UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA DE LISBOA

Neuropsychological contribution to the study of White Matter Changes:

a 10-year longitudinal study

Sofia Ribeiro Esperança Silva Madureira

Orientador: Prof. Doutor José Manuel Morão Cabral Ferro

Tese especialmente elaborada para a obtenção do grau de Doutor em Ciências e Tecnologias da Saúde, especialidade de Desenvolvimento Social e Humano

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- Madureira S, Verdelho A, Moleiro C, Ferro JM, Erkinjuntti T, Jokinen H, Pantoni L, Fazekas F, Van der Flier W, Visser M, Waldemar G, Wallin A, Hennerici M, Inzitari D (2010). Neuropsychological Predictors of Dementia in a Three-Year Follow-Up Period: Data from the LADIS Study. *Dementia and Geriatric Cognitive Disorders*, 29(4), 325-334

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Resumo em português

Contributo da neuropsicologia para o estudo das alterações da substância branca: um estudo longitudinal a 10 anos

A melhoria da saúde e da qualidade de vida constitui um objetivo final de muita da investigação que é realizada nas mais variadas áreas e domínios científicos na atualidade, com implicações que abrangem aspetos tão diversos como os impactos económicos e o desenvolvimento de políticas públicas e sociais. O envelhecimento da população constitui um dos pilares das abordagens de inovação de cuidados de saúde, já que a diminuição das taxas de natalidade e o aumento da esperança média de vida se têm revelado vetores demográficos importantes com consequências nos cuidados de saúde. Com efeito, o envelhecimento, acompanhado com o aumento de doenças crónicas e doenças degenerativas, coloca exigências acrescidas quer na prestação de cuidados formais de saúde, quer de cuidados informais.

A presente investigação enquadra-se neste contexto, inserindo-se num projeto longitudinal multinacional de carácter descritivo - o estudo LADIS (*Leukoaraiosis and Disability Study*) financiado pela União Europeia através do 5º Programa Quadro '*Quality of life and management of living resources*'. Este projeto procurou investigar o significado clínico das alterações da substância branca cerebral (ASBC) associadas à idade, em particular, o seu papel enquanto preditor independente da transição para a incapacidade, numa amostra de 639 pessoas funcionalmente independentes, de idade avançada. O estudo envolveu 11 centros Europeus (Amsterdão, Copenhaga, Florença, Graz, Göteborg, Lisboa, Helsínquia, Huddinge, Mannheim, Newcastle, Paris), que constituíram uma rede de colaboração em 2000, para a investigação em 6 domínios: (1) metodologia, (2) incapacidade, (3) neuro-imagem, (4) cognição, (5) humor, e (6) motor. Os participantes eram (i) pessoas com idade igual ou superior a 65 anos; (ii) com ASBC de qualquer grau (Escala de Fazekas, versão revista), avaliada por Ressonância Magnética (RM) e (iii) ausência de incapacidade funcional (nenhum ou apenas um item alterado nas atividades de vida diária, avaliadas pela Escala de Lawton); (iv) existindo um/a informante regular contactável e (v) detendo capacidade de consentimento informado para a participação no estudo. Critérios

de exclusão incluíram a existência de doença grave (hepática, cardíaca, renal, oncológica, neurológica, ou imunológica, ou qualquer outra doença sistémica), presença de doença mental grave, ou contra-indicações para estudo com RM. Uma extensa avaliação clínica, funcional, motora e neuropsicológica ocorreu no início do projeto (*baseline*) e anualmente até o final de um período de 3 anos. A sub-amostra investigada no centro de Lisboa (N=66) foi, posteriormente, avaliada num *follow-up* de longo prazo (10 anos), sendo nessa altura submetida a uma avaliação clínica, neuropsicológica, e de imagem (RM) com a mesma metodologia. Foram também avaliados os cuidadores informais daqueles participantes que, no período de 10 anos, se encontravam dependentes em algum grau.

Deste modo, o presente trabalho insere-se no domínio do estudo longitudinal do desempenho cognitivo, no âmbito de um projeto internacional, tendo os seguintes objetivos principais:

1. Avaliar o grau em que as alterações da substância branca relacionadas com a idade influenciam o desempenho cognitivo e determinar quais os domínios mais afetados e que constituem um preditor independente da transição do funcionamento autónomo e saudável para a incapacidade funcional relacionada com o declínio cognitivo e demência, numa população idosa, num período de seguimento de médio (3 anos) e longo prazo (10 anos);

2. Testar o efeito da transição para a dependência na sobrecarga dos cuidadores informais, explorando os seus processos de *coping.*

Considerando estes objetivos, exploramos as seguintes hipóteses:

1. a) Uma bateria neuropsicológica adequada é capaz de diferenciar o desempenho cognitivo de indivíduos idosos independentes com alterações da substância branca de diferente gravidade, tendo em conta variáveis demográficas específicas (idade e educação);

1. b) Défices cognitivos subtis são identificáveis no desempenho cognitivo global numa população de idosos independentes com alterações da substância branca, enquanto preditores de demência a médio prazo (período de 3 anos).

