relatively small, up until the point at which the diagnosis of AD is rendered (Linn *et al.*, 1995; Small *et al.*, 2000). In younger samples of cognitively impaired people this stability on performance is even more noticeable, with obvious compromise of specificity for predictive diagnosis (Anstey *et al.*, 2008). Episodic memory deficit is a constant, precocious, and reliable neuropsychological marker of AD in relation to early involvement of medial temporal structures, namely hippocampal formation (Deweer *et al.*, 1995). Memory impairment, in close association to reduced hippocampal volume, contributes to the decrease in temporoparietal metabolism associated with AD (Kuczynski *et al.*, 2008). Other studies also mention motor speed as an early predictor of AD, representing a type of age-related slowing of functions that associated with deficits in episodic memory could indicate a preclinical phase of AD (Jungwirth *et al.*, 2009). Importantly, the inability to recall information from a prose passage suggests impaired encoding of the contextual information that makes up complex events (Rubin *et al.*, 1998). Since the episodic memory deficit of AD patients is due in large part to ineffective consolidation or storage of new information, the assessment through tasks of word list learning may also be very useful to identify reduced free and cued recall, impaired recognition, and impaired associative learning. Indices of rapid forgetting have clinical utility for the early detection of prodromal AD, but decreased use of memory aids might also be a relevant marker and was associated with poorer performance on verbal memory tests (Archer *et al.*, 2007). Brain areas underlying acquisition and consolidation of new information are expected to be impaired at a very early stage of AD process. Regarding the brain correlates of consolidation, hippocampal structures are responsible for the efficacy of learning and initial storage of new information, whereas acquisition is associated with a broader brain network and is severely impaired earlier in AD

progression than short or even long-term consolidation, sometimes referred to as retention (Genon *et al.,* 2012). The explicit semantic encoding of new information, namely through association, is affected in AD patients, reflecting decreased metabolism in the hippocampus, which accounts for the described acquisition deficits in these patients (Sperling *et al.,* 2003). Besides acquisition, the retrieval component of episodic memory was shown to be altered through increased sensitivity to interference associated to decreased inhibitory processes, which leads to the production of more intrusion errors in AD patients (Delis *et al.,* 1991). Similarly, confabulation in episodic memory has been described in AD patients, particularly the "provoked" confabulation present in story recall tasks, while spontaneous confabulation is detected in the more advanced stages of disease (Kopelman, 1987). Beyond impairment in semantic encoding, AD patients show deficits in semantic memory, probably due to progressive loss of semantic knowledge (Mårdh, Nägga and Samuelsson, 2012), even though the semantic alteration has been previously proposed to be dependent of inhibitory deficits affecting semantic search (Duong *et al.,* 2006). Semantic deficits are revealed in cognitive assessment of AD patients by impairment of lexical or perceptual means of semantic access, rather than on word and object meaning, more consensually associated with semantic dementia (Balthazar *et al.,* 2007; Reilly *et al.,* 2011). AD patients show deficits in semantic category fluency more frequently than deficits in letter fluency, which relies on initiative and retrieval supported by subcortical frontostriatal circuits (Rosser and Hodges, 1994). Despite the presence of executive or frontal components in the initiative nature of fluency tasks, they are often defined as language tests (Lezak, Howieson and Loring, 2004). Language impairment is not considered a foregoing indicator of prodromal AD, however the tasks that imply reaction time, such as category fluency, are sensitive to MCI and predictive of future conversion to AD, even if mainly for amnestic MCI patients (Taler and Phillips, 2008). Not only semantic fluency, but also complex language abilities have been described to be impaired in MCI patients (Ribeiro, de Mendonça and Guerreiro, 2006). Indeed, despite the importance given to the memory deficits in prodromal phases of AD, the presence of deficits in other cognitive areas has been pointed out consistently in patients at risk of conversion to dementia (Lekeu *et al.,* 2010). Beyond the expected deficits in episodic memory, individuals at risk of future conversion to dementia might show deficits in executive functioning as well (Chen *et al.,* 2000; Reinvang, Grambaite and Espeseth, 2012). Impairment in executive functioning might be a potential marker of conversion to AD, particularly of a more rapid

progression (Rozzini *et al.,* 2007; Musicco *et al.,* 2010). Deficits in executive functioning have been hypothesized to reflect AD pathology, especially neurofibrillary tangle burden in prefrontal cortex (Weintraub, Wicklund and Salmon, 2012). The dorsolateral prefrontal cortex is required for the efficient working memory performance, although the contribution of all working memory components is not expected to be equal, since there is primarily a disruption of the central executive control with relative sparing of immediate memory (Baddeley *et al.* 1991; Collette *et al.* 1999). Noteworthy in prediction on cognitive decline are the attentional systems, because they represent an important neuropsychological criterion for the diagnosis of Alzheimer's disease, may precede other cognitive impairments, and most of all have a substantial impact on the patient's capacity to cope independently (Perry and Hodges, 1999). The capacity to divide attention with dual-task performance is of interest because it appears to be qualitatively different in AD patients as compared to normal ageing (Baddeley *et al.,* 2001). According to Perry, Watson and Hodges (2000), capacity to resist distraction and rapidly switch attention may be the most sensitive aspect of attentional resources that decline even earlier than sustained and divided attention. Since cognitive impairment is not restricted to verbal memory impairment, and assessment of other cognitive areas may add relevant insight concerning the stage of impairment, a comprehensive neuropsychological battery is an essential tool to identify subjects at risk of future conversion to dementia. Importantly, so far literature has suggested that cognitive markers at baseline could be as robust predictors of conversion as other biomarkers, like regional brain volumes, cerebrospinal fluid levels of $A\beta_{1-42}$ and total tau (Gomar *et al.*, 2011).

One common criticism made to studies using biomarkers and/or cognitive measures as predictors of future conversion to dementia is the limited follow-up periods (Jack *et al.,* 2010b; Biagioni and Galvin, 2011; Lo *et al.,* 2011; Tschanz *et al.,* 2011; Mattsson *et al.,* 2012a,b; Thurfjell *et al.,* 2012; Zabel *et al.,* 2012; Zhang and Shen, 2012). Longitudinal studies testing biomarkers predictive value for the conversion of MCI patients to dementia have highlighted the fact that, since conversion occurs at a rate of 8–15% a year, it is relevant to have a long follow-up period (>4 years) (Hansson *et al.*, 2006).

Extensive work has been done to more reliably identify the earliest phases of Alzheimer's disease, in parallel with scientific research on the discovery of new ways of more effectively managing the disease and its symptoms. Importantly, some studies allow patients to undergo interventions that might involve manipulation of risk and protection environmental factors.

Efforts have been made to offer to the patients the participation in cognitive rehabilitation procedures and clinical trials with putative new neuroprotective drugs. Research into disease modifying drugs for AD has received much attention on the premise that the earlier these drugs can be administered, before accumulation of significant neuronal damage, the higher the likelihood of maintaining and improving cognitive function. In this context, sensitive cognitive screening tools for earlier phases of neurodegeneration are needed to identify non-demented patients with cognitive complaints that have a high probability of progression to dementia. One possible path to reach this goal is the development of advanced statistical classification methods derived from data mining and machine learning methods, like Neural Networks, Support Vector Machines and Random Forests, that could be used to improve accuracy, sensitivity and specificity of predictions obtained from neuropsychological testing. Since verbal memory performance is a core predictor of future conversion in AD, it would be relevant to compare prediction accuracies of differente verbal memory tests currently used in clinical practice. Perhaps even more important, the predictive accuracy of neuropsychological assessment may be critically dependent upon the follow-up time defined to establish conversion to dementia. Longer follow-up periods may improve the reported sensitivity/specificity rates of cognitive markers and therefore contribute to the earlier diagnosis of AD, and also establish a more clinically relevant prognosis. As an ultimate goal, it would be needed to find better cognitive markers for the evaluation of non-demented patients with cognitive complaints, in order to establish if there is a low probability of progression to dementia, in which case a regular follow-up and general preventive measures might be indicated, or a high probability of progression to dementia, so that in this case the patient could be a possible candidate to undergo complex ancillary examinations and new disease-modifying treatments.

PART II – STUDY DESIGN

2.1 Objectives

The **main objective** is to improve the predictive accuracy provided by neuropsychological tests for future conversion to dementia of non-demented patients presenting with cognitive complaints. For this purpose, four secondary goals will be addressed.

The first is to review the literature of published longitudinal studies assessing the sensitivity, specificity and effect sizes of neuropsychological tests to predict future conversion to dementia of patients with Mild Cognitive Impairment (MCI).

The second is to compare the accuracy of statistical traditional classifiers vs. newer data mining methods to predict future conversion to dementia of non-demented patients with cognitive complains.

The third is to determine the best memory test to include in MCI diagnostic criteria to improve the predictive value of MCI regarding conversion to dementia.

And finally, to determine the clinical and neuropsychological factors that predict long-term (5 years) conversion to dementia.

2.2 General methodology

The Cognitive Complaints Cohort (CCC) is a clinical cohort of non-demented patients with cognitive complaints referred for neuropsychological examination during the period 1999-2007. This cohort was established at the Institute of Molecular Medicine, Lisbon, with the collaboration of Centro de Neurociências de Coimbra, and a private memory clinic in Lisbon, Memoclínica, and was financed by FCT (grant PIC/IC/82796/2007). The purpose of the CCC is to investigate the outcome of subjects with cognitive complaints based on a comprehensive neuropsychological evaluation and other biomarkers. The study was approved by the local ethics committee. CCC is a large clinical cohort, many subjects have long follow-ups and all underwent detailed neuropsychological testing. The CCC comprises 775 subjects. Of these, 568 (73.3%) were reevaluated, 154 (27.1%) converted to dementia (follow-up 2.5±1.8 years) and 414 (72.9%) did not (follow-up 2.8±2.1 years). For the reevaluations of the patients, it was possible to take advantage of the fact that most patients have regular clinical consultations at the participating institutions to schedule the reassessments. Subjects who did not attend clinical consultations were contacted by telephone and invited to come to one of the participating institutions to perform the same neuropsychological battery of baseline assessment. Whenever it was not be possible to re-assess the patient in person, a preliminary evaluation was performed during a telephone call using two validated telephone questionnaires to identify mild cognitive impairment or dementia (Van Uffelen *et al.*, 2007; Kawas *et al.*, 1994). The selection of patients to enter CCC was established according to the following criteria:

Inclusion criteria:

1) Presence of cognitive complaints;

2) Referral to neuropsychological examination, during the period 1999-2007, at the Laboratory of Language, Faculty of Medicine of Lisbon; Memoclínica, a private memory clinic in Lisbon; and the Dementia Clinics, Hospitais da Universidade de Coimbra.

Exclusion criteria:

1) dementia (according to DSM-IV criteria (APA, 2000));

2) disorders that may cause cognitive impairment, like stroke, tumour, significant head trauma, haematoma, epilepsy, psychiatric disorders, uncontrolled medical illness (hypertension, metabolic, endocrine, toxic and infectious diseases);
3) treatments interfering with cognitive function;
4) alcohol or illicit drug abuse.

Neuropsychological assessment

The neuropsychological results were standardized according to the age and education norms for the Portuguese population (BLAD; Garcia, 1984). Impairment on any test was considered if a subject scored more than 1.5 standard deviations below the mean for his age and education.

The detailed neuropsychological assessment was carried out by the same team of trained neuropsychologists and comprised:

Battery of Lisbon for the Assessment of Dementia (BLAD; Garcia, 1984) – the battery includes tests for the following cognitive domains: attention (Cancellation Task), Verbal Semantic Fluency (food products), Motor and Graphomotor Initiatives, verbal comprehension (a modified version of the Token Test), verbal and non-verbal abstraction (Interpretation of Proverbs and the Raven Progressive Matrices), visuo-constructional abilities (Cube Copy) and executive functions (Clock Draw), calculation (Basic Written Calculation), short-term memory and working memory (Digit Span), verbal memory and learning (Logical Memory, Verbal Paired-associate Learning and Word Recall).

Mini-Mental State Examination (MMSE; Folstein, Folstein and McHugh, 1975; Guerreiro, 1998) – the MMSE is one of the most widely used clinical instruments for a brief evaluation of cognitive status in adults.

Trail Making Test – part A and part B (TMT; Reitan, 1958) – the TMT part A measures psychomotor speed and attention, and part B assesses the ability to shift strategy, executive functions and visual spatial working memory.

Toulouse-Piéron Test (TP; Toulouse Y and Piéron H, 1986; Mendelsohn, 2000) – the TP assesses two components of focused attention: processing speed (sustained attention) and accuracy (selective attention).

California Verbal Learning Test (CVLT; Delis *et al.*, 1987; Ribeiro, Guerreiro and de Mendonça, 2007) – the CVLT measures verbal learning assessing constructs such as

repetition learning, serial position effects, semantic organization, intrusion, and proactive interference. The word lists (List A and List B) are made up of 16 items from 4 different categories of "shopping list" items. The trials of interest for the present study are: A1 (number of words from List A correctly recalled on the first trial); A5 (number of words from List A correctly recalled on the fifth trial); Atot (the total number of words from List A correctly recalled on the five learning trials); B (number of words from List B correctly recalled); SDFR/Short-delayed free recall (number of words from List A correctly recalled after spontaneous recall of List B); SDCR/Short-delayed cued recall (number of words from List A recalled in a semantic cued task after short-delayed free recall); LDFR/Long-delayed free recall (number of words from List A correctly recalled after an interference period of 20 minutes); LDCR/Long-delayed cued recall (number of words from List A correctly recalled in a semantic cued task after long-delayed free recall); Rec/Recognition hits (number of words from List A correctly recognised on the recognition trial).

Clinical Dementia Rating scale (CDR; Morris, 1993; Portuguese version in *Escalas e Testes na Demência. 2nd Ed., 2008*) – a structured-interview protocol that assesses a patient's cognitive and functional performance in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care, in order to quantify the severity of dementia symptoms.

Blessed Dementia Rating Scale (BDRS; Blessed *et al.,* 1968; Portuguese version in *Escalas e Testes na Demência. 2nd Ed., 2008*) – the BDRS is a brief behavioural scale based on the interview of a close informant, it assesses functional capacity for activities of daily living and changes in personality.

Geriatric Depression Scale (GDS; Sheikh JI and Yesavage JA, 1986; Almeida and Almeida, 1999; Portuguese version in *Escalas e Testes na Demência. 2nd Ed., 2008*) – the GDS is a 30-item self-report assessment used specifically to identify depression in the elderly. For this study a short-form (15 items) of the self-report instrument was used.

Outcome

The outcome of subjects in the CCC will be determined in a consensus meeting with the neurologist and the neuropsychologist. Participants will be considered demented if they have multiple cognitive deficits and decline from a previous level, with clear social and

occupational impairment, not explained by a delirium, according to the DSM-IV-TR criteria (DSM-IV-TR, APA, 2000).

PART III – RESULTS

3.1 Neuropsychological assessment and progression to dementia: systematic review (manuscript in preparation)

3.1.1 Rationale

Neuropsychological assessment has been a crucial diagnostic tool for the characterization of cognitive deficits along progressive stages of dementia. Importantly, cognitive decline begins several years before clinical diagnosis of dementia and subjects in prodromal phases already reveal significantly poorer cognitive performance than normal elderly on several neuropsychological tests, as a corollary of the underlying pathologic processes (Wilson *et al.*, 2011). Presence of impairment in neuropsychological tests was associated to further cognitive decline and progression to Alzheimer's disease (AD). This progression, or in other words, the transitional stage between normal aging and AD, is known nowadays as a clinical entity named Mild Cognitive Impairment (MCI). Although MCI patients are known to be at higher risk for cognitive decline than healthy elderly, there is relevant heterogeneity associated to the concept, since MCI patients decline at different rates and some never develop AD. The amnestic form of MCI (aMCI; i.e., patients presing with isolated deficit in verbal episodic memory assessment) is considered the prodromal phase of AD (Petersen *et al.*, 2001a), nevertheless the predictive value of diagnosis is dependent on the type of verbal episodic assessment applied, follow-up duration, among other conditions (Visser *et al.*, 2006). For several years now, longitudinal studies of clinical cohorts of patients diagnosed as MCI to predict future conversion to AD based on neuropsychological tests have been published. The purpose of the present review is to collect from original published articles the values of sensitivity, specificity and effect sizes for neuropsychological tests to predict conversion to dementia in patients at risk of future cognitive decline.

Procedure

Search strategy

Selection of eligible studies was conducted on Pubmed and Web of Science databases, searched from inception to May 2012. Search terms delimited first the condition in study or outcome (dementia OR AD OR alzheimer OR alzheimer's OR "cognitive decline" OR "cognitive deterioration" OR "cognitive impairment"), then the baseline features of interest

(AND ("mild cognitive impairment" OR MCI OR presymptomatic OR incipient OR "memory impairment" OR preclinical OR "memory impaired" OR "questionable dementia")), and finally, the independent variable in study ("cognitive test" OR neuropsychol* OR memory OR "executive function" OR "executive functions" OR language OR orientation OR visuospatial OR attention OR "abstract reasoning" OR initiative). Filters for the type of study and statistical analysis of interest were applied ((cohort OR prospective OR longitudinal OR follow-up) AND (sensitivity OR specificity OR "odds ratio" OR "hazard ratio" OR "relative risk")). Key words were screened as text words in Pubmed to increase sensitivity, however that option was not always possible for Web of Science where only titles were screened. Other restrictions were the limitation to human research and English language. Studies published either as full paper or as abstract were considered, as long as relevant information could be extracted.

Selection criteria

Studies were selected according to the following criteria: longitudinal cohort studies; baseline sample of cognitively impaired non-demented patients; and report of sensitivity, specificity or effect sizes of baseline neuropsychological testing to predict conversion to dementia. Some studies had a sub-sample of cognitively normal subjects included in the cohort, and as long as the cohort was not limited to cognitively normal subjects they were included. Access to full content of published paper was compulsory to extract the data. Data presentation in the paper should also be clear and straightforward to allow the proper fulfilling of the predefined form.

Data extraction

Data from selected studies were inserted in the predefined form filling demographic, procedural and neuropsychological information. Predefined form was established in a consensus meeting with experts on literature review and meta-analysis. Information extracted from each study corresponded to: first author and year of publication; country of origin and designation of cohort study; main sample characteristics; follow-up time and outcome; cognitive domain and neuropsychological tests; predictive value of neuropsychological tests for conversion to dementia reported as sensitivity, specificity and different types of effect sizes. Authors were not contacted to provide additional data. More specific information

concerning cut-off scores or adjustment for confounders was not included in the present predefined form for a better synthesis of information but will be explored in further studies.

3.1.2 Results

Five hundred and four studies were retrieved from Pubmed database and 34 from Web of knowledge from inception to May 2012. Twenty-four studies were considered eligible according to selection criteria already mentioned and the summary of data extracted is shown in Table 3.1.1.

Studies selected for the present review were published in the last 20 years and are representative of population from Europe (United Kingdom, France, Austria, Italy, Belgium and Ireland), as well as North and South America (USA and Brazil).

Cohort characteristics differed widely across studies in sample size and criteria for diagnosis of cognitive impairment at baseline. Sample sizes ranged from 31 to 320 subjects that were considered mildly impaired according to Global Deterioration scale, Clinical Dementia Rating scale, "questionable dementia/Alzheimer's disease" criteria, and Mild Cognitive Impairment criteria (see Table 3.1.1).

Some studies (n=5) presented conversion rates higher than expected from what has been usually reported, for instance, conversion rates ranging from 41% to 72% of the sample in a follow-up period of approximately 2.5 years. Nevertheless, the majority of the studies showed in Table 3.1.1 and analysed for the present review have annually conversion rates not overcoming 15%.

Approximately half of the studies presented a number of females that outnumbered males. Mean age reported for the baseline sample was more than 60 years old for the 24 studies. Mean years of education ranged from 7.5 to 17 years. Follow-up times reported were of around 2/3 years for 80% of the studies.

Neuropsychological tests administered varied considerably among studies, yet the battery of tests applied always assessed verbal memory performance, and many included also cognitive areas such as executive functions, attention and language (Flicker, Ferris and Reisberg, 1991; Tierney *et al.*, 1996; Devannand *et al.*, 1997; Griffith *et al.*, 2006; Tabert *et al.*, 2006; Blacker *et al.*, 2007; Dickerson *et al.*, 2007; Rozzini *et al.*, 2007; Sarazin *et al.*, 2007; Gallagher *et al.*, 2010; Lekeu *et al.*, 2010; Aretouli *et al.*, 2011).

Some studies have reported rather disparate global sensitivity and specificity values for the neuropsychological tests to predict conversion to dementia (Devannand *et al.*, 1997; Sarazi *et*

al., 2007; Rabin *et al.*, 2009; Gallagher *et al.*, 2010). Conversely, other studies reported high and balanced sensitivity/specificity ratios (≥80%) and effect sizes (HR=4.68, RR=12.26,), mainly for verbal episodic memory tests, and also for verbal initiative and executive functions tests, however the follow-up period of those studies was generally short (≈2 years) (Flicker, Ferris and Reisberg, 1991; Lehrner *et al.*, 2005; Sarazin *et al.*, 2007; Landau *et al.*, 2010; Aretouli *et al.*, 2011).

Table 3.1.1 – Review of literature concerning predictive value of neuropsychological tests for future conversion to dementia

First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**			Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
Flicker, 1991 USA	32 mildly impaired subjects consecutively screened at the Aging and Dementia Research Center of NYU Medical Center with Global Deterioration Scale (GDS) rating of 3; **Follow-up:** 23 decliners and 9 nondecliners;**Gender:** NS (not specified); **Age:** 71.3±1.4; **Education:** 13.1±0.6.	2.11±0.09; significant cognitive deterioration	Verbal recall		Shopping List	90.0	94.7	Not reported (NR)
			Visuospatial recall		Misplaced Objects	70.0	93.3	NR
			Language		Object Function Recognition	85.7	100.0	NR
					Object Identification	57.1	100.0	NR
Tierney, 1996 Canada	123 non-demented patients with memory impairment (Global Deterioration Scale of 2 or 3); **Follow-up:** 29 converted to Probable AD and 94 were cognitively impaired; **Gender:** NS; **Age:** 13.48±3.02 Probable AD group; 71.51±7.83 cognitively impaired group (p=0.14); **Education:** 13.48±3.02 Probable AD group; 14.13±3.26 cognitively impaired group (p=0.35).	≈ 2 years; Probable AD	Composite measure	Verbal episodic memory and learning	Rey Auditory Verbal Learning Test (RAVLT)	75.9	93.6	NR
					Wechsler Memory Scale (WMS; Paired-Associate Learning subtest)			
					Wechsler Memory Scale (WMS; Logical Memory subtest)			
				Mental control	Wechsler Memory Scale (WMS; Mental Control subtest)			
				Sustained attention	Trail Making Test A			
				Verbal Fonologic Fluency	Controlled Oral Word Association Test (F,A,S)			
				Executive functions	Trail Making Test B			
Devanand, 1997 USA	62 cognitively impaired patients defined as “questionable dementia”; **Follow-up:** 26 converted to dementia; 36 did not converted; **Gender:** 59.1% females; **Age:** 66.2±10.0 (68.6±9.8 dementia group at follow-up and 63.0±8.5 stable group, p=0.010); **Education:** 14.2±3.1 (no significance difference among follow-up groups).	2.5±1.7; dementia	Verbal memory		Mini-Mental State Examination (MMSE) three words delayed recall task	66.7	71.0	NR
					Selective Reminding Test (long-term retrieval)	76.0	55.6	NR
			Language and initiative		Category Fluency (naming animals)	59.3	55.6	NR
			Abstract reasoning, visuospatial abilities and processing speed (WAIS-R)		Digit subtest	74.1	43.5	NR
					Picture Arrangement subtest	80.0	58.3	NR
					Block Design subtest	78.6	50.0	NR

Table 3.1.1 – Review of literature concerning predictive value of neuropsychological tests for future conversion to dementia

First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
Tian, 2003 UK	129 "questionable dementia" patients seen in a National Health Service hospital outpatient clinic **Follow-up:** 37 converted to dementia; 92 remained stable; **Gender:** 47.3% females; **Age:** 73.2±8.5 dementia group; 68.7±10.2 stable group (p=0.020); **Education:** 10.8±3.0 dementia group; 10.9±2.6 stable group (p=0.848).	2.04±1.64; dementia	Episodic memory, initiative and executive functions	Hopkins Verbal Learning Test (verbal recognition) and Letter Fluency	64.4	76.7	NR
Amieva, 2004 France	90 elderly volunteers diagnosed as MCI **Follow-up:** 29 converted to dementia and 61 remained MCI; **Gender:** Converters females 24.1%; non-converters females 54.1%; **Age:** 73.3±5.8 converters; 68.7±7.9 non-converters (p=0.0025); **Education:** Primary school diploma 89.7% converters; 88.5% non-converters (p=0.99).	≈ 2 years; dementia	Selective attention ability	Letter Cancellation Task (LCT) – total score	NR	NR	OR=0.98*
				LCT-subtest 1 (crossing of a target letter randomly distributed among distractor items)	NR	NR	OR=0.96*
				LCT-subtest 2 (crossing of a target letter surrounding a space)	NR	NR	OR=0.94*
				LCT-subtest 3 (task combining both LCT1 and LCT 2 instructions)	NR	NR	OR=0.95*
Lehrner, 2005 Austria	107 patients with memory complaints (22 aMCI; 85 cognitively normal); **Follow-up:** 14 converters; 93 non-converters; **Gender:** 40.9% females in the aMCI group; 60% females in the cognitively normal group; **Age:** 71.8±4.6 demented group; 66.1±8.6 non-demented group (p=0.017); **Education:** 10.0±3.7 demented group; 11.8±3.6 non-demented group (p=0.085).	1.84±0.68; Convertion of patients with memory complaints to dementia	Global cognitive status	Mini-mental Status Examination	83	68	NR
			General intelligence	Wortschatztest (WST) vocabulary test	64	63	NR
			Verbal short-term memory	Digit Span (HAWIE-R)	35	72	NR
			Non-verbal short-term memory	Corsi Block Tapping (block span)	72	60	NR
			Concentration capacity	Alters-Konzentrations (AKT)	63	67	NR
			Visuospatial abilities and processing speed	Wechsler Adult Intelligence Scale (digit-symbol)	81	76	NR
			Visual associative memory	Memory Assessment Clinics (MAC) (misplaced objects)	83	73	NR
			Verbal memory	MAC (name-face association)	71	75	NR
				MAC (selective reminding total recall)	79	78	NR
				MAC (selective reminding delayed recall)	87	85	NR
				MAC (first-last names)	66	68	NR

Table 3.1.1 – Review of literature concerning predictive value of neuropsychological tests for future conversion to dementia

First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
			Facial memory	MAC (recognition of faces)	58	65	NR
			Spatial/topographic memory	MAC (topographic memory)	63	71	NR
Griffith, 2006 USA	49 Mild Cognitive Impairment patients; 49 normal control participants **Age:** 68.47±8.65 MCI patients; 65.92±7.66 controls **Education:** 13.39±2.03 MCI patients; 13.55±1.40 controls	≈ 2 years; MCI conversion to dementia	Memory and executive functions	Dementia Rating Scale (initiation/perseveration item) and Visual Reproduction Percent Retention	76.9	88.9	NR
Tabert, 2006 USA	148 patients reporting memory problems (Mild Cognitive Impairment) (and a sub-sample of 115 MCI patients with a fixed follow-up period of 3 years); combined sample of 83 controls recruited by advertisement and participation in other studies; **Follow-up** (n=148): 39 (26.4%) MCI patients converted to AD; **Gender** (n=148): 56.4% females converters; 55.0% females non-converters (p=0.85); **Age** (n=148): converters 72.6±7.2; non-converters 65.0±10.0 (p=<0.001); **Education** (n=148): converters 14.1±4.4; non-converters 15.4±4.2 (p=0.11).	3 years; MCI conversion to dementia	Verbal memory, visuospatial abilities and processing speed	Selective Reminding Test (SRT; immediate recall) and Wechsler Adult Intelligence Scale-R (Digit Symbol test)	76%	90%	NR
		3.9 ±2.1; MCI conversion to dementia	Verbal memory	SRT (immediate recall)	NR	NR	OR=1.10* [1.06-1.14]
				SRT (delayed recall)	NR	NR	OR=1.09* [1.05-1.12]
			Non-verbal memory	Wechsler Memory Scale-visual reproduction subtest	NR	NR	OR=1.03* [1.01-1.06]
			Visuospatial abilities and processing speed	Wechsler Adult Intelligence Scale -R Digit Symbol Test	NR	NR	OR=1.09* [1.04-1.14]
			Language	Action Naming Test **(**ANT)	NR	NR	OR=1.04* [1.01-1.08]
				Boston Naming Test **(**BNT)	NR	NR	OR=1.01* [1.00-1.03]
Blacker, 2007 USA	235 Mild Cognitive Impairment patients; 107 cognitively normal subjects **Follow-up:** 69 of MCI converted in AD; 7 of normal converted in AD **Gender:** 56.6% females in the MCI group; 59.8% females in the normal group (p>0.05); **Age:** 72.90±5.8 MCI; 71.38±4.6 normal group (p=0.009); **Education:** 15.41±2.9 MCI; 15.64±2.9 normal group (p>0.05).	4.1±3.2; MCI conversion to AD	Episodic memory	California Verbal Learning Test (total score from trials 1-5)	NR	NR	HR=0.59* [0.44-0.78]
				Selective Reminding Test	NR	NR	HR=0.52* [0.40-0.66]
			Language and executive functions	Trail Making Test B	NR	NR	HR=1.64* [1.28-2.10]
				Letter Fluency Test (total of F, A, and S)	NR	NR	HR=0.64* [0.48-0.84]
				Self Ordering Test	NR	NR	HR=1.04 [0.98-1.10]
				Alpha Span Test	NR	NR	HR=0.76 [0.58-1.00]
Dickerson, 2007	244 community volunteers (167 Mild Cognitive Impairment, Clinical Dementia Rating (CDR)=0.5; 77 normal, CDR=0)	≈ 5 years; conversion of community volunteers to probable AD	Severity of cognitive impairment in daily life	Clinical Dementia Rating (sum of boxes)	NR	NR	OR=4.8* [3.0-7.8]

Table 3.1.1 – Review of literature concerning predictive value of neuropsychological tests for future conversion to dementia

First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
USA	**Follow-up:** 107 (44%) subjects evidenced clinical decline (increase in CDR-SB_1.0) of whom 42 (17% of the sample) were diagnosed with probable AD; 137(56.1%) remained stable; **Gender:** 92% females in the MCI group; 47% females in the normal group (p>0.05); **Age:** 72.7±5.8 MCI; 71.6±4.5 normal group (p>0.05); **Education:** 15.3±2.9 MCI; 15.4±2.8 normal group (p>0.05).		Verbal memory	Free and cued Selective Reminding Test (free recall measure)	NR	NR	OR=0.57* [0.42-0.76]
				California Verbal Learning Test (CVLT; total learning score)	NR	NR	OR= 0.62* [0.45-0.87]
				CVLT (delayed retention score)			OR= 0.61* [0.46-0.81]
			Executive functions	Trail Making Test (part B)	NR	NR	OR= 0.57* [0.42-0.79]
				Self-Ordering Test	NR	NR	OR= 0.60* [0.43-0.83]
Perri, 2007(a) Italy (ITINAD)	190 subjects with amnesic Mild Cognitive Impairment; 87 healthy subjects **Follow-up:** 79 aMCI converted to dementia; 111 remained aMCI; **Gender:** 44 (55.7%) females converted; 64 (57.7%) females did not converted; 51 (58.6%) females in the control group (p>0.05); **Age:** 73.2±5.5 in the group that converted; 67.8±7.5 in the group that remained aMCI; 68.04±10.86 in the control group (p<0.001); **Education:** 7.5±3.2 in the group that converted; 7.7±3.6 in the group that remained aMCI; 8.13±4.27 in the control group (p>0.05).	≈ 2 years; MCI conversion to dementia	Staging severity of dementia	Clinical Dementia Rating (CDR)	NR	NR	OR=1.04* [1.01-1.07]
			Episodic memory	Rey's Figure Form B Reproduction (delayed recall)	35.4	NR	OR=0.92* [0.87-0.97]
				Word-List Recall (semantically related; immediate recall)	50.6	NR	NR (no significance)
				Word-List Recall (semantically related; delayed recall)	77.2	NR	NR (no significance)
				Word-List Recall (semantically unrelated; immediate recall)	35.4	NR	NR (no significance)
				Word-List Recall (semantically unrelated; delayed recall)	63.3	NR	OR=0.84* [0.74-0.97]
				Word-List Recognition (related word list)	54.4	NR	NR (no significance)
				Word-List Recognition (unrelated word list)	38.0	NR	OR=0.66* [0.48-0.91]
				Prose Recall (immediate)	35.4	NR	NR (no significance)
				Prose Recall (delayed)	59.5	NR	NR (no significance)
Rozzini, 2007	119 subjects with amnesic Mild Cognitive	1.0±0.2; conversion to	Executive functions	Trail Making Test B	NR	NR	OR=1* [1.0-1.0]

Table 3.1.1 – Review of literature concerning predictive value of neuropsychological tests for future conversion to dementia

First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
Italy	Impairment **Follow-up:** 40 demented; 79 stable; **Gender:** 72.5% female in the demented group; 57% female in the stable group (p>0.05); **Age:** 73.5±8.5 demented group; 69.2±7.0 stable group (p=0.006); **Education:** 7.7±3.7 demented group; 7.9±3.7 stable group (p>0.05).	dementia	Global cognitive function	Alzheimer's Disease Assessment Scale-Cognitive part (ADAS-Cog)	NR	NR	OR=1.4* [1.1-1.8]
			Basic and instrumental daily functions	IADL	NR	NR	OR=35.9* [6.7-191.5]
			Language and initiative	Letter fluency	NR	NR	OR=1.0 (no significance)
			Non-verbal abstraction	Raven's coloured matrices	NR	NR	OR=1.1 (NS)
			Sustained attention and motor speed	Trail Making Test A	NR	NR	OR=1.1 (NS)
Sarazin, 2007 France (PreAl study)	217 patients with Mild Cognitive Impairment **Follow-up:** 59 converted in Alzheimer disease; 158 stable MCI; **Gender:** 54.2% females in the demented group; 60.1% females in the stable MCI group (p=0.61); **Age:** 74.8±4.1 demented group; 70.9±5.4 stable MCI group (p<0.0001); **Education:** Bachelor degree 39% demented group; 44.3 % stable MCI group (p=0.39).	≈ 3 years; conversion to AD	Verbal memory	Free and Cued Selective Reminding Test (FCSRT) (total recall)	79.7	89.9	RR=12.26 * [6.37-23.60]
				FCSRT (index of cueing)	78.0	84.8	RR=10.26* [5.47-19.28]
				FCSRT (free recall)	71.2	91.8	RR=8.68* [4.76-15.82]
				FCSRT (delayed free recall)	76.3	90.5	RR=10.64* [5.66-20.01]
				FCSRT (delayed total recall)	69.5	88.6	RR=7.22* [4.11-12.70]
				FCSRT (number of intrusions)	64.4	85.4	RR=0.18* [0.10-0.34]
				FCSRT (false recognition)	20.3	98.1	RR=0.25* [0.15-0.43]
			Visual perception and memory	Benton Visual Retention Test	42.4	77.2	RR=1.27* [1.12-1.45]
			Language and Initiative	Category Fluency	55.9	82.3	RR=2.84* [1.60-5.04]
				Letter Fluency (letter S)	57.6	56.3	RR=1.46 [0.86-2.48]
				DENO 100	55.9	67.7	RR=1.90* [1.12-3.23]
			Working memory	Serial Digit Learning test	57.6	67.7	RR=1.89 [1.12-3.19]
				Double task of Baddeley	50.8	56.3	NR
			Conceptual elaboration	Wechsler Adult Intelligence Scale (WAIS) (similarities)	49.2	72.2	RR=3.21* [1.82-5.64)

Table 3.1.1 – Review of literature concerning predictive value of neuropsychological tests for future conversion to dementia

First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
			Executive functions, visuospatial abilities, sustained attention and motor speed	WAIS Digit Symbol test	37.3	71.5	RR=1.64 [0.92-2.92]
				Stroop test (inhibition condition)	52.5	58.2	RR=1.24 [0.72-2.13]
				Trail Making test A	62.7	58.9	RR=1.58* [0.33-1.00]
				Trail Making test B	62.7	67.1	RR=0.43* [0.25-0.75]
Devanand, 2008 USA	148 MCI patients (73% of patients met criteria for amnestic MCI with or without other cognitive domain deficits, 13.5% had non-amnestic MCI, and 13.5% did not meet diagnostic criteria for MCI according to authors but had cognitive scores < 1.5 SD below norms; **Follow-up:** 39 converted to AD (31 had probable AD and 8 had possible AD); 109 did not progressed to AD; **Gender:** 56.4% females converted to AD; 55.1% females remained MCI (p=0.971); **Age:** 73.2±7.1 group that progressed to AD; 64.9±9.9 group that remained stable (MCI) (p<0.0001); **Education:** 14.0± 4.7group that progressed to AD; 15.4±4.1 group that remained stable (MCI) (p=0.0014).	1-9 years of follow-up (mean ≈ 4 years: 41.5±18.5 for the group that progressed to AD; 57.3±28.3 for the group that remained stable in MCI); conversion to AD (CDR rating was confirmatory (≥ 1, indicating dementia))	Global cognitive status	Mini-Mental State Examination (MMSE)	26.8	90.0	LR+ = 4.5 [1.6-12.7] LR – = 0.8* [0.7-1.0]
			Verbal memory	Selective Reminding Test (SRT) immediate recall score (SRT Imm Rec)	50.9	90.0	LR+ = 5.8 [2.6-13.1] LR – = 0.6* [0.4-0.8]
Dierckx, 2009 Belgium	31 MCI patients; **Follow-up:** 7 (23%) fulfilled criteria for probable AD; 21 (68%) MCI- patients remained stable; 2 (6%) improved; 1 (3%) was diagnosed with progressive nonfluent aphasia; **Gender:** 14 (45%) females at follow-up; **Age:** 75.4± 6.2 in the group with follow-up; **Education:** 11.6±3.3 in the group with follow-up.	≈18 months (17±1.98); Dementia diagnosed according to DSM-IV criteria	Verbal learning with category cues	MISplus (Dutch version of the original Memory Impairment Screen plus)	71.5	91.5	OR=0.28* [0.10–0.79]
Rabin, 2009 USA	32 MCI patients **Follow-up:** 9 (28%) converted to AD; **Gender:** 20 (62.5%) females in the MCI	2.97±1.16; probable mild AD (defined by the NINCDS-ADRDA criteria)	Verbal episodic memory and learning	Mini-Mental State Examination (MMSE; three words delayed recall task)	100	00	OR=1.18

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First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
	baseline group; **Age:** 71.58±6.21 in the MCI baseline group;; **Education:** 16.55±3.16 in the MCI baseline group.			California Verbal Learning Test (16-item) (5 learning trials)	96	11	OR=0.93
				CVLT (short delay free recall)	91	44	OR=0.59*
				CVLT (long delay free recall)	100	44	OR=0.44*
				Wechsler Memory Scale III - Logical Memory (LM; immediate recall)	91	33	OR=0.84*
				LM (Story A delay recall)	87	67	OR=0.65*
				LM (delay recall)	83	56	OR=0.79*
				LM (recognition)	96	63	OR=0.53*
			Remote memory	WAIS-III Information subtest	100	0	OR=0.99
Gallagher, 2010 Ireland	182 consecutive new referred patients to a memory clinic with a diagnosis of MCI; **Follow-up:** 75 (41%) converted to AD; 107 (59%) did not progress to dementia; **Gender:** 53.3% females converted to AD; 58.9% females remained MCI (p=0.46); **Age:** 73.9±5.9 demented group; 73.8±7.2 stable MCI group (p=0.88); **Education:** primary level of education 48% demented group; 42% stable MCI group (p=0.59).	2.17±1.46; conversion to AD	Core cognitive functions required for a diagnosis of dementia	Cambridge cognitive examination battery (CAMCOG; total)	80	68	NR
				CAMCOG (orientation)	38	89	NR
				CAMCOG (memory)	78	74	NR
				CAMCOG (language)	78	49	NR
				CAMCOG (attention)	82	41	NR
				CAMCOG (abstraction)	64	64	NR
				CAMCOG (calculation)	42	83	NR
				CAMCOG (praxis)	56	60	NR
				CAMCOG (perception)	37	80	NR
			Verbal initiative	Letter fluency	52	65	NR
				Category fluency	94	48	NR
			Language	Boston naming test	81	58	NR
			Verbal memory	Delayed word recall (DWR) test (free recall)	77	76	NR
				DWR (recognition)	57	85	NR