1. c) Uma bateria neuropsicológica adequada permite identificar diferentes perfis de desempenho cognitivo numa evolução a longo prazo (10 anos) de uma população idosa, inicialmente independente;

1. d) A progressão das alterações da substância branca constitui-se como um preditor independente de demência num acompanhamento a longo prazo (período de 10 anos);

2. a) Uma mudança de um estatuto independente e autónomo para a incapacidade (em qualquer grau) tem um impacto sobre a qualidade de vida do cuidador informal;

2. b) A sobrecarga do cuidador informal que decorre da progressão da doença está relacionada com os mecanismos de *coping* utilizados para lidar com a incapacidade funcional do doente.

Para testar as hipóteses delineadas, foram desenvolvidos quatro estudos, apresentados em diferentes capítulos.

Num primeiro estudo (Desenvolvimento de uma Bateria Neuropsicológica para um Estudo Multinacional: Experiência e dados iniciais), foi desenvolvida a bateria neuropsicológica que esteve na base do projeto, de forma a homogeneizar a avaliação psicológica nos diversos países envolvidos. Esta incluiu o Mini-Mental State Examination (MMSE), uma versão modificada da Vascular Dementia Assessment Scale (VADAS-Cog), e os testes Trail Making e Stroop. Os dados neuropsicológicos foram analisados para cada teste, bem como para três medidas compostas (memória, funções executivas, e velocidade de processamento). Verificou-se que os participantes com idade mais avançada tiveram pior desempenho nos três domínios. A escolaridade (> 8 anos) revelou-se um preditor importante de melhor desempenho cognitivo. Este estudo permitiu o desenvolvimento de uma bateria neuropsicológica utilizável em diversos contextos culturais e linguísticos, possibilitando comparações do desempenho cognitivo entre amostras dos diversos centros.

O segundo estudo (Identificação dos preditores neuropsicológicos de demência num período de acompanhamento de 3 anos) procurou investigar preditores da evolução do desempenho cognitivo num acompanhamento a médio prazo. Dos

639 participantes iniciais, 430 foram avaliados no final do projeto (3 anos), dos quais 90 foram diagnosticados com demência. Diferenças significativas no desempenho cognitivo de *baseline* foram encontradas entre os grupos de participantes que vieram a desenvolver demência ou defeito cognitivo sem demência, ou que se mantiveram sem defeito cognitivo. Através de modelos de regressão logística, verificou-se que os valores do MMSE e da VADAS-Cog na *baseline* foram preditores significativos da presença de demência após 3 anos. Este estudo permitiu a identificação de instrumentos neuropsicológicos sensíveis às alterações de substância branca associadas à idade e capazes de prever o risco de progressão para demência.

Num terceiro estudo (Alterações da substância branca num período de 10 anos de seguimento: um estudo piloto), feito com a amostra recolhida no centro de Lisboa (N=66), foi possível investigar a evolução do desempenho cognitivo deste grupo de participantes durante um período de 10 anos. Este estudo procurou descrever os perfis de desempenho cognitivo de participantes que, ao final desse período, tivessem sido diagnosticados com demência, defeito cognitivo sem demência, ou sem defeito cognitivo. Teve ainda como propósito identificar preditores neuropsicológicos da ausência de defeito cognitivo a 10 anos de seguimento. Dos 41 participantes sobreviventes, 37 foram re-avaliados (15 com demência, 12 com defeito cognitivo sem demência, e 10 sem defeito cognitivo). Os três grupos de participantes revelaram diferentes perfis de desempenho cognitivo em diversas baterias. Valores mais elevados no MMSE na *baseline* constituíram-se como os únicos preditores significativos de pertencer ao grupo sem defeito cognitivo ao final de 10 anos. Estes resultados apontam para a utilização de pontos de corte elevados em baterias neuropsicológicas globais, como o MMSE, como preditores de evolução (ou não) de defeito cognitivo.