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First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
Forlenza, 2010 Brazil	97 amnestic MCI (20 with single-domain amnestic MCI and 77 multiple-domain amnestic MCI); **Follow-up:** 13 (from 76 that had at least one follow-up assessment - 17%) converted to AD; **Gender:** 74 (76%) females in the MCI baseline group; **Age:** 70.7±6.5 in the MCI baseline group; **Education:** 9.1±4.9 in the MCI baseline group.	38.8 ± 17.7 months; conversion to AD (according to the NINCDS-ADRDA criteria)	Episodic memory	Rivermead Behavioural Memory Test (RBMT)	NR	NR	OR= 0.78*
Grober, 2010 USA	194 non-demented participants; 101 (53%) patients with normal cognition (CDR 0) and 91 (47%) patients with questionable cognition (CDR 0.5); **Follow-up:** 28 converted to dementia; 166 remained non-demented; **Gender:** 82% females demented; 84% females non-demented (p=0.78); **Age**: 83.25±6.0 demented group; 77.4±6.6 non-demented group (p=0.0001); **Education:** 12.4±2.9 demented group; 12.5±3.4 non-demented group (p=0.75).	2.6 years; conversion to dementia (DSM-IV)	Verbal episodic memory	Free and Cued Selective Reminding Test (FCSRT) (total recall)	54	90	NR
				FCSRT (free recall)	78	90	NR

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First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
Landau, 2010 USA (ADNI database)	85 MCI patients; **Follow-up:** 28 converted to AD; 57 remained MCI; **Gender:** 9 (32%) females in the group that converted to AD; 20 (35%) females in the group that remained MCI (p>0.05); **Age:** 78.3±7.5 for the group that converted to AD; 78.0±7.4 for the group that remained MCI (p>0.05); **Education:**16.4±2.6 for the group that converted to AD; 16.3±2.8 for the group that remained MCI (p>0.05).	1.9±0.4; conversion to AD (according to the NINCDS-ADRDA criteria)	Verbal memory and learning	Auditory Verbal Learning Test (AVLT; 5 immediate recall trials)	93	88	HR=4.68* [1.37–15.98]
Lekeu, 2010 Belgium (NEST-DD European multicentre study)	34 questionable Alzheimer's disease; **Follow-up:** 17 converted to AD; 17 remained QAD; **Gender:** 12 (71%) females in the group that converted to AD; 6 (35%) females in the group that remained QDA (p>0.05); **Age:** 72.0± 5.9 for the group that converted to AD; 66.6 ±6.9 for the group that remained MCI (p>0.05); **Education:** 10.8±2.5 for the group that converted to AD; 12.3 ±5.2 for the group that remained MCI (p>0.05).	36 months; conversion to AD (according to the NINCDS-ADRDA criteria)	Working memory	Digit span	NR	NR	ES=0.021*
				Block Tapping Test	NR	NR	ES=0.131*
			Visual episodic memory	Rey's figure (delayed recall)	76	76	ES=0.383*
			Verbal memory and learning	California Verbal Learning Test (CVLT; 5 trials total free recall)	NR	NR	ES=0.479*
				CVLT (Short-delay free recall)	NR	NR	ES=0.499*
				CVLT (Short-delay cued recall)	NR	NR	ES=0.477*
				CVLT (Long-delay free recall)	NR	NR	ES=0.496*
				CVLT (Long-delay cued recall)	NR	NR	ES=0.419*
				CVLT (Free recall - list B)	NR	NR	ES=0.337*
				CVLT (Total intrusion errors)	NR	NR	ES=0.091
				CVLT (Total false recognitions)	NR	NR	ES=0.283*
				CVLT (False recognitions - list B)	NR	NR	ES=0.351*
				CVLT (Discrimination index)	NR	NR	ES=0.329*
				CVLT (Response bias)	NR	NR	ES=0.007
				CVLT (Primacy index)	NR	NR	ES=0.018
				CVLT (Recency index)	73	72	ES=0.407*
				CVLT (Constancy learning)	NR	NR	ES=0.164
				CVLT (Semantic clustering)	NR	NR	ES=0.198
				CVLT (Serial order clustering)	NR	NR	ES=0.054
			Language and initiative	Category fluency	NR	NR	ES=0.29*
				Letter fluency	NR	NR	ES=0.139

Table 3.1.1 – Review of literature concerning predictive value of neuropsychological tests for future conversion to dementia

First author, publication year Country (Cohort Study)	**Sample characteristics** [Cohort and follow-up groups; gender %; mean age±standard deviation (SD) or standard error of the mean (SEM); mean years of formal education ±standard deviation (SD) or standard error of the mean (SEM)]	**Follow-up time** [mean years±SD or approximated value]; **Outcome**	**Cognitive domain / Neuropsychological Test**		Sensitivity (%)	Specificity (%)	Hazard Ratio; Odds Ratio; Relative Risk and Likelihood ratio [HR/OD/RR/LR; 95%; CI]
			Executive functions	Stroop test (interference index)	NR	NR	ES=0.088
			Visuoperceptive function	Rey's figure (copy)	NR	NR	ES=0.027
Lonie, 2010 UK	44 amnestic MCI; **Follow-up:** 18 (41%) converted to dementia; 26 remained aMCI; **Age:** 76.0 ±1.6 for the group that converted to dementia; 73.2±5.4 for the group that remained aMCI (p>0.05).	≈ 4.18 years; clinical diagnosis of dementia (most often Alzheimer's disease)	Global cognitive status	Addenbrooke's Cognitive Examination (total)	65 (LR final model)	80 (LR final model)	OR=0.86* [0.75-1.00]
			Verbal memory and learning	Hopkins Verbal Learning Test – Revised (HVLT–R; discrimination index)			OR=0.73* [0.53-1.00]
			Semantic memory	Graded Naming Test	38	68	NR
				Graded Faces Test	44	68	NR
Aretouli, 2011 USA	104 MCI patients (68 aMCI and 36 non-amnestic MCI); **Follow-up:** 19 (18%) progressed to dementia (CDR≥1); 76 (73.1%) remained stable; 9 (9%) reverted to CDR=0; **Gender:** 8 (26.7%) females in the aMCI single domain at baseline; 14 (36.8%) females in the aMCI multiple domain at baseline; 8 (34.8%) females in the non-aMCI single domain at baseline; 10 (76.9%) females in the non-aMCI multiple domain at baseline; **Age:** 74.97±5.82 in the aMCI single domain at baseline; 78.32±7.25 in the aMCI multiple domain at baseline; 74.04±8.18 in the non-aMCI single domain at baseline; 76.62±7.34 in the non-aMCI multiple domain at baseline; **Education:** 16.17±2.17 in the aMCI single domain at baseline; 16.53±2.42 in the aMCI multiple domain at baseline; 15.22±2.91 in the non-aMCI single domain at baseline; 15.08±2.25 in the non-aMCI multiple domain at baseline.	≈ 2 years; progression to dementia (CDR≥1)	Verbal episodic memory, visuospatial/praxis abilities, language and initiative (cognitive screening battery for this study)	Wechsler Memory Scale-R Logical Memory (delayed recall)	94 (LR final model)	71 (LR final model)	OR=0.820* [0.702-0.957]
				Clock Drawing Test			OR=0.665* [0.471-0.939]
				Category Fluency			OR=0.914* [0.842-0.991]
			Executive functions (flexibility, inhibition and initiative) and semantic memory	Alternate Uses Test	NR	NR	OR=0.894* [0.808-0.989]
				Hayling Test	NR	NR	OR=0.637* [0.457-0.890]
				Verbal Concept Attainment Test	NR	NR	OR=0.872 [0.761-0.999]
Gomar, 2011 USA (ADNI	320 MCI patients; **Follow-up:** 116 converted to AD; 204 remained MCI;	≈2 years; probable AD (according to the NINCDS-ADRDA	Verbal episodic memory and learning	Alzheimer's Disease Assessment Scale-Cognitive part (ADAS-Cog; memory)	NR	NR	OR=1.07* [1.01-1.14]

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database)	**Gender:** 45 (38.8%) females in the group that converted to AD; 72 (35.3%) females in the group that remained MCI (p>0.05); **Age:** 74.6±7.2 for the group that converted to AD; 75.1±7.4 for the group that remained MCI (p>0.05); **Education:** 15.6±2.83 for the group that converted to AD; 15.6±3.25 for the group that remained MCI (p>0.05).	criteria)		Wechsler Memory Scale (WMS; Logical Memory subtest)	NR	NR	OR=1.01* [0.96-1.06]
				Auditory Verbal Learning Test (AVLT; delay recall)	NR	NR	OR=0.95* [0.85-1.07]
			Visuospatial/praxis abilities and semantic knowledge	Clock Drawing test	NR	NR	OR=0.80* [0.70-0.91]
			Speed of processing	Trail Making Test A	NR	NR	OR=0.99* [0.98-0.99]

* p-value < 0.05; † p-value not reported.

3.1.3 Discussion

The present systematic review of the literature reported the results of twenty-four longitudinal studies that evaluated the predictive value of neuropsychological tests for future conversion to dementia. The selection of tests to apply varied considerably across studies. A comprehensive neuropsychological assessment through a wide battery of cognitive areas tested on different levels of difficulty was the most frequent option to discriminate individuals at risk for future cognitive decline. However, due to time restrictions, sometimes the cognitive assessment was limited to one composite or global measure of cognitive function such as the Mini-Mental Status Examination (MMSE; Folstein, Folstein and McHugh, 1975). These global assessments are considered screening instruments since they provide a brief overview of functioning in terms of basic attention, memory, language, and spatial-constructional skills. Certainly, it is difficult to offer screening measures sensitive and specific enough to accurately detect those at risk for dementia, essentially because they have a ceiling effect, thus lacking sensitivity for patients with very mild impairment (Devannand *et al.*, 1997; Devannand *et al.*, 2008; Tierney *et al.*, 2000). Hence, these global measures do not substitute for a detailed neuropsychological assessment, but should still be indicative of an index of functioning in primary cognitive domains. The MMSE is a widely used screening test but there are several more, for instance, the Short Test of Mental Status, that revealed a slightly better accuracy for identification of MCI cases in comparison to the MMSE (AUC 0.82 vs. 0.75, p=0.002, respectively) (Tang-Wai *et al.*, 2003). Another instrument extensively used to screen for MCI patients is the Montreal Cognitive Assessment (MoCA), with a very good sensitivity and specificity profile (90% and 87%, respectively) (Nasreddine *et al.*, 2005). The MoCA has evidenced to be more sensitive than MMSE (0.97 vs 0.65), but less specific (0.60 vs 0.89), with better diagnostic accuracy (area under Receiver Operating Characteristic curve 0.91 vs 0.83) (Larner, 2012; Freitas *et al.*, 2011). The MMSE remains the most frequently used cognitive screening instrument for dementia, however, the improved sensitivity and consideration of other relevant deficits, such as executive functions, in MoCA have complemented the standard screening scope. Also to address limitations of MMSE in assessment of verbal, frontal-executive and visuospatial functions the Addenbrooke's Cognitive Examination (ACE) (Mathuranath *et al.*, 2000), and subsequently its revised version of ACE-R (Mioshi *et al.*, 2006), have been proposed to screen for cognitive decline. The ACE-R and MoCA total scores showed to be similar, having high sensitivity but low

specificity (Lonie *et al.*, 2010; Ahmed, de Jager and Wilcock, 2011). Another important screening tool is the Cambridge Cognitive Examination (CAMCOG), which is part of Cambridge Examination for Mental Disorders in the Elderly (Roth *et al.*, 1986). The CAMCOG also presented very good accuracy in the discrimination of MCI from AD patients, particularly for those with multiple-domain MCI (AUC=0.92±0.02; CI 0.88–0.96; $p<0.001$) (Aprahamian *et al.*, 2011). For the prediction of MCI patients' future conversion to dementia, the CAMCOG presented high sensitivity (> 75%) in the measures of attention, memory, language and total score, for a mean follow-up time of approximately 2 years (Gallagher *et al.*, 2010).

Several more comprehensive batteries are used to assess in more detail the cognitive performance of elderly and determine the risk of future conversion to dementia. Noteworthy, published studies over the last twenty years indicated that verbal memory tasks included in neuropsychological batteries of tests are the best measures to predict future conversion to dementia.

The verbal memory assessment is routinely present and the story recall test (SRT) is one of the most reliable measurements for distinguishing normal aging from mild cognitive impairment (MCI) and AD, but also to assess the degree of progression (Storandt *et al.*, 1984). The most representative test of the SRT is the logical memory test in Wechsler Memory Scale (Wechsler, 1981). It requires attention, learning ability, language comprehension, and provides a specific examination of the encoding, storage, and retrieval processes of the memory system (Lezak, 1995). Baek and colleagues (2011) have shown that immediate recall test (sensitivity, 72%; specificity, 71%) and the 20-minute delayed recall test (sensitivity, 74%; specificity, 73%) can discriminate MCI and AD, but the recognition test (sensitivity, 83%; specificity, 46%) revealed a ceiling effect that reduced the specificity of this measure to AD-typical memory decline (Wolk, Signoff and Dekosky, 2008). Several studies have shown very reasonable predictive values for future conversion to dementia by the administration of SRT (Tierney *et al.*, 1996; Tabert *et al.*, 2006; Rabin *et al.*, 2009; Aretouli *et al.*, 2011; Gomar *et al.*, 2011). Sensitivity to semantic cueing seemed relatively preserved in the early stages of AD but decreased with the progression of the disease. Neuropsychological characterization of suspected prodromal AD in research settings should therefore include such cued recall measures. In clinical settings, cued recall measures (more than recognition measures from frequently applied list learning tasks) likely add specificity with regard to the

memory deficit indicative of prodromal AD, while free recall measures may be the most sensitive screening tools (Tounsi *et al.*, 1999; Wagner *et al.*, 2012).

List learning tasks have provided remarkable sensitivity and specificity values for decline or conversion to AD, ranging from 90% sensitivity / 94.7% specificity (Flicker, Ferris and Reisberg, 1991; Shopping List applied to small sample of already mildly impaired individuals) and 71.2% sensitivity / 91.8% specificity (Sarazin *et al.*, 2007; Free and Cued Selective Reminding Test (FCSRT) free recall applied to MCI patients followed for approximately 3 years). Delayed recall tasks presented inferior results for prediction of conversion to dementia but even though, the Memory Assessment Clinics selective reminding delayed recall evidenced 87% sensitivity and 85% specificity to predict conversion of individuals with cognitive complaints followed for approximately 2 years (Lehrner *et al.*, 2005). Sensitivity and specificity values presented by these studies are very good but seemed to correspond to MCI patients at an advanced stage of progression that converted soon after cognitive assessment. More studies with longer follow-ups and individuals with no established diagnosis of MCI are needed to better ascertain the predictive value of cognitive tests to future conversion to dementia. Since the conversion occurs at different times for distinct individuals and distribution of time to conversion is rarely normal, survival analysis may provide relevant information about the effect of cognitive deficits on time to conversion to dementia. Blacker and colleagues (2007) reported that by each standard deviation rise in FCSRT, the score risk of conversion to dementia decreased by 48%. Remarkably, Sarazin and colleagues (2007) study demonstrated a relative risk of progression from MCI to AD for patients with a low baseline FCSRT total recall of about 12 times (95% CI [6.24 to 23.2]; $p<0.0001$).

Visuospatial abilities, processing speed and executive functions have showed predictive values for conversion similar to verbal memory tests mentioned previously (Wechsler Adult Intelligence Scale – digit symbol: sensitivity 81% and specificity 76%; Trail Making Test part B: HR=1.64, $p<0.05$) (Lehrner *et al.*, 2005; Blacker *et al.*, 2007).

Likewise, short batteries of carefully selected tests proved to be a fruitful option reaching good predictive values for future conversion to dementia. For instance, Aretouli and colleagues (2011) reported for a short battery assessing verbal episodic memory, visuospatial/praxis abilities, language and initiative the values of 94% and 71% for sensitivity and specificity, respectively.

Some studies proposed models combining neuropsychological measures and different biomarkers to establish predictive values for future conversion to dementia (Gomar *et al.,* 2011; Ewers *et al.,* 2012). Including neuropsychological measures in biomarker prediction models might help to overcome misleading data, for instance when age-dependent increase of AD-type brain pathology is detected in cognitively unaffected elderly. Despite acknowledging their different nature, the combination of predictive markers might be interestingly complementary, and a significant and specific association between $A\beta_{1-42}$ or tau and episodic memory recall measures has been demonstrated (Wagner *et al.,* 2012). Accordingly, other studies found significant correlations between episodic memory performance and $A\beta_{1-42}$ burden in the brain measured with PIB-PET (Pike *et al.,* 2007; Forsberg *et al.,* 2008; Mormino *et al.,* 2009). Importantly, Schmand, Huizenga and Van Gool (2010) reported recently in a meta-analysis study that baseline cognitive markers were better predictors of conversion than brain volumetric or CSF biomarkers. Therefore, because cognitive changes are a prominent and early feature of AD, focusing on neuropsychological markers would seem appropriate, as they can be reliable and non-invasive instruments for the prediction of future conversion to dementia.

3.2 Data mining methods in the prediction of Dementia *(BMC Research Notes)*

3.2.1 Rationale and Procedure

It is estimated that about 25 million people suffer from dementia today and, as a consequence of the population aging, the number of people affected is expected to double every 20 years (Ferri and Brayne, 2005). The presence of cognitive complaints is very common in aged people and may be the first sign of an on-going dementing disorder like Alzheimer's disease. Nowadays, it is possible to identify people with cognitive complaints who are at risk for the progression to dementia, that is to say, who have Mild Cognitive Impairment (MCI) (Petersen *et al.*, 2001a,b; Portet *et al.*, 2006). Since the establishment of MCI requires the demonstration of cognitive decline greater than expected for an individual's age and education level, neuropsychological testing is a key element in the diagnostic procedures (de Mendonça *et al.*, 2004). Recently, it has become possible to identify the traces, or biomarkers, of Alzheimer's disease in patients with MCI, by the use of Magnetic Resonance Imaging (MRI) volumetric studies, neurochemical analysis of the cerebrospinal fluid, and Positron Emission Tomography (PET) scan (Dubois *et al.*, 2007). These studies, however, are expensive, technically challenging, some invasive, and not widely available. Longitudinal studies assessing the predictive value of neuropsychological tests in progression of MCI patients to dementia have shown an area under the receiver operating characteristic curve of 61-94% (being higher for tests assessing verbal episodic memory) but with lower accuracy and sensitivity values (Chong and Sahadevan, 2005; Lehrner *et al.*, 2005; Fleisher *et al.*, 2007; Perri *et al.*, 2007b; Sarazin *et al.*, 2007). It would be important to improve the value of neuropsychological tests to predict the progression of MCI patients to dementia. This can be achieved at a clinical level by increasing the number of patients with longer clinical follow-ups. Predictive power of these tests may be also increased through innovating statistical classification and Data Mining techniques. Traditional statistical classification methods (e.g., Fisher's Linear Discriminant Analysis (LDA) and Logistic Regression (LR)) have been extensively used in medical classification problems for which the criterion variable is dichotomous (Efron, 1975; Goss and Ramchandani, 1995; Fan and Wang, 1999; Lei and Koehly, 2003; Pohar, Blas and Turk, 2004; Michael *et al.*, 2006; Peter, 2007). More recently, research has been steadily building on the accuracy and efficiency of Data Mining, with classifiers like Neural Networks (NN), Support Vector Machines (SVM), Classification Trees

(CTrees) and Random Forests (RF) used for medical prediction and classification tasks (Goss and Ramchandani, 1995; Pitarque, Roy and Ruiz, 1998; Kestler and Schwenker, 2001; Poon *et al.*, 2001; Nabney, 2004; Sommer, Olbrich and Arendasy, 2004; Peter, 2007; Suka *et al.*, 2007; Sut and Senocak, 2007; Maglogiannis *et al.*, 2008; Zollner, Emblem and Schad, 2010). Research on the comparative accuracy of traditional classifiers (LDA and LR) vs. new, computer intensive, Data Mining methods have been growing steadily. Several authors defend that Data Mining classifiers have higher accuracy and lower error rates than the traditional classification methods (Ivanciuc, 2007; Suka *et al.*, 2007; Sut and Senocak, 2007; Kurt, Ture and Kurum, 2008). However, this superiority is not apparent with all data sets, especially with real data (Gelnarova and Safarik, 2005; Finch and Schneider, 2006; Michael *et al.*, 2006; Finch and Schneider, 2007; Peter, 2007). Results regarding the superiority of classification accuracy of newer classification methods as compared to traditional, less computer demanding methods, as well as the stability of the findings are still controversial (Duin, 1996; Meyer, Leischa and Hornik, 2003; Behrman *et al.*, 2007; Finch and Schneider, 2007). Most comparisons between methods are based only on total classification accuracy and/or error rates; they involve human intervention for training and optimization of the data mining classifiers vs. out-of-the-box results for the traditional classifiers. Accordingly to Duin (1996) "(…) a straight forward fair comparison demands automatic classifiers with no user interaction". Furthermore, in medical contexts, sensitivity (the ability to predict the condition when the condition is present), specificity (the ability to predict the absence of the condition when the condition is not present) as well as the classifier discriminant power (as estimated from the area under the Receiver Operating Characteristic (ROC)) are key features that need to be considered when comparing classifiers and diagnosis methods.

In this paper we evaluated the sensitivity, specificity, overall classification accuracy, area under the ROC and Press' Q of Data Mining classifiers like Neural Networks (Multilayer Perceptrons and Radial Basis Networks), Support Vector Machines, Classification Trees and Random Forests as compared to the traditional Linear, Quadratic Discriminant analysis and Logistic Regression in the prediction of the evolution into dementia of 400 elderly people with Mild Cognitive Impairment.

Classifiers

Discriminant Analysis: The oldest classifier still in use was devised almost 100 years ago by Sir R. Fisher. Fisher's Linear Discriminant Analysis (LDA; Fisher, 1936) builds discriminant functions that estimate scores for each subjects classified into groups, from linearly independent predictor variables. Discriminant analysis predicts membership in two or more mutually exclusive groups from a set of predictors, when there is no natural ordering on the groups. Linear and quadratic discriminat functions are estimated using within vs. between sum of square minimization optimisation and then the subject is classified into the group for which its classification function score is higher (McLachlan, 2004).

Logistic Regression: Binomial Logistic regression (LR) models the probability of occurrence of one (success) of the two classes of a dichotomous criterion. A linear combination of predictors is used to fit a Logit transformation of the probability of success for each subject. Regression coefficients are fitted by maximum likelihood estimation and the probability of success for each subject is then estimated. If the estimated probability is greater than 0.5 (or other pre-defined threshold value), the subject is classified into the success group; otherwise, it is classified into the failure group (Hosmer and Lemeshow, 2000).

Neural Networks: Neural Networks (NN) methods have been used extensively in classification problems and this is one of the most active research and application areas in the Neural Networks field (Yang, 2010). Inspired from the biological neuron cells, a NN is a multi-stage, multi-unit classifier, with input, hidden or processing, and output layers as illustrated by figure 3.2.1.

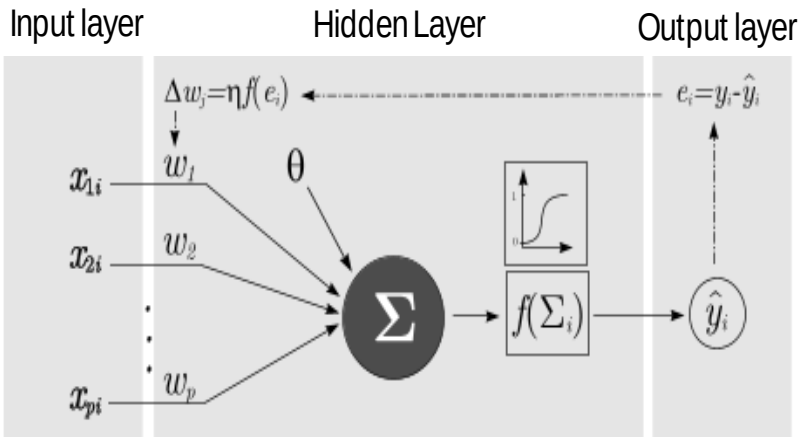

Figure 3.2.1 – Pictorial representation of a neural network (multilayer perceptron) with input layer (dendrites), hidden layer (nucleus) and output layer (axon) (see text for a description of the neural networks components).

Activation functions for the hidden layer and the output layer are one of the general linear, logistic, exponential or gaussian function families. Several topologies of Neural Networks (NN) can be used in binary classification problems. Two of the most used NN are the Multilayer Perceptron (MLP) and the Radial Basis Function (RBF). The main differences between these two NN reside in the activation functions of the hidden layer: For the MLP the activation function belongs, generally, to a linear or logistic activation function family, for the RBF function the activation function belongs to the Gaussian family. A NN is generally trained in a set of iterations (epochs) for a subset of the data (train set) and tested for the remaining subset (test set). The vector of synaptic weights of the NN is upgraded in each iteration in way to maximize the correct classification rate and or minimize a function of the classification errors; either a function of the sum of squares of the errors for continuous criterion or the Cross-entropy error function for a binary criterion (for a detailed description see Bishop, 1995).

Support Vector Machines: Support Vector Machines (SVM) are machine-learning derived classifiers which map a vector of predictors into a higher dimensional linear plane through either linear or non-linear kernel functions (Cortes and Vapnik, 1995). In a binary classification problem, the two groups, say {-1} and {+1}, are separated in a higher-dimension hyperplane accordingly to a structural risk minimization principle. The objective is to find a linear separating hyperplane constructed from a vector of predictors, a vector of weights and a bias offset that classifies all the observation in one of the two groups {-1; +1}. The training patterns that respect the above constrains are called support vectors, and carry all the relevant information about the classification problem. Since, in a binary classification problem, there are infinite separation hyperplanes, the goal is to find the optimum plane, which separates best the two groups (for more detailed information see Cortes and Vapnik, 1995; Bennett and Campbell, 2000; Karatzoglou, Meyer and Hornik, 2006; Ivanciuc, 2007).

Classification trees: Classification trees (CTrees) are non-parametric classifiers that construct hierarchical decision trees by splitting data among classes of the criterion at a given step (node) accordingly to an “if-then” criterion applied to a set of predictors, into two child nodes repeatedly, from a root node that contains the whole sample. Thus, CTrees can select the predictors and its interactions that are most important in determining an outcome for a criterion variable. The development of a CTrees is supported on three major elements: (1) choosing a sampling-splitting rule that defines the tree branch which connects the

classification nodes; (2) the evaluation of classification produced by the splitting rule at each node and (3) the criteria used for choosing an optimal or final tree for classification purposes. According to the features of these major elements, the most usual CTrees can be classified into: Classification and Regression Tree (CART; Breiman *et al.*, 1984), Chi-squared Automatic Interaction Detector (CHAID; Kass, 1980) and Quick Unbiased Efficient Statistical Tree (QUEST; Loh and Shih, 1997).

Random forests: Random forests (RF) were proposed by Leo Breiman (2001). This "ensemble learning" classification method construct a series of CART using random bootstrap samples of the original data sample. Each of these trees is build from further random sub-set of the total predictors who maximize the classification criteria at each node. An estimate of the classification error-rate can be obtained using each of the CART to predict the data not in the bootstrap sample ("out-of-the bag") used to grow the tree, and then average the out-of-the bag predictions for the grown set of trees (forest). These out-of-the bag estimates of the error-rate can be quite accurate if enough trees have been grown (Liaw and Wiener, 2002). Object classification is then predicted from the majority of predictions given by the trees in the random forest. Although this classification strategy may lack a perceivable advantage over single CTrees, accordingly to its creator (Leo Breiman) it has unexcelled accuracy among current algorithms, performing very well when compared to many classifiers including LDA, NN and SVM (for a detailed description of RF see Breiman, 2001). Furthermore, this method is quite user-friendly since it has only two parameters that the user needs to define: the number of random trees in the forest; and the number of predictor variables in the random subset of tree at each node. These parameters can be easily optimized although random forests are not very sensitive to their values (Liaw and Wiener, 2002).

Procedure

Data mining settings and classifiers evaluation: To prevent overfitting and artificial accuracy improvement due to the use of the same data for training and testing of classifiers, a 5-fold cross-validation strategy was followed to train and evaluate the classifiers. The total sample was divided into 5 proportional sub-samples. In each of the 5 steps, 4/5 of the sample was used for training and 1/5 was used for testing. Test results for the 5 runs, gathered from the 5 test samples, were then aggregated. The comparative performances (total accuracy, sensitivity, specificity, AUC and Press' Q) of the different classifiers where compared with

Friedman's ANOVA on Ranks followed by Dunn's post-hoc multiple comparisons of mean ranks. Statistical significance was assumed for $p<0.05$. Equal a priori classification probabilities were used for Linear Discriminant Analysis, Quadratic Discriminant Analysis and Logistic Regression. The Multilayer Perceptron was trained with 11 inputs in the input layer, 1 hidden layer with 4-7 neurons and a hyperbolic tangent activation function. The activation function for the output layer was the Softmax with a cross-entropy error function. Synaptic weights were obtained from an 80%:20% train: test setup. The Radial Basis Function Neural Network had 11 inputs, one hidden layer with 2-8 neurons and a Softmax activation function. The activation function for the output layer was the identity function with a sum of squares error function. The radial Gaussian function was the kernel used in the SVM. Cost (*c*) and γ parameters were optimized by a grid search in the intervals $[2^{-3}; 2^{15}]$ for *c* and $[2^{-15}; 2^{3}]$ for γ, followed by cross-validation of each of the SVM obtained in the 5 train sets. The classification function was the sign of the optimum margin of separation. CHAID, CART and QUEST classification trees used α to split and α to merge of 0.05, with 10 intervals. Tree growth and pruning of CART were set with a minimum parent size of 5 and minimum child size of 1. Classification priors for both trees were fixed at 0.5:0.5. Random Forests were composed of 500 CART trees with 2-9 predictors per tree cross-validation optimization. The Predictive Analytic Software (PASW) Statistics (v. 18, SPSS Inc., Chicago, Ill) was used for Discriminant Analysis, Logistic Regression, Neural Networks and Classification trees. Support Vector Machines and Random Forests were performed with R (v. 2.8, CRAN) with the *e1071* (Meyer, 2001) and *random-Forest* (Liaw and Wiener, 2002) packages, respectively.

3.2.2 Results

Sample: Subjects were recruited as part of a cohort study of 775 elderly non-demented patients with cognitive complaints referred for neuropsychological evaluation at 3 institutions, the Laboratory of Language Studies, Santa Maria Hospital, and a Memory Clinic, both in Lisbon, and of the Neurology Department, University Hospital, Coimbra, from 1999 to 2007. Inclusion criteria consisted in the diagnosis of Mild Cognitive Impairment (according to the criteria of the European Consortium on Alzheimer's disease, Portet *et al.*, 2006); presence of at least one follow-up neuropsychological assessment or clinical re-evaluation. Patients with dementia (according to DSM-IV-TR; APA, 2000) or other disorders that may cause cognitive

impairment, like stroke, brain tumor, significant head trauma, epilepsy, psychiatric disorders, uncontrolled medical illness (hypertension, metabolic, endocrine, toxic and infectious diseases); medical treatments interfering with cognitive function; and alcohol or illicit drug abuse were excluded from the study sample. At the follow-up, the subjects were classified as having: Mild Cognitive Impairment (according to the same criteria); or Dementia (according to the DSM-IV-TR (APA, 2000) criteria). The final sample was composed by 400 patients (see table 3.2.1 for sample demographics) who gave voluntary consent to participate in this study. The local ethics committee approved the study.

Table 3.2.1 Sample demographics: The two groups in the criterion were "MCI" - Mild Cognitive impaired patients; and "Dementia" patients. The class to predict was "Dementia". P-values for group comparison were obtained from Student's-t test (†) or χ^2 test (‡).

	MCI	**Dementia**	***p-value***
Group size (%)	275 (69%)	125 (31%)	$<0.001^{‡}$
Age (M±SD)	67.8 ± 8.8	71.6 ± 8.4	$<0.001^{†}$
Sex (♀/♂)	165/ 110	78 / 47	$0.649^{‡}$
Schooling years (M±SD)	8.1 ± 4.7	8.64 ± 4.9	$0.469^{†}$
Time between assessments (year)(M±SD)	2.3 ± 1.6	2.2 ± 1.4	$0.517^{†}$

Criterion and Predictors: The criterion was a dichotomous variable with two groups: MCI and Dementia. Neuropsychological predictors were a subset of tests with criterion validity ($p<0.1$) from the Battery of Lisbon for the Assessment of Dementia (BLAD; Garcia, 1984), which includes multiple neuropsychological tests representing key cognitive domains and was validated for the Portuguese population. The selected 11 neuropsychological tests assessed the following cognitive areas: verbal initiative (Verbal Semantic Fluency) (Benton and Hamsher, 1976); verbal and non-verbal abstraction (Interpretation of Proverbs) (Wechsler, 1981); visuo-constructional abilities and executive functions (Freedman *et al.*, 1994); immediate memory (Wechsler and Stone, 1945); working memory (Digit Span backward) (Wechsler and Stone, 1945); learning and verbal memory (Word Recall, Verbal Paired-associate Learning and Logical Memory) (Wechsler and Stone, 1945) and Orientation (adapted from the Mini-Mental State Examination (MMSE) Test (Folstein, Folstein and McHugh, 1975; Guerreiro, 1998)) (Garcia, 1984). A Forgetting Index was also studied as a predictor variable. This Index is

calculated based on the correct information evoked between the immediate and the delayed condition of the Logical Memory Test (Forgetting Index= [(LM delayed recall – LM immediate) / LM immediate)] × 100) (Ribeiro, Guerreiro and de Mendonça, 2007). Figure 3.2.2 gives the scatter biplots for all pairs of predictors and their frequency histograms. None of the predictors showed a normal distribution judging from Kolmogorov-Smirnov with Lilliefors correction tests ($p<0.05$), but criterion group variances were homogenous according to the Levene's test ($p>0.05$). No multicollinearity problems were apparent (Variance Inflation Factors<5) but several bivariate outliers were detected.

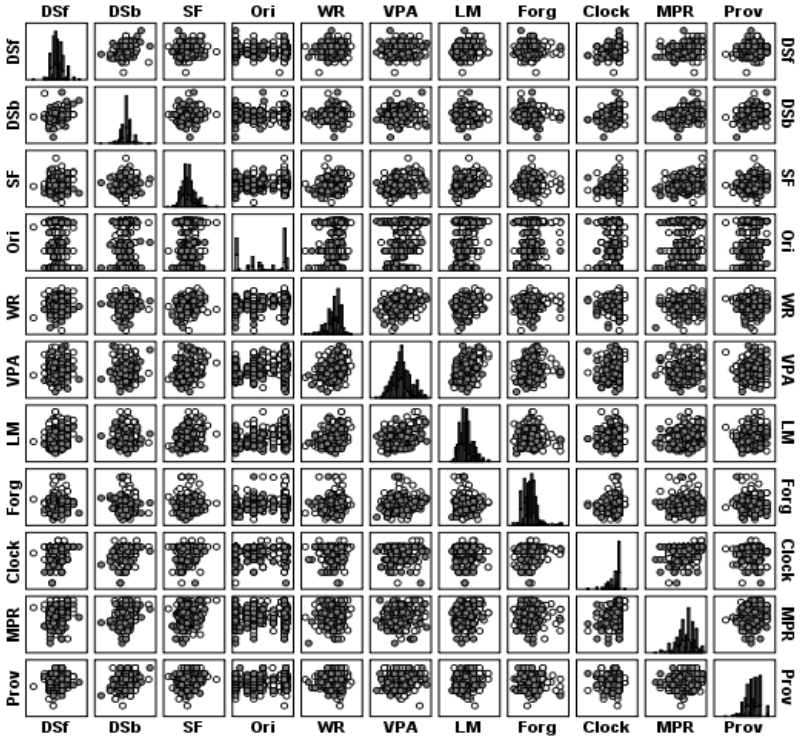

Figure 3.2.2 – Scatter biplots for MCI (○) and Dementia (●) patients in the 11 predictors and its histograms (DSf – Digit Span Forward; DSb – Digit Span Backward; SF – Verbal Semantic Fluency; Ori – Orientation; WR – Word Recall; VPA – Verbal Paired-associate Learning; LM – Logical Memory; Forg – Forgetting Index; Clock- Clock Drawing; MPR – Raven Progressive Matrices; Prov – Interpretation of Proverbs). See text for tests descriptions.

Classification accuracy, sensitivity, specificity, area under the ROC and Press' Q statistic were evaluated in the 5 test sets resulting from the 5-fold cross validation strategy as described before. Data gathered is illustrated in box-plots for the different classifiers.

Total Accuracy

Figure 3.2.3 shows the box-plots of the total classification accuracy for the 10 classifiers studied. Judging from the Friedman test on ranks, there were statistical significant differences between distributions of the total accuracy ($\chi^2_{Fr}(9)=22.211$; $p=0.008$). Post-hoc, multiple mean rank comparisons revealed the SVM and RF had higher mean ranks than the other classifiers who did not differ significantly in mean rank accuracy ($p>0.05$).

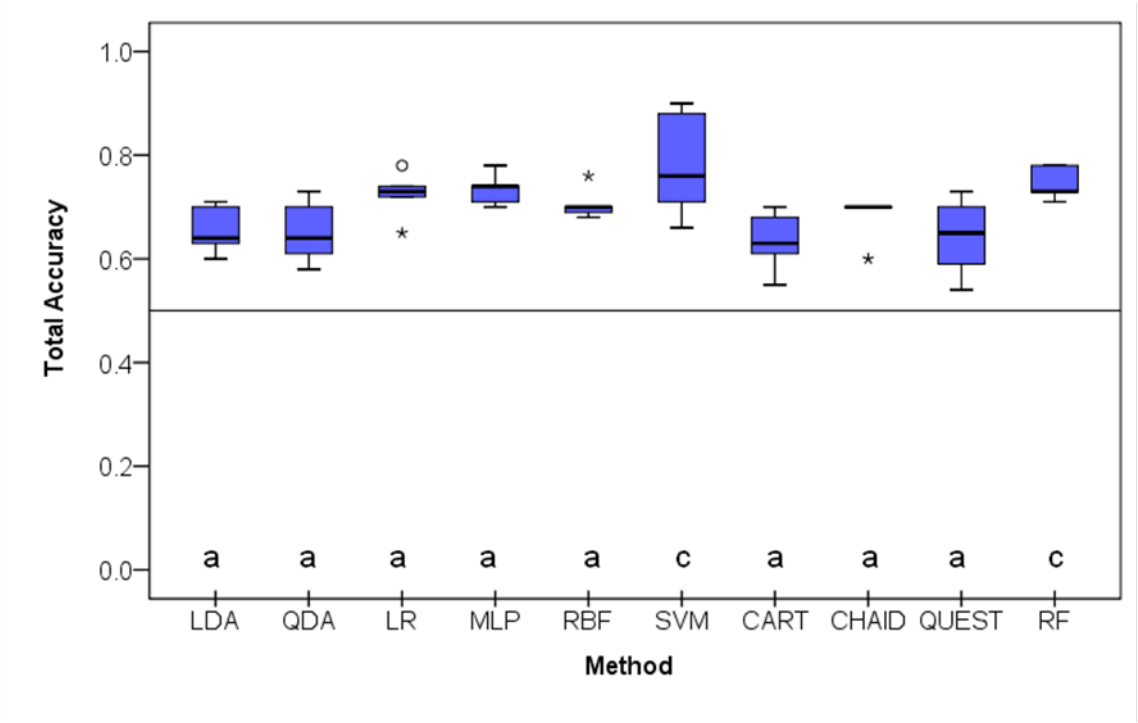

Figure 3.2.3 – Box-plot distributions of classification accuracy (number of correct classifications / total sample size) for the 5 test samples resulting from the 5-fold cross-validation procedure (see text for abbreviations) ($\chi^2_{Fr}(9)=22.211$; $p=0.008$). Different letters correspond to methods with statistically significant differences according to Dunn's mean rank post-hoc comparisons ($p<0.05$). Circles represent outliers (observations greater than the 3rd quartile plus 1.5 times the interquartile range or smaller than the 1st quartile minus 1.5 times the interquartile range; stars represent extreme outliers that correspond to observations greater than the 3rd quartile plus 3 times the interquartile range or smaller than the 1st quartile minus 3 times the interquartile range.

Specificity

The distributions of the specificity (the proportion of subjects that did not convert to dementia and were correctly predicted) are shown in figure 3.2.4. The differences in the specificity distributions were statistically significant ($\chi^2_{Fr}(9)= 37.292$; $p<0.001$). SVM scored the highest in specificity followed by a second group composed by MLP, LR and RBF with significant differences from a third group composed by LDA, QDA, CTrees and RF.

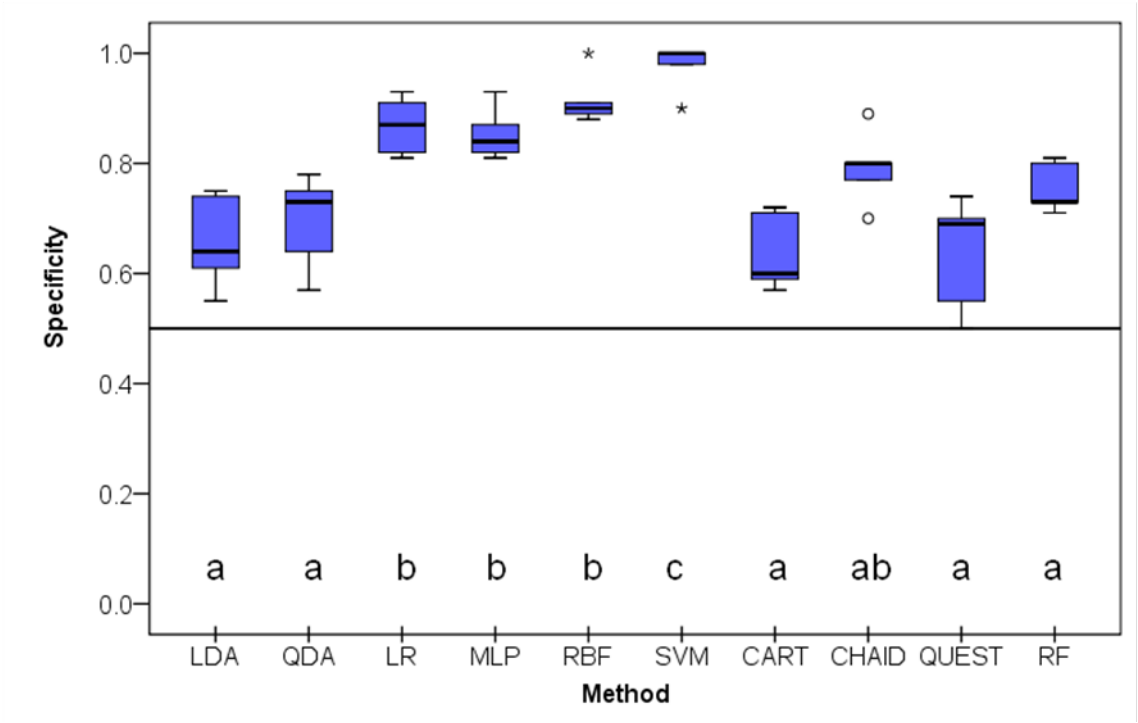

Figure 3.2.4 – Box-plot distributions of specificity (number of MCI predicted / number of MCI observed) for the 5 test samples resulting from the 5-fold cross-validation procedure (see text for abbreviations) ($\chi^2_{Fr}(9)=37.292$; $p<0.001$). Different letters indicate statistically significant differences between classifiers on Dunn's mean rank comparison procedure. Circles and stars represent outliers and extreme outliers respectively.

Sensitivity

Figure 3.2.5 illustrates the distributions of the sensitivity (proportion of subjects that were correctly predicted to convert into dementia) values obtained by the 10 classifiers in the 5 test samples. There were statistically significant differences in the distribution of the sensitivity values of the analyzed classifiers ($\chi^2_{Fr}(9)=29.0$; $p=0.001$). LDA, CART, QUEST and RF had the highest sensitivity values, which were significantly different from a second group composed by LR, MLP, RBF and CHAID. It is worthwhile to mention that this second group

had median sensitivity lower than 0.5, and that SVM was the classifier with significantly lowest sensitivity.

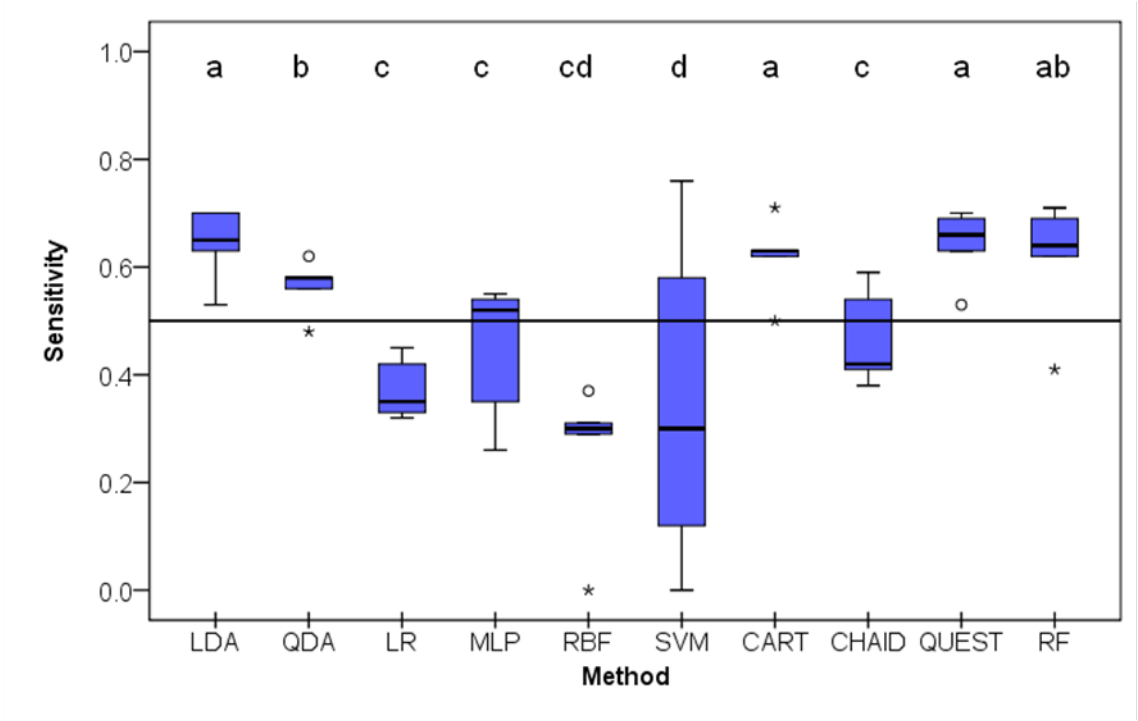

Figure 3.2.5 – Box-plot distributions of sensitivity (number of Dementia predicted / number of Dementia observed) (see text for abbreviations) ($\chi^2_{Fr}(9)= 29.0$; $p=0.001$). Different letters indicate statistically significant differences between classifiers on a multiple mean rank comparison procedure. Circles and stars represent outliers and extreme outliers respectively.

Area under the ROC

The distribution of the areas under the ROC (AUC) for the 10 classifiers in the 5 test samples is shown in figure 3.2.6. There are statistically significant differences between classifiers ($\chi^2_{Fr}(9)= 23.745$; $p=0.005$). SVM shows the highest AUC, however an extreme low value removes the significance of the differences with the AUC distributions from the other classifiers. LDA, LR, MLP, RBF and RF are a homogenous group statistically different from the group composed by QDA, CHART and QUEST who are plagued by extreme low values.

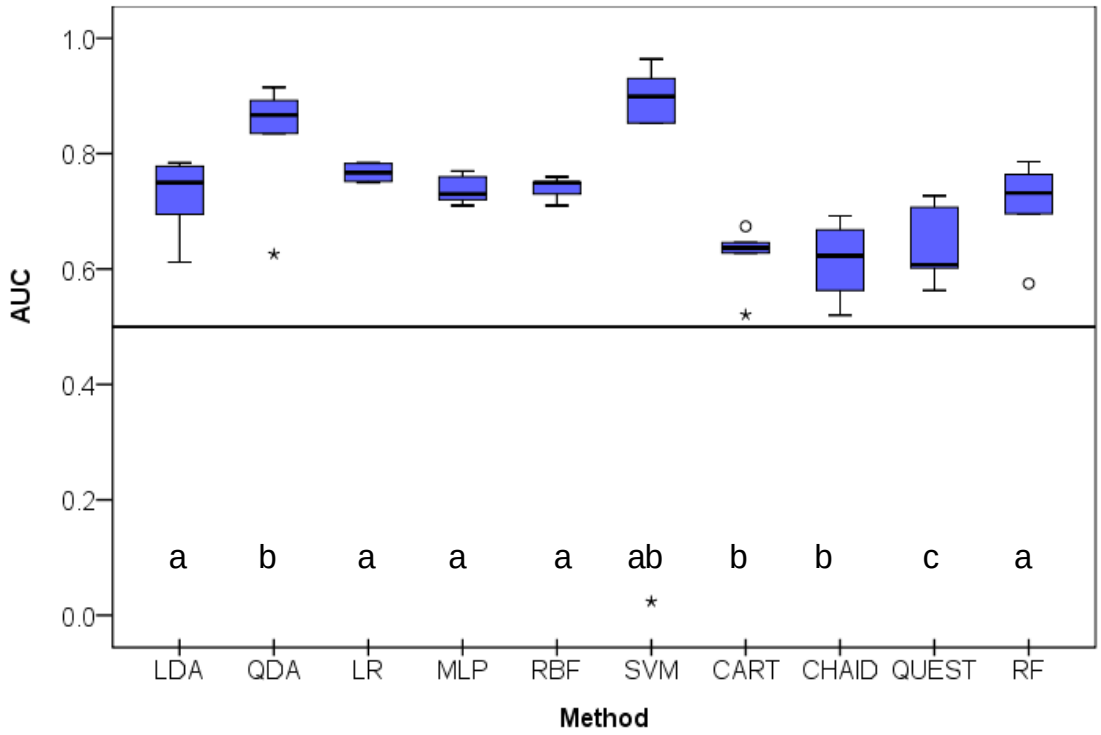

Figure 3.2.6 – Box-plot distributions of area under the Receiver Operating Characteristic curve (AUC) (see text for abbreviations) ($\chi^2_{Fr}(9)= 23.745$; $p=0.005$). Different letters indicate statistically significant differences between classifiers on a multiple mean rank comparison procedure. Circles and stars represent outliers and extreme outliers respectively.

Classification by chance alone

Press' Q evaluates the performance of a classifier as compared to chance alone. Under the null hypothesis that the classifier is no better than chance alone, Press' Q has a chi-square distribution with 1 degree of freedom. Thus, classifiers with Q≥3.84 classify significantly better than chance alone for 0.05 significance level. The Q distributions in the 5 sample tests are given by figure 3.2.7. There were statistically significant differences between the Q distributions (χ^2Fr(9)=21.582; p=0.01). Dunn's multiple mean rank comparisons revealed that SVM had the highest mean rank followed by RF, MLP, CHAID and LR. The smallest mean ranks were observed for LDA, QDA, CART and QUEST. All classifiers, with the exception of QUEST, had 1st quartiles higher than 3.84.

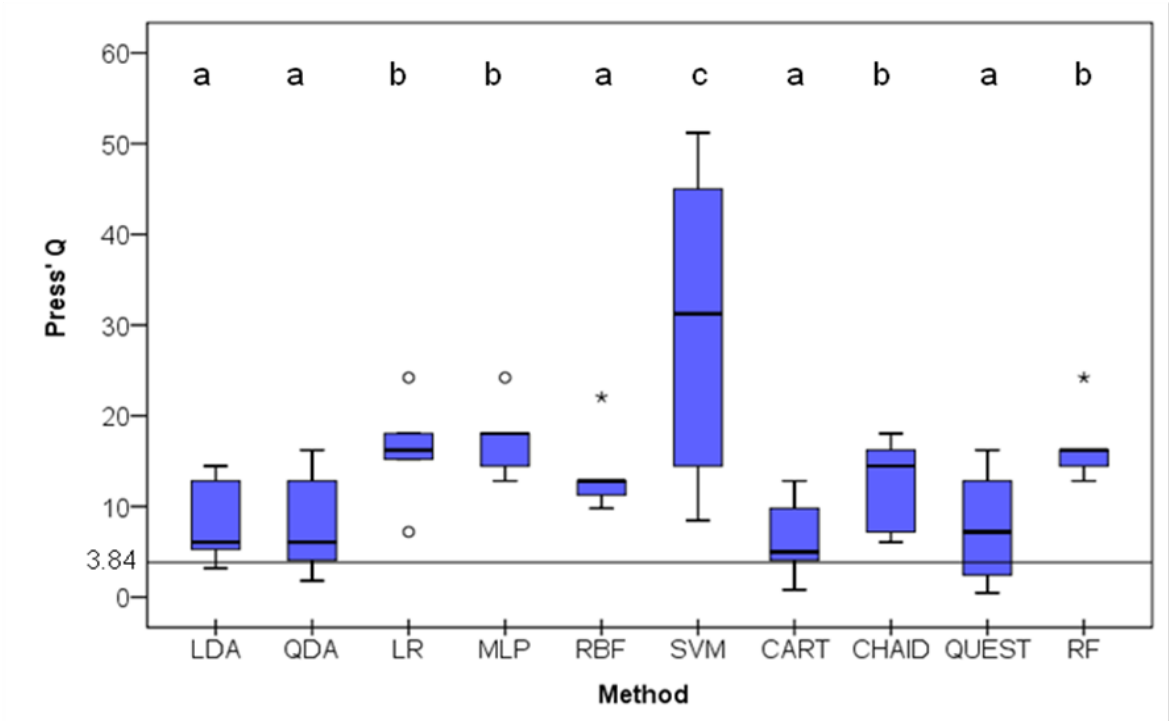

Figure 3.2.7 – Box-plot distributions of Press' Q (see text for abbreviations) (χ^2Fr(9)=21.582; p=0.01). Different letters indicate statistically significant differences between classifiers on Dunn's multiple mean rank comparison procedure. Classifiers with Q≥3.84 classify significantly better than chance alone for a 0.05 significance level. Circles and stars represent outliers and extreme outliers respectively.

3.2.3 Discussion

All classifiers evaluated showed better median classification than chance alone in the prediction of evolution into dementia of elderly people with Mild Cognitive Impairment. Median Press's Q statistic was larger or equal to 5 for all classifiers, although in QUEST the 1st quartile was below the critical level for this statistics. Discriminant power of the classifiers, as judged by the AUC, was appropriate for most classifiers (greater than 0.7) with the exception for classification trees (median AUC of 0.6). No statistically differences were found in the total accuracy of the 8 of the 10 evaluated classifiers (Medians between 0.63 and 0.73), but RF (Me=0.74) and SVM (Me=0.76) obtained statistically significant higher classification accuracy values. Median specificity ranged from a minimum of 0.64 (CART and LDA) to a maximum of 1 (SVM). With the exception of CART and QUEST, all the other classifiers were quite efficient in predicting group membership in the group with larger number of elements (the MCI group corresponding to 69% of the sample; median specificity larger than 0.6). Judging from total accuracy and specificity, SVM and RF rank highest amongst the

classifiers tested as has been suggested elsewhere (Burges, 1998; Breinam, 2001; Liaw and Wiener, 2002; Lehmann *et al.*, 2007). However, a quite different picture emerges from the analysis of the sensitivity of the classifiers. Prediction for the group with lower frequency (the Dementia group, 31% of the sample) was quite poor for several of the tested classifiers, including the ones with some of the highest specificity values. Minimum median sensitivity was 0.30 (SVM) and maximum median sensitivity was 0.66 (QUEST, followed by 0.64 for LDA and RF). Only six of the ten classifiers tested showed median sensitivity larger than 0.5 (and only five had 1st quartile sensitivity larger than 0.5). Considering that conversion into dementia is the key prediction in this biomedical application and thus higher sensitivity of classifiers is required, classifiers like Logistic Regression, Neural Networks, Support Vector Machines and CHAID trees are inappropriate for this type of binary classification task. Similar findings were observed in studies comparing different classifiers in other biomedical conditions (Meyer, Leischa and Hornik, 2003; Lehmann *et al.*, 2007; Maglogiannis *et al.*, 2008). Total accuracy of classifiers is misleading since some classifiers are good only at predicting the larger group membership (high specificity) but quite insufficient at predicting the smaller group membership (low sensitivity). Some of the classifiers with the highest specificity (Neural Networks (MLP and RBF) and SVM) are also the classifiers with the lowest sensitivity. Unbalance of classification efficiency for small frequency vs. large frequency groups has been found in other real-data studies for Logistic Regression and Neural Networks (Orr, 1997; Schwarzer, Vach and Schumacher, 2000; Meyer, Leischa and Hornik, 2003; Finch and Schneider, 2006). Taking in account total accuracy, specificity and sensitivity, the oldest Fisher's Linear Discriminant Analysis does not rank much lower than Multiple Layer Perceptrons or Random Forests, the newest member of the binary classification family. Similar observations have been made by other authors when classifiers were compared on more than total accuracy or total error rates. For example, Breiman and colleagues (1984) stated, "LDA does as well as other classifiers in most applications". Meyer, Leischa and Hornik (2003) point out in their comparison study of data mining classifiers, including Neural Networks and SVM, that LDA is a very competitive classifier, producing good results "*out-of-the-box* without the inconvenience of delicate and computationally expensive hyperparameter tuning". In a similar application of Random Forests, SVM, Neural Networks and Linear Discriminant Analysis for recognition of Alzheimer's disease based on electrical brain activity, Lehmann and colleagues (2007) demonstrated that "even though

modern computer-intensive classification algorithms such as RF, SVM and Neural Networks show a slight superiority, more classical classification algorithms performed nearly equally well".

It must be pointed out that the relatively small sample size, although in the range of most biomedical experimental studies with dementia and cognitive impairment, may limit the performance of some data mining methods assessed in this study. Sample size has been known to play an important role in the accuracy of Neural Networks (Fukunaga and Hayes, 1989; Raudys and Jain, 1991). In our study, the number of cases for the training and testing sets are at lower limit for recommended data set dimensions for Neural Networks (several hundred) (Fukunaga and Hayes, 1989; Raudys and Jain, 1991; Vach, Roβner nd Schumacher, 1996). Large data sets requirements are also found in LR, but less in LDA if the model assumptions are met. The present sample size was not, apparently, limiting for the achievement of an acceptable accuracy, specificity and sensitivity of both Random Forests and LDA, as reported elsewhere (Vach, Roβner nd Schumacher, 1996; Pohar, Blas and Turk, 2004). Furthermore, there are studies with relatively small samples where data mining techniques, like SVM and Neural Networks have been used with high accuracy in classification problems (Lehmann *et al.*, 2007; Jahandideh, Abdolmaleki and Movahedi, 2010; Oliveira *et al.*, 2010; Zhu *et al.*, 2010). Equivalent or even superior performances have been reported for Linear Discriminant Analysis and Random Forest when compared with Neural Networks, Classification trees and Support Vector Machines (Breiman, 2001; Meyer, Leischa and Hornik, 2003; Lehmann *et al.*, 2007; Statnikov and Aliferis, 2007; Smith, Sterba-Boatwright and Mott, 2010). However, controversy still prevails regarding the effects on classifiers performance of different combinations of predictors, data assumptions, sample sizes and classifiers (Fan and Wang, 1999; Lisboa, 2002; Lei and Koehly, 2003; Lemon *et al.*, 2003; Finch and Schneider, 2007; Lehmann *et al.*, 2007).

In conclusion, for binary classification problems, like prediction of dementia, where classes can be linearly separated and sample size may compromise training and testing of popular data mining and machine learning methods, Random Forests and Linear Discriminant Analysis proved to have high accuracy, sensitivity, specificity and discriminant power. On the contrary, data mining classifiers like Neural Networks and Classification Trees showed low sensitivity, recommending against its use in classification problems where the class of interest is less represented. It is noteworthy to mention that Fisher's Linear Discriminant Analysis, a

classifier devised almost a century ago, stands up as a simple, efficient and time-proof classifier.

3.3 Comparison of four verbal memory tests for the Diagnosis and predictive value of MCI *(Dementia and Geriatric Cognitive Disorders Extra)*

3.3.1 Rationale and Procedure

Many elderly people suffer from memory and other cognitive decline that is not severe enough to meet the criteria for dementia. These elderly people may be diagnosed as having mild cognitive impairment (MCI), implying a high risk of progression to dementia, usually Alzheimer's disease (AD), in the forthcoming years. In the initial formulation by Petersen and colleagues (1999), MCI was based on (1) memory complaint, preferably corroborated by an informant; (2) memory impairment documented according to appropriate reference values; (3) essentially normal performance in non-memory cognitive domains; (4) generally preserved activities of daily living, and (5) absence of dementia. As repeatedly pointed out, several of these criteria would need operationalization. In particular, the test used to document the memory impairment and the cut-off score should be specified (Petersen, 2004). In spite of further refinements in the concept of MCI (Winblad *et al.*, 2004; Portet *et al.*, 2006; Chertkow *et al.*, 2007; Matthews *et al.*, 2008; Visser and Verhey, 2008; Jak *et al.*, 2009; Petersen *et al.*, 2009; Saxton *et al.*, 2009), there is still no consensus about the specific memory test that should be used for the diagnosis of MCI or prodromal phase of AD (Dubois and Albert, 2004; Albert *et al.*, 2011). Thus, there is the need to compare systematically and prospectively the inclusion of different verbal memory tests in the MCI criteria, and to examine how this modifies the predictive value of the MCI diagnosis for conversion to dementia.

Deficits in episodic memory are associated with impaired encoding of the contextual information and consolidation of new verbal material (Wang and Zhou, 2002; Moulin *et al.*, 2004; Belleville *et al.*, 2008), and a lower performance on tests of episodic verbal memory is a forerunner of future cognitive decline (Almkvist *et al.*, 1998; Blacker *et al.*, 2007; Guarch *et al.*, 2008; Rabin *et al.*, 2009). A deficit in delayed recall assessment of episodic long-term memory, as opposed to the short-term or implicit memory assessment would be particularly characteristic of initial AD (Perri *et al.*, 2007a), since it reflects involvement of the hippocampus and related medial temporal lobe structures. Significant verbal memory impairment, confirmed by neuropsychological testing, is considered the hallmark of both

amnestic MCI and AD (Portet *et al.*, 2006; Dubois *et al.*, 2007). So far, distinct tests of memory and learning have been used to establish the presence of memory impairment in order to fulfill the criteria for MCI, namely the Logical Memory (LM) test (Cunje *et al.*, 2007; Brooks *et al.*, 2008; Guo *et al.*, 2009; Rabin *et al.*, 2009), the Verbal Paired-Associate Learning (VPAL) test (Brooks *et al.*, 2008; Pike *et al.*, 2008), and the California Verbal Learning Test (CVLT) (Greenaway *et al.*, 2006; Blacker *et al.*, 2007; Ribeiro, Guerreiro and de Mendonça, 2007; Wehling *et al.*, 2007; Bläsi *et al.*, 2009; Rabin *et al.*, 2009; Teng *et al.*, 2009; Riepe *et al.*, 2010).

The LM test (Wechsler, 1945) has been used for a long time to discriminate between healthy older adults and individuals with very mild dementia (Storandt and Hill, 1989) and is still commonly used for the assessment of memory impairment in MCI patients nowadays. Recent studies associate the presence of impairment in LM with a higher rate of conversion to AD as compared with other episodic memory tests (Guo *et al.*, 2009; Baek *et al.*, 2011). Furthermore, the LM test was recently proposed as a screening tool for MCI in the Alzheimer's disease Neuroimaging Initiative (ADNI) study (Aisen *et al.*, 2010).

Previous studies showed that impairment in list learning tests might as well predict accurately the conversion to AD (Blacker *et al.*, 2007; Maruff *et al.*, 2004). Rabin and colleagues (2009) showed that the impairment in the total learning score from the CVLT (Delis *et al.*, 1987) had superior overall accuracy in distinguishing MCI from normal aging, even though that accuracy might be enhanced by the inclusion of the delayed recall condition of the LM test. The VPAL test was proposed to reveal the presence of memory deficits in MCI and AD patients, although the facilitation of the encoding process through the cued recall format could lead to a different memory deficit profile than in patients assessed with the CVLT (Pike *et al.*, 2008).

Besides verbal memory impairment, some studies have evidenced that other memory domains are also altered in MCI, namely those related to working memory (Belleville *et al.*, 2008). The Digit Span (DS) test measures auditory attention, immediate span of learning, and working memory. Impairment in the DS test was associated with future cognitive decline (Kurt, Yener and Oguz, 2011; Wilson *et al.*, 2011). However, it appears that working memory does not decline early in the neurodegenerative process of AD (Wiechmann, Hall and O'Bryant, 2011). Therefore, the DS test was used in this study as a negative control to other applied tests that represent earlier markers of the neurodegenerative process observed in AD

patients (e.g., tests assessing episodic memory and verbal learning). Another type of memory that evidenced more resistance to AD progression is semantic memory, since the lexical semantic system might be spared until the initial phase of dementia (Balthazar *et al.*, 2007).
In the present study, non-demented patients with cognitive complaints who had a neuropsychological battery assessing different types of memory were followed prospectively. The aim was to determine whether the inclusion of four distinct memory tests, i.e., LM test, CVLT, VPAL test, and DS test, in the diagnostic criteria could modify the predictive value of MCI regarding conversion to dementia.

Procedures

Research Participants: Participants were selected from the Cognitive Complaints Cohort (Maroco *et al.*, 2011), which is a prospective study conducted at the Institute of Molecular Medicine, Lisbon, to investigate the cognitive stability or evolution to dementia of subjects with cognitive complaints based on a comprehensive neuropsychological evaluation and other biomarkers. The study was approved by the local ethics committee.

Inclusion Criteria: The inclusion criteria were: (1) presence of cognitive complaints; (2) neuropsychological testing including all four memory tests compared in the present study, and (3) follow-up >6 months.

Exclusion Criteria: The exclusion criteria were: (1) presence of neurological or psychiatric disorders that may induce cognitive deficits; patients with major depression according to DSM-IV-TR (APA, 2000) or serious depressive symptoms (indicated by a score on the Geriatric Depression Scale short version (GDS 15) > 10 points) were excluded; (2) systemic illness with cerebral impact; (3) history of alcohol abuse or recurrent substance abuse or dependence, and (4) presence of dementia according to DSM-IV-TR (APA, 2000), or a Mini-Mental State Examination (MMSE) score below the cutoff for the Portuguese population, or significant impairment on activities of daily life according to the Blessed Dementia Rating Scale (BDRS) (Blessed, Tomlinson and Roth, 1968; Garcia, 2008).

The baseline comprehensive neuropsychological assessment was carried out by the same team of trained neuropsychologists, supervised by M.G., following a standard protocol and comprising several tests and scales:

(1) MMSE (Folstein, Folstein and McHugh, 1975; Guerreiro, 1998): the MMSE is one of the most widely used brief instruments for the clinical evaluation of cognitive state in adults;

(2) Battery of Lisbon for the Assessment of Dementia (BLAD) (Garcia, 1984): the BLAD is a comprehensive neuropsychological battery evaluating multiple cognitive domains and validated for the Portuguese population. Tests of interest for the present study were: LM (immediate and delayed recall; Wechsler Memory Scale, WMS); VPAL (immediate recall; WMS), and DS (forward and backward; WMS) (Wechsler, 1945);

(3) CVLT (Delis *et al.*, 1987; Ribeiro, Guerreiro and de Mendonça, 2007): the CVLT measures verbal learning assessing constructs as repetition learning, serial position effects, semantic organization, intrusion, and proactive interference. The word lists (list A and list B) are made up of 16 items from 4 different categories of 'shopping list' items. The trials of interest (trials with better discriminating ability for different stages of cognitive decline according to previous studies) (Greenaway *et al.*, 2006) considered for the present study were: the total number of words from list A correctly recalled on the five learning trials (Atot) and long-delayed free recall (LDFR; number of words from list A correctly recalled after an interference period of 20 min);

(4) BDRS (Blessed, Tomlinson and Roth, 1968; Garcia, 2008): the BDRS is a brief behavioral scale based on the interview of a close informant, assessing functional capacity for activities of daily living and changes in personality;

(5) Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1983; Sheikh and Yesavage, 1986; Barreto *et al.*, 2008): the GDS is a self-report assessment used specifically to identify depression in the elderly. For this study, a short-form (15 items) of the self-report instrument was used.

Diagnosis of MCI: Diagnosis of MCI was based on criteria given by the MCI Working Group of the European Consortium on Alzheimer's disease (Portet *et al.*, 2006):

(1) Cognitive complaints coming from the patients or their families;

(2) The reporting of a decline in cognitive functioning relative to previous abilities during the past year by the patient or informant;

(3) Presence of cognitive impairment: in this study, four distinct memory tests to fulfill this diagnostic criterion were compared: LM, CVLT, VPAL, and DS; 3 cutoffs to define impairment were also analyzed (1, 1.5, and 2 SD below the mean);
(4) Absence of major repercussions on daily life (the patient may report difficulties concerning complex day-to-day activities).

Patients were assessed at follow-up for the presence of dementia and diagnosis of AD, according to the DSM-IV-TR (APA, 2000) criteria.

Data Analysis: Demographic, clinical, and neuropsychological data were analyzed using the Mann-Whitney U test for numerical data and Pearson χ^2 test for nominal data. All tests were two-tailed and a p value < 0.05 was assumed as statistically significant.
The neuropsychological assessment was standardized according to the age and education norms for the Portuguese population and z scores were calculated. The 1, 1.5, and 2.0 SD cutoffs below the mean were compared for establishing impairment on the memory tests. Survival methods were chosen for analysis, since MCI conversion to dementia occurred at different times and the observations were censored. To explore the effect of impairment in different memory tests on the conversion to dementia during follow-up, univariate and multivariate Cox proportional hazards regression models were performed. For multivariate models, the Enter selection method was used to build the regression models. The memory tests were introduced as a binary variable (presence or not of impairment, coded as 0 and 1, respectively, and according to the cutoffs established, 1, 1.5, and 2.0 SD). Since converters to dementia were older at the baseline than non-converters, the multivariate model was adjusted for age.
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. A forest plot with the estimated hazard or risk of conversion to dementia for the different memory tests and cutoffs was displayed. Statistical analyses were performed using IBM SPSS Statistics 19 for Windows (2010 SPSS Inc., an IBM Company) and GraphPad Prism 5 for Windows (GraphPad Software, Inc., San Diego, Calif., USA) for graphical displays.

3.3.2 Results

At baseline, 272 patients reporting subjective cognitive complaints and not demented were included. During the follow-up time (3.0±1.9 years), 58 patients (21%) converted to dementia, and 214 (79%) did not. Most cases that progressed to dementia were diagnosed as AD (85%). The presence of depressive symptoms and functional capacity did not differ between converters and non-converters (table 3.3.1). Likewise, the follow-up time was not significantly different between the two groups (table 3.3.1). The converters were older than the non-converters at the baseline assessment (table 3.3.1).

Statistically significant differences between the converters and non-converters were present in all measures of verbal memory administrated with the exception of the DS test and a measure of forgetting from the CVLT (table 3.3.2).

Table 3.3.1 - Baseline demographic and clinic characterization data

	Converters (n=58)	**Non-converters (n=214)**	***p*-value**
Age, years, mean (SD)	69.9 (8.7)	66.2 (9.3)	**0.004**#*
Gender, female/male, n	38/20	122/92	0.293‡
Formal education, years, mean (SD)	9.3 (5.1)	10.1 (4.8)	0.221#
Follow-up time, years, mean (SD)	2.8 (1.7)	3.1 (1.9)	0.427#
Geriatric Depression Scale, mean (SD)	4.8 (3.7)	4.8 (4.1)	0.831#
Blessed Dementia Scale, mean (SD)	3.4 (2.5)	2.9 (1.9)	0.450#
Mini-Mental State Examination, mean (SD)	25.4 (2.5)	28.3 (1.9)	**0.001**#*

#, Mann-Whitney test; ‡, χ^2 Pearson Chi-Square test; *, Statistically significant ($p< 0.05$)

Table 3.3.2 – Verbal memory tests at the baseline

		Converters (n=58)	Non-converters (n=214)	*p*-value #
Logical Memory	Immediate recall, mean (SD)	-1.46 (1.09)	-0.89 (1.00)	**<0.001***
	Delayed recall, mean (SD)	-1.61 (1.11)	-0.84 (1.08)	**<0.001***
	Forgetting index, mean (SD)	-0.38 (0.47)	-0.11 (0.45)	**0.001***
Verbal Paired-Associate Learning	mean (SD)	-1.48 (1.14)	-0.74 (1.15)	**<0.001***
California Verbal Learning test	Five learning trials total, mean (SD)	-3.22 (1.45)	-1.81 (1.44)	**<0.001***
	Long delayed recall, mean (SD)	-3.30 (1.77)	-1.64 (1.61)	**<0.001***
	Forgetting index, mean (SD)	-0.11 (0.65)	0.06 (0.44)	0.142
Digit Span	Forward, mean (SD)	0.40 (1.63)	0.41 (1.27)	0.837
	Backwards, mean (SD)	0.05 (1.30)	0.30 (1.15)	0.084

Means of *z* scores, calculated according to the equation [*z*= (x-mean)/SD]; # Mann-Whitney test; * Statistically significant ($p< 0.05$).

The analysis of other neuropsychological tests from the BLAD also showed significantly lower performances in converters as compared to non-converters, namely in measures of attention, initiative, and conceptual thinking; however, all scores were within 1 SD of the mean, showing that the converters had no major impairments in non-memory cognitive domains that would qualify them for a diagnosis of dementia (results not shown). Of the 272 patients reporting subjective cognitive complaints and not demented, 33 (12%) had no alterations at the baseline in the memory tests selected for the present study (considering the cutoff < 1.5 SD), 72 (26%) had deficits at only 1 of the memory tests, 167 (62%) showed deficits in ≥ 2 memory tests (from those, 4 (2%) had deficits in at least 1 measure of all memory tests). The number of patients diagnosed as having MCI based on each specific memory test and 3 different cutoff values is shown in table 3.3.3. The CVLT test was the verbal memory test that categorized more subjects as MCI across the 3 cutoffs (table 3.3.3).

Table 3.3.3 – Number of subjects diagnosed as MCI according to distinct measures and cut-offs of memory tests

		1 SD	1.5 SD	2 SD
Logical Memory	Immediate recall, n (%)	152 (55.9)	106 (39)	47(17.3)
	Delayed recall, n (%)	137 (50.4)	98 (36)	55 (20.2)
California Verbal Learning test	Five learning trials total, n (%)	195 (71.7)	166 (61)	123 (45.2)
	Long delayed recall, n (%)	147 (54)	117 (43)	91 (33.5)
Verbal Paired-Associate Learning	N (%)	132 (48.5)	86 (31.6)	47 (17.3)
Digit Span	Forward, n (%)	31 (11.4)	24 (8.8)	3 (1.1)
	Backward, n (%)	36 (13.2)	14 (5.1)	9 (3.3)

Since the conversion to dementia occurred during the follow-up time at different moments, a survival analysis was performed. The diagnosis of MCI on the basis of an abnormal value for each of the memory tests, LM, CVLT, and VPAL, according to the cutoffs determined for impairment, carried a significant risk of conversion to dementia during the follow-up (univariate Cox regression model fitted to the results of each memory test; figure 3.3.1). The diagnosis of MCI on the basis of an abnormal value for the DS backward condition (all cutoffs) and forward condition (1 and 2 SD cutoffs) was not significantly associated with the risk of conversion to dementia during the follow-up (figure 3.3.1). The three significant memory tests showed overlapping hazard risks for conversion to dementia (figure 3.3.1).

To test whether the verbal memory tests used in the diagnostic criteria of MCI (LM, CVLT, and VPAL) that individually had shown to accurately predict future conversion to dementia, could be combined to improve their predictive value, a multivariate Cox regression analysis was performed. In an attempt to increase the power of multivariate analysis, we reduced the number of measures in the study and selected two at maximum for each memory test. The measures not selected for the present study also showed overlapping hazard risks and did not add any further accuracy for predicting future conversion to dementia. In the multivariate Cox regression analysis only the CVLT (learning measure for the cutoff < 1.5 SD and long delayed recall for the other cutoffs) remained significant as a predictor of conversion to dementia (table 3.3.4). Non-demented patients with cognitive complaints diagnosed with MCI according to abnormal (cutoff commonly used of < 1.5 SD) learning in the CVLT had a 3.61

higher risk of becoming demented in the follow-up as compared to those who had normal learning in the CVLT (table 3.3.4).

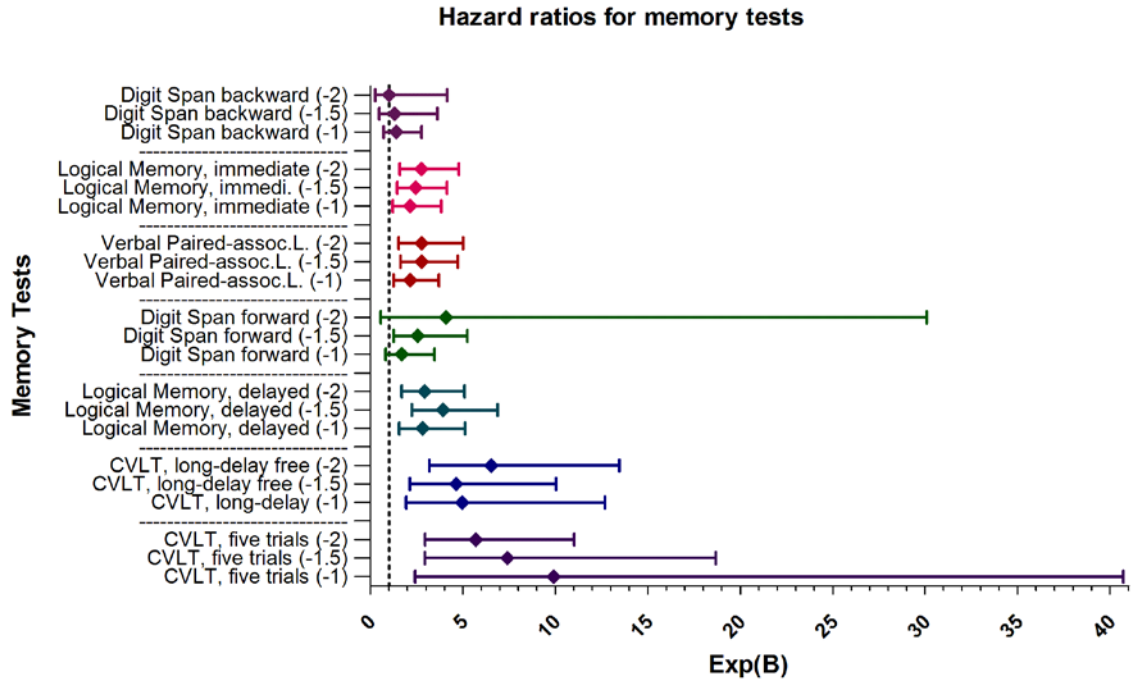

Figure 3.3.1 - Verbal memory tests and risk of progression to dementia (hazard ratios and confidence intervals from univariate Cox regression analysis).

Table 3.3.4 – Verbal memory tests and risk of progression to dementia (Multivariate Cox Regression Analysis)

			B	SE	Exp (B)	95% CI for Exp (B)	Wald statistic	*p*
-1 SD	**Logical Memory test**	Immediate recall	0.03	0.54	1.04	[0.36-2.97]	0.004	0.95
		Delayed recall	0.71	0.50	2.04	[0.77-5.44]	2.04	0.15
	California Verbal Learning test	Five learning trials	1.24	0.78	3.45	[0.75-15.91]	2.52	0.11
		Long delayed recall	1.30	0.57	3.65	[1.20-11.09]	5.22	**0.02***
	Verbal Paired-Associate Learning test		0.25	0.35	1.29	[0.65-2.55]	0.53	0.47
	Digit Span test	Forward	0.29	0.53	1.34	[0.47-3.78]	0.30	0.58
		Backwards	0.31	0.47	1.37	[0.55-3.43]	0.45	0.50
-1.5 SD	**Logical Memory test**	Immediate recall	0.03	0.43	1.03	[0.44-2.41]	0.004	0.95
		Delayed recall	0.52	0.45	1.68	[0.69-4.06]	1.31	0.25
	California Verbal Learning test	Five learning trials	1.28	0.57	3.61	[1.19-10.99]	5.12	**0.02***
		Long delayed recall	0.76	0.49	2.13	[0.81-5.60]	2.37	0.12
	Verbal Paired-Associate Learning test		0.55	0.38	1.73	[0.83-3.61]	2.12	0.15
	Digit Span test	Forward	0.92	0.53	2.51	[0.89-7.06]	3.04	0.08
		Backwards	0.60	0.75	1.82	[0.42-7.97]	0.64	0.43
-2 SD	**Logical Memory test**	Immediate recall	0.64	0.43	1.89	[0.82-4.37]	2.21	0.14
		Delayed recall	0.43	0.43	1.53	[0.66-3.58]	0.96	0.33
	California Verbal Learning test	Five learning trials	0.79	0.55	2.21	[0.75-6.54]	2.07	0.15
		Long delayed recall	1.45	0.59	4.26	[1.35-13.43]	6.11	**0.01***
	Verbal Paired-Associate Learning test		0.28	0.43	1.32	[0.57-3.05]	0.41	0.52
	Digit Span test	Forward	-8.63	408.64	<0.001	[0.00-nd]	<0.001	0.98
		Backwards	-0.07	1.03	0.94	[0.12-7.11]	0.004	0.95

* Statistically significant ($p < 0.05$).

3.3.3 Discussion

The present study shows that different verbal memory tests, LM, CVLT, and VPAL, when used in non-demented patients with cognitive complaints to establish memory impairment in the diagnosis of MCI, are not significantly different to predict the progression to dementia. However, the MCI criteria using the CVLT had the highest predictive value, which was not improved by adding other memory tests.

Although it has been argued that the use of a memory test battery offers a better sensitivity to the earlier diagnosis of MCI (de Jager and Budge, 2005), we showed that only the CVLT remains significant on the multivariate Cox regression model as a predictor of progression to dementia, and other memory tests did not significantly add to the predictive value. The assessment of verbal memory based on list learning was found to be predictive of future conversion to dementia in earlier phases, possibly due to the reduced use of learning strategies (Schrijnemaekers *et al.*, 2006). Previous studies have also suggested that list learning represents a more demanding encoding test than story recall, is more sensitive to executive dysfunction, and offers a better prediction of conversion to dementia (Rabin *et al.*, 2009; Tremont *et al.*, 2000, 2010). The higher frequency of impaired performance for CVLT at baseline highlights the demanding character of the task, indicating that it might be an early marker for cognitive decline (Blacker *et al.*, 2007).

Different measures of verbal memory tests used for the diagnosis of MCI may assess different stages of the neurodegenerative process by relying on distinct cognitive resources, so the contribution to diagnostic accuracy and predictive value is unique (Moulin *et al.*, 2004). Both measures of immediate and delayed free recall were analyzed, because there is some evidence that long-term memory is more extensively impaired in MCI patients than short-term memory and, more importantly, it has evidenced a greater sensitivity for the identification of amnestic MCI which will progress to dementia (Perri *et al.*, 2007a). Verbal memory impairment can possibly correspond to either a defective consolidation of information relying on an alteration of mesiotemporal areas, or to a difficulty in elaborative encoding and afterwards correct retrieval of information, which in this case is associated with an alteration of frontal areas. MCI patients at risk of conversion to AD are expected to present deficits in learning (encoding and storage) rather than in the retrieval process (Traykov *et al.*, 2007; Carlesimo, Perri and Caltagirone, 2011). Some verbal memory tests assess primarily the capacity of storage, and for that aim semantic cues are systematically provided during the encoding phase

in order to facilitate the retrieval process. For instance, the Free and Cued Selective Reminding Test (Buschke, 1984) assesses specifically the storage capacity of MCI patients with focus on the amnestic syndrome of the medial temporal type associated with a future progression to dementia (de Jager and Budge, 2005; Schrijnemaekers *et al.*, 2006). According to a recent review, the studies that determined the predictive value of this test for future conversion to dementia also evidenced that delayed recall measures were less sensitive and specific than immediate recall measures, supporting the hypothesis of a failure at the initial learning process (although providing semantic cues), instead of forgetting due to inadequate storage of the information (Carlesimo, Perri and Caltagirone, 2011). Other studies have shown that MCI patients at risk of conversion to dementia (namely AD) could benefit from semantic cues on the encoding phase in a similar way as normal controls, suggesting that the deficits in encoding correctly the information during the learning process, and not a difficulty in the storage process itself, would lead to retrieval impairment (Buschke, 1984; Perri *et al.*, 2005; Ribeiro, Guerreiro and de Mendonça, 2007; Sarazin *et al.*, 2007; Auriacombe *et al.*, 2010; Carlesimo, Perri and Caltagirone, 2011).

Bearing in mind the above mentioned, we decided to examine the CVLT performance for the total learning and delayed recall, which are also the measures associated with a better discrimination between normal aging, MCI, and AD (Greenaway *et al.*, 2006). Verbal learning tests were analyzed on associative (VPAL) and non-associative (CVLT) conditions in order to assess different stages of impairment progression. Deficits in associative learning tests are present in a more advanced stage of progression in MCI (Egerházi *et al.*, 2007) and, therefore, may not be the best predictors for conversion at earlier phases. Interestingly, the use of different cutoffs for CVLT impairment did not considerably modify the risk of progression to dementia, although 1.5 standard deviation below mean score for the subjects reference group has been considered the most conservative strategy for diagnosing MCI because of the greatest stability longitudinally (Petersen *et al.*, 1995; Albert *et al.*, 2001; Arnáiz *et al.*, 2004; Lopez *et al.*, 2006; Tabert *et al.*, 2006; Guarch *et al.*, 2008; Jak *et al.*, 2009; Chang *et al.*, 2010).

The present results suggest that a measure of working memory, like the DS backward, should not be used to qualify for memory impairment in the MCI diagnostic criteria, and the prediction of future conversion to dementia would be unreliable. Working memory and visuospatial ability have been proposed as functions that decline slowly in MCI patients

(Bennett *et al.*, 2002). A recent study showed that subjects presenting subjective cognitive complaints and impairment in DS might have a higher risk of future conversion to MCI but did not compare the DS predictive value to other memory tests (Kurt, Yener and Oguz, 2011).
One limitation of the present study is the focus on a restricted number of verbal memory tests commonly used in clinical practice to evaluate memory in non-demented patients with suspected cognitive decline. Clearly, it would be interesting to evaluate other memory modalities, with visual or semantic memory tests. Nevertheless, several studies showed that their diagnostic value in the identification of MCI patients at risk of conversion to dementia do not clearly overtake that of verbal episodic memory tests (Alescio-Lautier *et al.*, 2007; Ahmed *et al.*, 2008; Guarch *et al.*, 2008; Gigi *et al.*, 2010). Another limitation of the present study was that it focused on neuropsychological data, and other biomarkers were not considered. Recently, many studies have been published combining different biomarkers in non-demented subjects with cognitive complaints for predicting future conversion to dementia. Consequently, the choice of specific verbal memory tests in the neuropsychological assessment, in conjunction with other biomarkers, may be crucial to accurately predict future conversion to dementia.
In conclusion, different memory tests, namely LM, CVLT, and VPAL, can be used to establish the diagnosis of MCI and predict the progression to dementia. Considering our results, the MCI criteria using the CVLT had the highest predictive value, which was not improved by adding other memory tests, and taking into account that there are frequent limitations in clinical practice to apply an extensive neuropsychological battery to all individuals with suspected cognitive decline (Celsis, 2000), we propose that a list learning task could be the preferred test to establish memory impairment in MCI diagnosis.

3.4 Prediction of long-term (5 years) conversion to dementia using neuropsychological tests *(submitted)*

3.4.1 Rationale and Procedure

The early diagnosis of Alzheimer's disease (AD) has become very important. Many people now search for medical help when they notice subtle cognitive difficulties. The reliable identification of the patients who already have Alzheimer's disease may open new frontiers in the management of the disease, allowing interventions that might involve manipulation of risk and protection environmental factors, cognitive rehabilitation procedures, and clinical trials with putative neuroprotective drugs.

The diagnosis of Mild Cognitive Impairment (MCI), initially proposed by Petersen and colleagues (1999) as a clinical entity with a high risk of progression to Alzheimer's disease, relied on the presence of cognitive impairment, namely memory deficits. Cognitive deficits required to established MCI diagnosis were considered in a more global scope in the revised criteria of MCI proposed by Portet and colleagues (2006), however cognitive impairment assessed through neuropsychological testing remained an indispensable condition for diagnosis. Likewise, the most recent criteria for early diagnosis of Alzheimer's disease, namely prodromal AD (Dubois *et al.*, 2007) and mild cognitive impairment due to Alzheimer's disease (Albert *et al.*, 2011) still include the presence of cognitive impairment in the core diagnostic criteria. Thus, in spite of the advances in the development of novel imaging and biochemical biomarkers, the demonstration of cognitive impairment using neuropsychological tests remains a core feature for the early detection of AD. Importantly, neuropsychological assessment is more widely available and rather inexpensive in comparison to the novel research biomarkers. Moreover, recent studies have shown that cognitive markers can provide predictive values for future conversion to dementia as accurate as brain volumetric or CSF biomarkers (Schmand, Huizenga and Van Gool, 2010; Palmqvist *et al.*, 2012).

Significant advances have been gathered to determine the first cognitive alterations and temporal onset of cognitive decline in the early phases of AD. Longitudinal studies based on large epidemiological cohorts followed-up for decades have evidenced the stability of

cognitive performance in the oldest who did not progress to AD, supporting the consideration that cognitive decline is not an inevitable consequence of old age, and suggesting a greater risk of conversion to AD for those that have experienced gradual cognitive impairment in the previous years (Wilson *et al.*, 2011; Amieva *et al.*, 2008; Johnson *et al.*, 2009). Thus, by the time clinical criteria for AD diagnosis is met, the person has already experienced many years of aggravating cognitive impairment.

Even so, the use of neuropsychological tests to detect the initial phases of cognitive decline in AD still has significant limitations that should be improved. In first place, decline in cognitive functions is known to occur earlier in some cognitive domains than in others (Johnson *et al.*, 2009; Grober *et al.*, 2008), reflecting the evolving neurodegenerative progress, but there is still no consensus about which neuropsychological tests should be selected to assess these domains, as well as the most appropriate cut-off to use (De Santi *et al.*, 2008; Schink *et al.*, 2010; Silva *et al.*, 2012) to pinpoint the initial process of decline.

In second place, most studies published so far were cross-sectional, or longitudinal with relatively short follow-up periods (Flicker, Ferris and Reisberg, 1991; Tierney *et al.*, 1996; Devanand *et al.*, 1997; Kluger *et al.*, 1999; de Jager, Milwain and Budge, 2002; Tian *et al.*, 2003; Amieva *et al.*, 2004; Atchison, Bradshaw and Massman, 2004; Lehrner *et al.*, 2005; Blacker *et al.*, 2007; Mickes *et al.*, 2007; Carter *et al.*, 2012; Johnson *et al.*, 2012a). The importance of conducting longitudinal studies with longer follow-up periods should be emphasised. As an example, in the large ADNI cohort, using neuropsychological as well as extensive brain imaging and CSF neurochemical biomarkers, a predictive accuracy for MCI conversion to dementia of only 64% was obtained (Ewers *et al.*, 2012). This is not surprising, since the average follow-up was 2.3 years, and presumably many converters just had not the time to progress to dementia. A follow-up period of 2 or 3 years may not be enough and longer follow-ups are needed to provide reliable and clinically significant predictive values in patients with memory complaints (Stephan *et al.*, 2010; Ewers *et al.*, 2012).

We believe that, to be clinically meaningful, the clinical and neuropsychological evaluation must predict the outcome, in this case dementia, at long term, namely 5 years. Therefore, the aim of the present study is to assess the predictive value for future conversion to dementia of a comprehensive neuropsychological battery applied to a cohort of non-demented patients followed-up for more than 5 years (if patients have not converted to dementia earlier).

Research Participants

Participants were selected from the Cognitive Complaints Cohort (CCC; Maroco *et al.*, 2011; Silva *et al.*, 2012), which is a prospective study conducted at the Institute of Molecular Medicine, Lisbon, to investigate the cognitive stability or evolution to dementia of subjects with cognitive complaints based on a comprehensive neuropsychological evaluation and other biomarkers. The study was approved by the local ethics committee.

Inclusion Criteria:

(1) Subjective complaints of cognitive deficits;

(2) Cognitive assessment with a comprehensive neuropsychological battery;

(3) Follow-up ≥ 5 years or conversion to dementia.

Exclusion criteria:

(1) Presence of neurological or psychiatric disorders that may induce cognitive deficits; patients with major depression according to DSM-IV-TR (APA, 2000) or serious depressive symptoms (indicated by a score in Geriatric Depression Scale short version (GDS 15; Barreto *et al.*, 2008) of more than 10 points) were excluded;

(2) Systemic illness with cerebral impact;

(3) History of alcohol abuse or recurrent substance abuse or dependence;

(4) Presence of dementia according to DSM-IV-TR (APA, 2000) or significant impairment on daily life activities detected by the presence of a score ≥ 3 on the first part (items 1-8) of the Blessed Dementia Rating Scale (Ribeiro, de Mendonça and Guerreiro, 2006).

Procedures

The baseline comprehensive neuropsychological assessment was carried out by the same team of trained neuropsychologists, supervised by M.G., following a standard protocol and comprised several tests and scales:

(1) Battery of Lisbon for the Assessment of Dementia (BLAD) (Garcia, 1984; Guerreiro, 1998) – the BLAD is a comprehensive neuropsychological battery evaluating multiple

cognitive domains and validated for the Portuguese population. This battery includes tests for the following cognitive domains: attention (Cancellation Task); verbal initiative (Semantic Fluency), motor and graphomotor initiatives; verbal comprehension (a modified version of the Token Test); verbal and non-verbal abstraction (Interpretation of Proverbs and the Raven Progressive Matrices – Ab series-B); orientation (personal, spatial and temporal); visuo-constructional abilities (Cube Copy); planning and visuospatial/praxis abilities(Clock Draw); calculation (Basic Written Calculation); immediate memory (Digit Span forward); visual memory (Visual Reproduction test); working memory (Digit Span backward); learning and verbal memory (Verbal Paired-associate Learning, Logical Memory and Word Recall);

(2) Blessed Dementia Rating Scale (BDRS; Blessed, Tomlinson and Roth, 1968; Garcia, 2008) – the BDRS is a brief behavioural scale based on the interview of a close informant; the first part of the scale refers to daily life activities, the second part to habits and the third part to changes in personality;

(3) Geriatric Depression Scale (GDS; Yesavage *et al.*, 1983; Sheikh and Yesavage, 1986; Barreto *et al.*, 2008) – the GDS is a self-report assessment used specifically to identify depression in the elderly. For this study a short-form (15 items) of the self-report instrument was used.

Outcome

Patients were assessed at follow-up and the outcome established. The diagnosis of dementia and Alzheimer's disease was established according to the DSM-IV-TR (APA, 2000) criteria, in a consensus meeting with the neurologist and the neuropsychologists.

Data analysis

Demographic, clinical and neuropsychological data were analysed using independent samples Student's *t* test for numerical data and $\chi 2$ Pearson Chi-Square test for nominal data. All tests were 2-tailed and a probability value of <0.05 was assumed as statistically significant.

The neuropsychological assessments were standardized according to the age and education norms for the Portuguese population, *z* scores were calculated and the presence of impairment on cognitive tests was established for a cut-off 1.5 SD below the mean.

To determine the value of neuropsychological tests to predict long term (5 years) conversion to dementia, a Linear Discriminant Analysis (LDA) classificatory model was used, since this

traditional classifier ranked high among several traditional and data mining classifiers for prediction of dementia in a previous study (Maroco *et al.*, 2011). A binary classification function (converters vs. non-converters) was built from the stepwise LDA to analyse sensitivity, specificity, accuracy and area under the ROC curve for prediction of long-term conversion to dementia. Equal *a priori* classification probabilities were used for Linear Discriminant Analysis to avoid biases from the data sets. A 5-fold cross-validation strategy was followed to assess the model against a set of data that was not used to create the model. The total sample was randomly divided into 5 proportional sub-samples. In each of the 5 steps, 4/5 of the sample was used for training and 1/5 for testing. Mean values of the 5 test samples were considered for further comparisons. In all neuropsychological tests the proportion of missing data was generally low and tolerable, i.e. < 10%, with the exception for Visual Reproduction test (55.6%). LDA was first performed with all neuropsychological tests more impaired in converters than in non-converters using a stepwise method to ascertain if the presence of Visual Reproduction test would affect significantly the classificatory function model, but this test did not impact the final model and because of the elevated rate of missing values it was excluded from further analysis. The Logical Memory delayed recall revealed considerable collinearity with Logical Memory immediate recall (r=0.676), and for that reason the Forgetting Index, a measure that assesses the rate of forgetting between immediate and delayed condition, was used instead of Logical Memory delayed recall. Besides, Forgetting Index can be preferable since it is a measure of information encoded but not retrieved after a long delay period, while Logical Memory delayed recall represents the total of information retrieved regardless to whether information was successfully encoded before.
Statistical analyses were performed using IBM SPSS Statistics 19 for Windows (2010 SPSS Inc., an IBM Company) package.

3.4.2 Results

From the CCC cohort of 568 non-demented patients with cognitive complaints referred for neuropsychological examination, 250 cases followed for at least 5 years (or until conversion to dementia) were selected. During the follow-up period (2.6±1.8 years for converters and 6.1±2.1 for non converters), 162 patients (64.8%) progressed to dementia, and 88 (35.2%) did not. Most cases that progressed to dementia were diagnosed as Alzheimer's disease (93.2%).

Demographic and clinical data are reported in Table 3.4.1. The converters at the baseline assessment were older than the non-converters and were more affected functionally (Table 3.4.1).

Table 3.4.1 – Baseline demographic and clinical characterization data

	Converters (n=162)	**Non-converters (n=88)**	***p*-value**
Age, years, mean (SD)	71.0 (8.4)	65.8 (9.0)	**<0.001**[*]
Gender, female/male, n	106/56	57/31	1.000[#]
Formal education, years, mean (SD)	8.5 (4.8)	9.5 (4.6)	0.103
Follow-up time, years, mean (SD)	2.6 (1.8)	6.1 (2.1)	**<0.001**[*]
Geriatric Depression Scale, mean (SD)	5.8 (3.8)	5.6 (4.9)	0.848
Blessed Dementia Scale, mean (SD)	3.8 (2.1)	2.5 (2.0)	**0.002**[*]

Group comparisons were performed with independent samples *t*-tests (or χ^2 Pearson Chi-Square test when appropriate[#]); [*]Statistically significant ($p< 0.05$)

Table 3.4.2 – Baseline neuropsychological performances of converters and non-converters to dementia**.**

Cognitive Domain Neuropsychological Tests	**Converters (n=162)** mean (SD)	**Non-converters (n=88)** mean (SD)	***p* – value**
Attention and Executive Functions			
Cancellation Task	-0.07 (1.24)	0.46 (1.37)	**0.003**[*]
Digit Span Backward	-0.05 (1.03)	0.29 (0.98)	**0.013**[*]
Clock Draw	0.43 (1.03)	0.69 (0.67)	**0.020**[*]
Initiative			
Verbal Semantic Fluency	-0.89 (1.44)	0.39 (1.53)	**<0.001**[*]
Motor Initiative	-0.22 (1.54)	-0.19 (1.55)	0.870
Graphomotor Initiative	-0.18 (0.88)	0.23 (0.61)	**<0.001**[*]
Conceptual Thinking			
Raven Progressive Matrices	-0.50 (1.15)	0.32 (0.99)	**<0.001**[*]
Interpretation of Proverbs	0.35 (1.13)	0.84 (1.22)	**0.002**[*]
Orientation			
Personal, spatial and temporal	-2.70 (2.26)	-0.58 (1.81)	**<0.001**[*]

Means of *z* scores, calculated according to the equation [*z*= (x-mean)/SD]; Group comparisons were performed with independent samples *t*-tests; [*]Statistically significant ($p< 0.05$)

Converters scored at baseline lower than non-converters for all the neuropsychological tests administered with the exception of Motor Initiative, Basic Written Calculation, Token test and Digit Span forward (Table 3.4.2).

Table 3.4.2 (cont.) – Baseline neuropsychological performances of converters and non-converters to dementia.

Cognitive Domain Neuropsychological Tests	**Converters (n=162)** mean (SD)	**Non-converters (n=88)** mean (SD)	***p* – value**
Calculation			
Basic Written Calculation	-0.34 (1.31)	-0.10 (0.94)	0.116
Visuo-constructional Abilities			
Cube Copy	-0.05 (1.37)	0.54 (1.11)	**0.001***
Language			
Token Test	-0.47 (1.60)	-0.14 (1.42)	0.107
Memory and Learning			
Visual Reproduction	0.14 (1.17)	0.88 (1.45)	**0.004***
Digit Span Forward	-0.39 (0.71)	-0.27 (0.50)	0.134
Word Recall	-1.65 (1.35)	-0.82 (1.14)	**<0.001***
Logical Memory (immediate recall)	-2.04 (1.09)	-0.63 (1.31)	**<0.001***
Logical Memory (delayed recall)	-2.71 (1.42)	-0.69 (1.53)	**<0.001***
(1)Forgetting Index	-1.98 (2.50)	-0.23 (2.10)	**<0.001***
Verbal Paired-associate Learning	-1.73 (1.05)	-0.65 (1.10)	**<0.001***

Means of *z* scores, calculated according to the equation [*z*= (x-mean)/SD]; Group comparisons were performed with independent samples *t*-tests; *Statistically significant ($p< 0.05$); (1)Forgetting Index = [(LM delayed recall – LM immediate) / LM immediate)]*100.

To determine the value of neuropsychological tests to predict long term (5 years) conversion to dementia Linear Discriminant Analysis (LDA) was performed. The Wilks' λ test indicated that the discriminant model constituted by four measures, Digit Span backward, Semantic Fluency, Logical Memory (immediate recall) and Forgetting Index, was significant (λ Wilks=0.64; $\chi 2(4)=81.95$; $p<0.001$; RCanonical=0.60). Logical Memory (immediate recall) was the strongest predictor with a standardized canonical discriminant function coefficient of 0.70 (Table 3.4.3). The cross-validated classification showed that overall 78.6% were correctly classified. The LDA classificatory model showed good sensitivity and specificity

(78.8% and 79.9%, respectively) of the neuropsychological tests to predict long-term conversion to dementia (Table 3.4.4).

Table 3.4.3 – Neuropsychological tests contribution to the discrimination of converters and non-converters to predict long-term (5 years) dementia.

	$\beta^{\ddagger}$	Wilks' λ	$F^{\dagger}$	*p*-value*
Executive Functions				
Digit Span Backward	0.36	0.97	6.1	**0.027***
Initiative				
Semantic Fluency	0.38	0.86	30.0	**<0.001***
Episodic Memory				
Logical Memory (immediate recall)	0.70	0.76	59.2	**<0.001***
Forgetting Index	0.39	0.89	23.4	**<0.001***

‡Standardized canonical discriminant function coefficients; †Wilks' lambda ANOVA (F) test of mean differences for independent variables; *Statistically significant (p<0.05).

Table 3.4.4 – Accuracy, sensitivity, specificity and discriminant power of the neuropsychological evaluation to predict long-term (5 years) dementia.

	Linear Discriminant Function	
	Mean	SEM
Sensitivity (%)	78.8	3.7
Specificity (%)	79.9	6.6
Accuracy (%)	78.6	1.5
Area under the ROC curve (AUC)	0.79	0.02

3.4.3 Discussion

In the present study, a comprehensive battery of neuropsychological tests was applied to a cohort of non-demented patients with cognitive complaints followed for at least 5 years, to discriminate the patients converting to dementia from those who remain cognitively stable for a long time. The main finding is that neuropsychological tests predict long-term (5 years)

conversion to dementia with high rates of sensitivity, specificity and accuracy (approximately 80%).

The classificatory model also identified the neuropsychological tests that were the best predictors to discriminate between converters and non-converters. The Logical Memory test (immediate recall and rate of forgetting) (Wechsler, 1945/1997) was the most predictive of long-term conversion to dementia. Episodic memory, especially the consolidation of memory traces, was proposed to decline early in the neurodegenerative process, representing a neuropsychological correlate of the neuropathological changes that begin in the temporal areas, namely, hippocampal formation and the entorhinal cortex (Reed *et al.*, 2007; Amieva *et al.*, 2008; Devanand *et al.*, 2012). Several previous studies have shown that verbal memory tasks are among the best measures to predict future conversion to dementia (Flicker, Ferris and Reisberg, 1991; Tabert *et al.*, 2006; Sarazin *et al.*, 2007; Grober *et al.*, 2010). Accordingly, the Dubois' work group (Dubois *et al.* 2007) proposed the use of episodic memory impairment as the core of diagnostic criteria for prodromal AD. A previous study showed that not only Logical Memory, but also other verbal memory tests, namely Verbal Paired-Associate Learning, California Verbal Learning Test (CVLT) and Digit Span, could predict the conversion to dementia, and in a multivariate analysis combining the four memory tests only the CVLT test remained significant as a predictor of conversion to dementia (Silva *et al.*, 2012). It is possible that the use of more extensive or complex assessments of verbal memory, like the CVLT (Delis *et al.*, 1987) or the Grober-Buschke paradigm (Grober and Buschke, 1987) could improve further the predictive value of the Logical Memory test observed in the present study. Nevertheless, it should be noted that the Logical Memory test is relatively short to apply, and it allows the assessment of specific memory components affected in patients at risk for dementia, namely the forgetting index evaluates the information successfully encoded, but lost in delayed recall and not recovered with the cued condition. A further remark is that, although the converters showed worse performance than the non-converters at baseline in almost all neuropsychological tests, as found in previous studies (Fabrigoule *et al.*, 1998; Tabert *et al.*, 2006; Sarazin *et al.*, 2007; Jungwirth *et al.*, 2009), however the converters performed below the normative values (cut-off <1.5 standard deviations) only on the tests of verbal memory as well as orientation, which also relies heavily on memory resources.

Even though episodic memory has a well-established contribution in the prediction of future conversion to dementia, it is still important to assess the cognitive profile through a comprehensive neuropsychological battery to have a global understanding of cognitive performance and be able to predict more accurately future conversion (Johnson *et al.*, 2009; Wilson *et al.*, 2011). Manly and colleagues (2008) found that patients with impairment on at least one other non-amnestic domain besides the deficits in verbal memory, were about 4 times more prone to develop AD. In the present study, verbal initiative and working memory, assessed through Semantic Fluency and Digit Span backwards tests, contributed significantly to the classificatory model of progression to dementia. Impaired working memory tasks rely on executive functions and were found to be predictive of future decline in MCI patients (Gagnon and Bellevile, 2011). Neuronal loss is observed in the anterior cingulate in the initial phases of AD and may contribute to the executive function deficits (Baddeley *et al.*, 1986; Lafleche and Albert, 1995; Traykov *et al.*, 2007; Thillainadesan *et al.*, 2012). Fluency tasks were described as involving executive control, however tasks without a switching or shifting component, like the present task of Semantic Fluency, are more dependent of semantic knowledge, recruit brain regions (e.g., inferior frontal regions) involved in semantic memory processing and are known to be impaired in amnestic MCI (Nutter-Upham *et al.*, 2008). This semantic impairment evolves and affects more semantic abilities as the disease progresses until the dysfunction of temporoparietal-frontal-cingulate network seen in mild AD (Corbett *et al.*, 2012). Despite the contribution of executive functions for the classificatory model, with the Semantic Fluency and Digit Span backwards, scores of these tests observed at baseline were not clearly impaired, even in the converters, considering impairment as 1.5 SD below the mean score for the subjects reference group (matching age and formal education).

Cohort studies of cognitively impaired subjects have reported rather disparate global sensitivity and specificity values for the neuropsychological tests to predict conversion to dementia (Devanand *et al.*, 1997; Sarazin *et al.*, 2007; Rabin *et al.*, 2009; Gallagher *et al.*, 2010). Some studies reported high and balanced sensitivity/specificity ratios (≥80%), mainly for verbal episodic memory tests, and also for verbal initiative and executive functions tests, however the follow-up period of those studies was generally short (≈2 years) (Flicker, Ferris and Reisberg, 1991; Lehrner *et al.*, 2005; Landau *et al.*, 2010; Aretouli *et al.*, 2011). The present study shows that it is possible to obtain high rates of sensitivity, specificity and accuracy (approximately 80%) for the neuropsychological tests for long-term (5 years)

conversion to dementia. This value, 80%, has been the recommended cut-off for molecular and biochemical markers (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and, National Institute on Aging Working Group, 1998).

One of the strengths of the present study is the length of follow-up, since the patients were followed until they were clinically stable for at least 5 years, or converted to dementia. Other important point is the large sample size. The methodological option that patients did not necessarily meet criteria for MCI at the baseline is also an advantage, since there are differences in the available criteria for diagnosis of MCI, and more importantly, elderly patients with cognitive complaints may not fulfil the MCI criteria and nevertheless evolve to dementia (Nunes *et al.*, 2010). Another positive point is that a rather extensive neuropsychological battery was administered, encompassing distinct cognitive domains.

A couple of limitations also warrant consideration. Converters evidenced more functional difficulties than non-converters according to Blessed Rating Scale information at baseline, however they were not demented, both from the clinical criteria and the functional evaluation point of view. Another limitation is that other biomarkers were not included in the present study, which actually focused on the clinical and neuropsychological markers of progression to dementia.

It should be acknowledged that imaging and biochemical research biomarkers represent a major advance in the field. However, since they are very expensive and in some cases invasive, it is not reasonable that they might be offered to all patients with cognitive complaints. On the other hand, it is not expected that new treatments that are presently being tested, like those impacting on beta-amyloid, will be as unexpensive and safe as to be used broadly in patients with cognitive complaints. From a clinical point of view, it is essential to determine, on the basis of an initial clinical and neuropsychological evaluation, whether non-demented patients with cognitive complaints will probably convert to dementia, or remain stable, at a reasonably long and clinically relevant term. The present work shows that neuropsychological tests can predict long-term (5 years) conversion to dementia with high rates of sensitivity, specificity and accuracy (approximately 80%). It remains to be investigated whether the use of advanced classification methods, adding more sophisticated tests, or the combination with selective biomarkers, can improve the long-term predictive value of the clinical and neuropsychological evaluation in patients with cognitive complaints.

PART IV – DISCUSSION AND FINAL CONCLUSIONS

Cognitive impairment is present in Alzheimer's disease (AD) patients several years preceding a clinical diagnosis, reflecting the onset and progressive dissemination of the pathophysiological process associated to the disease. Neuropsychological assessment should offer an important contribution for the early diagnosis of the dementing disorder but also to determine a profile that unveils its cause.

Novel biomarkers emerged in the last decade due to advances in biochemical methods to assess the cerebrospinal fluid and sophisticated brain imaging techniques, however cognitive measures remain the most accessible, inexpensive and maybe accurately predictive marker of progression to dementia. Notwithstanding biomarkers represent a major advance in the field; it is not reasonable to believe that they could be offered to all patients with cognitive complaints. On the other hand, it is not expected that new treatments that are presently being tested, like those impacting on beta-amyloid, will be as inexpensive and safe as to be used broadly in patients with cognitive complaints. More studies addressing the improvement of predictive accuracy for neuropsychological tests are needed to screen more accurately the population with subjective cognitive complaints at risk for future progression to dementia. Such a tool would make the use of other biomarkers more efficient since they could be focused on those subjects with higher probability of having preclinical AD.

The aim of the present thesis was to improve the predictive value of neuropsychological assessment to foresee future conversion to dementia. For that purpose we defined four tasks.

The first was a review of literature that could synthesize the longitudinal studies focusing on the predictive value of neuropsychological assessment for future conversion to dementia. This work allowed us to identify limitations and to propose future work, namely the head-to-head comparison of neuropsychological tests, particularly in the core memory domain, consideration of different cut-offs, and the importance of looking at longer follow-up periods.

In the second task, we sought to determine the statistical classificatory method more suitable to the characteristics of cohorts recruiting patients with cognitive complaints. We found that Random Forests and Linear Discriminant Analysis were the best classifiers, the latter having the advantage of simplicity.

Thirdly, we compared the contribution of four commonly used verbal memory tests in the Mild Cognitive Impairment (MCI) diagnostic criteria to predict conversion to dementia. We found that these verbal memory tests were valuable to establish the diagnosis of MCI and

predict the progression to dementia, however the California Verbal Learning Test had the highest predictive value, which was not improved by adding other memory tests.

Finally, we studied a subset of the CCC cohort followed for at least 5 years, to overcome the bias of the converters that are censored prematurely, applying the best statistical classificatory method previously obtained. We found that the neuropsychological tests can predict conversion to dementia with high rates of sensitivity, specificity and accuracy (approximately 80%), at a long and clinically relevant term (5 years).

Nowadays, clinicians have to reconcile assistance to a large number of patients with cognitive complaints, novel expensive diagnostic techniques, promising disease-modifying treatments, and marked financial constraints. Therefore, it is crucial to assess as early as possible whether patients have a low probability of progression to dementia, in which case a regular follow-up and general preventive measures might be indicated, or a high probability of progression to dementia, so that the patient could undergo complex ancillary examinations and new disease-modifying treatments.

We have gone a long way, since the recognition of obvious cognitive decline in ancient times, to the description of a particular form of dementia by Alois Alzheimer, and to the present revolutionary understanding of the disease. Interestingly, the importance of the cognitive symptoms remained, in the sharp observations of Maximianus, in the talented clinical notes of Alois Alzheimer, and in the present effort to use better neuropsychological tests. This is because the loss of mental abilities is what matters most in the disease, and indeed frightens us all.

PART V – ANNEX

Table 5.1 Criteria for Mild Cognitive Impairment (MCI) according to Petersen and colleagues (1997; 1999) and NIA-AA (2011)

Petersen *et al.* (1997; 1999):

- Memory complaint, preferably corroborated by an informant;
- Objective memory impairment for age;
- Normal general cognitive function;
- Intact activities of daily living;
- Not demented.

Diagnosis of mild cognitive impairment due to Alzheimer's disease (NIA-AA, 2011) - Recommendations from the National Institute on Aging-Alzheimer's Association workgroups (Albert *et al.*, 2011)

- Presence of lower performance in one or more cognitive domains greater than would be expected for the patient's age and educational background (1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data);
- Presence of impairment in episodic memory (i.e., the ability to learn and retain new information) as associated to MCI patients who subsequently progress to a diagnosis of AD dementia (e.g. assessed by word-list learning tests with multiple trials that revealed the rate of learning over time, as well as the maximum amount acquired over the course of the learning trials, but also assessed the capacity of paying attention to the task on immediate recall, and the relative amount of material retained on delayed recall; other possible measure might be episodic memory, and complementary assessment domains such as executive functions (e.g., set-shifting, reasoning, problem-solving, planning), language (e.g., naming, fluency, expressive speech, and comprehension), visuospatial skills, and attentional control (e.g., simple and divided attention);
- If possible, follow-up with neuropsychological re-assessments should be conducted to confirm a decline in performance over time;
- Information concerning independence in daily life activities should revealed the need for minimal aids or assistance, however, performance in instrumental activities of daily living are expected to take more time and to be executed with more errors than in the past;

And obviously, MCI patient should not be demented.

To meet the core clinical criteria for MCI it is necessary to rule out other systemic or brain diseases that could account for the decline in cognition (e.g., vascular, traumatic, medical). If MCI patients presented an autosomal dominant form of AD (i.e., mutation in APP, PSEN1, PSEN2) or were APOE ε4 positive clearly would be more prone to progress to AD dementia.

Table 5.2 Criteria for diagnosis Alzheimer's disease according to: NINCDS-ADRDA, DSM-IV-TR, ICD-10, and NIA-AA, 2011

NINCDS-ADRDA Criteria to define Alzheimer's disease (McKhann *et al.*, 1984)

Definitive Diagnosis AD

- Clinical criteria for probable AD;
- Histopathological evidence from biopsy or autopsy.

Probable AD:

- Dementia established by clinical examination, documented by MMSE (Mini-Mental Status Examination) or equivalent and confirmed by neuropsychological tests;
- Deficits in two or more areas of cognition;
- Progressive worsening of memory and other cognitive functions;
- No disturbance of consciousness;
- Onset between ages 40 and 90, most often > 65;
- Absence of systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition.

Possible AD

- Dementia syndrome without any other neurologic, psychiatric or systemic disorders that could cause dementia, in the presence of variations in the onset, presentation, and clinical course;

Dementia syndrome in the presence of a second systemic or brain disorder capable of causing dementia but not considered to be responsible for the present symptoms.

DSM-IV-TR criteria (APA, 2000)

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information).

2. One (or more) of the following cognitive disturbances:

a. Aphasia (language disturbance).

b. Apraxia (impaired ability to carry out motor activities despite intact motor function.

c. Agnosia (failure to recognize or identify objects despite intact sensory function).

d. Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting).

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

1. Other central nervous systems, conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor).

2. Systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, neurosyphilis, HIV infection).

3. Substance-induced conditions.

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another disorder (e.g., major depressive disorder, schizophrenia).

ICD-10 criteria (WHO, 1992)

F00 - F09 Dementia – Evidence of each of the following:

- A decline in memory, which is most evident in the learning of new information, although in more severe cases, the recall of previously learned information may be also affected. The impairment applies to both verbal and non-verbal material and should have been present for at least six months for a confident clinical diagnosis. The decline should be objectively verified by obtaining a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments;
- A decline in other cognitive abilities characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information. Evidence for this should be obtained when possible from interviewing an informant, supplemented, if possible, by neuropsychological tests or quantified objective assessments. Deterioration from a previously higher level of performance should be established;
- Preserved awarenenss of the environment (i.e. absence of clouding of consciousness during a period of time long enough to enable the unequivocal demonstration of memory decline. When there are superimposed episodes of delirium the diagnosis of dementia should be deferred;
- A decline in emotional control or motivation, or a change in social behaviour, manifest as at least one of the following: emotional lability, irritability, apathy, and coarsening of social behaviour.

F00 – Dementia in Alzheimer's disease:

- The general criteria for dementia (see row above) must be met;
- There is no evidence from the history, physical examination or special investigations for any other possible cause of dementia (e.g. cerebrovascular disease, Parkinson's disease, Huntington's disease, normal pressure hydrocephalus), a sysytemic disorder (e.g. hypothyroidism, vit. B12 or folic acid deficiency, hypercalcaemia), or alcohol- or drug-abuse.

The diagnosis is confirmed by post mortem evidence of neurofibrillary tangles and neuritic plaques in excess of those found in normal ageing of the brain.

The following features support the diagnosis, but are not necessary elements: Involvement of cortical functions as evidenced by aphasia, agnosia or apraxia; decrease of motivation and drive, leading to apathy and lack of spontaneity; irritability and disinhibition of social behaviour; evidence from special investigations that there is cerebral atrophy, particularly if this can be shown to be increasing over time. In severe cases there may be Parkinson-like extrapyramidal changes, logoclonia, and epileptic fits.

Diagnosis of dementia due to Alzheimer's disease (NIA-AA, 2011) - Recommendations from the National Institute on Aging-Alzheimer's Association workgroups (McKhann et al., 2011)

Probable AD dementia[1] with increased level of certainty:

- Probable AD dementia with documented decline;
- Probable AD dementia in a carrier of a causative AD genetic mutation (causative genetic mutation in APP, PSEN1, or PSEN2).

Probable AD dementia[1]:

- Meets the criteria for all-cause dementia*;
- Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
- Clear-cut history of worsening of cognition by report or observation;

Initial and most prominent cognitive deficits can be amnestic or nonamnestic.

Possible AD dementia:

Atypical course - Evidence of the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either with a sudden onset of cognitive impairment or with insufficient historical detail or objective cognitive documentation of progressive decline;

Aetiologically mixed presentation - all core clinical criteria for AD dementia but has evidence of at least one of the following conditions:

- Concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment;
- The presence of multiple or extensive infarcts or severe white matter hyperintensity burden;
- Features of Dementia with Lewy bodies other than the dementia itself;
- Evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

[1]The diagnosis of probable AD dementia should **not be applied** when there is evidence of one of the following conditions:

- substantial concomitant cerebrovascular disease, defined
- by a history of a stroke temporally related to the onset or worsening of
- cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden;
- core features of Dementia with Lewy bodies other than dementia itself;
- prominent features of behavioral variant frontotemporal dementia;
- prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia;
- evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

*All-cause dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that: interfere with the ability to function at work or at usual activities; and represent a decline from previous levels of functioning and performing; and are not explained by delirium or major psychiatric disorder; cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis. The cognitive or behavioral impairment involves a minimum of two of the following domains: impaired ability to acquire and remember new information; impaired reasoning and handling of complex tasks, poor judgment; impaired visuospatial abilities; impaired language functions; changes in personality, behavior, or comportment.

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