Num quarto estudo (O impacto do declínio funcional nos cuidadores informais: um estudo exploratório) procurou-se responder ao segundo objetivo principal supracitado, isto é, perceber a relação entre o grau de dependência do participante e o grau de sobrecarga subjetiva do cuidador informal, colocando a hipótese desta ser mediada pelos mecanismos de *coping* deste último. Mais de metade dos cuidadores informais apresentou sobrecarga subjetiva. Apesar de uma associação entre estratégias de *coping* e perceção de sobrecarga, as

análises de regressão linear permitiram identificar o grau de dependência como o preditor independente de sobrecarga. Efeitos na qualidade de vida e saúde dos cuidadores foram descritos numa diversidade de domínios. Este estudo permitiu explorar os impactos sociais da transição para a dependência, apontando para importantes implicações ao nível da prevenção da sobrecarga de cuidadores informais.

Numa tentativa de caracterizar o desempenho a longo-termo de uma população idosa com alterações da substância branca, funcionalmente independente, o nosso estudo demonstrou que:

- os níveis de escolaridade mais elevados se associaram a melhor desempenho cognitivo, e quanto maior a idade mais dificuldades nas capacidades de memória e funcionamento executivo;

- mesmo numa população com este grau de autonomia funcional, a avaliação neuropsicológica permitiu detetar e associar alterações cognitivas subtis na avaliação de inclusão com a progressão para demência;

- pontuações elevadas no MMSE na avaliação de inclusão foram identificadas como os únicos preditores de não demência aos 10 anos;

- mais de metade dos cuidadores informais de participantes que transitaram para um estado de dependência apresentou um nível de sobrecarga subjectiva substancial. O grau de dependência funcional dos doentes foi identificado como único preditor de sobrecarga.

Com este trabalho confirmamos a importância da avaliação neuropsicológica na identificação de diferentes perfis de funcionamento cognitivo em indivíduos com alterações da substância branca, e na deteção de défices cognitivos subtis independentemente do grau de gravidade das ASBC, que funcionam como preditores de declínio cognitivo a médio e longo-prazo.

GENERAL SUMMARY

Key words: Neuropsychology, dementia, white matter changes, long term follow-up

This thesis, conceived as a longitudinal, descriptive and analytic observational investigation, aims to identify clear profiles of cognitive functioning in patients with white matter changes (WMC). The first part, presents the contribution to the multinational collaborative research known under the acronym of LADIS (Leukoaraiosis and Disability Study) which attempted to investigate the clinical significance of white matter changes as an independent predictor of the transition to disability in initially non-disabled elderly, to this end selecting and applying an appropriate test battery to assess specific domains in cognitive functions. The second part introduces the long-term follow-up of the Lisbon Centre group of participants in the LADIS study, and identifies the impact of functional and cognitive decline on caregivers who accompanied patients up to the state of full dependency. The constructed neuropsychological battery proved to be effective in identifying cognitive impairment appearing in early stages when comparing different evolutionary profiles, as well as in detecting predictors of good cognitive functioning in lengthy follow-up research, thus opening space for a renewed project to establish intervention programs. Though WMC are exclusively detected by imaging, the clinical expression of those changes, particularly as related to cognitive function, should become identified through sensitive adapted batteries. Neuropsychological assessment allows the definition of the extent of the cognitive impairment, as well as the determination of its impact on daily life and adaptation of intervention programmes either in early stages, or in later stages of the disease, allowing the introduction of non-pharmacologic complementary therapies. The identification of changes in cognitive functioning and the corresponding impact on patients and on their environment, mostly in the family, allows the adoption of broader intervention strategies when introducing future informal caregivers to more appropriate coping strategies as mediators of psychological and emotional well-being.

RESUMO GERAL

Palavras-chave: Neuropsicologia, demência, alterações da substância branca, seguimento de longo-termo

Esta tese foi concebida como investigação observacional e longitudinal, descritiva e analítica, e pretende identificar perfis de funcionamento cognitivo em pacientes idosos com alterações da substância branca cerebral. A primeira parte, constitui um contributo para a investigação colaborativa multinacional conhecida sob a sigla de LADIS (Leukoaraiosis and Disability Study), que analisou o significado clínico das alterações de substância branca cerebral (ASBC) como preditor da transição para a perda de autonomia em idosos inicialmente sem défice funcional. Para o efeito foi aplicada uma bateria neuropsicológica de modo a avaliar domínios específicos do funcionamento cognitivo, repetida anualmente ao longo de três anos. A segunda parte apresenta o seguimento a longo prazo do grupo português de participantes no LADIS e identifica o impacto do declínio funcional e cognitivo sobre cuidadores que acompanham os pacientes até o estado de dependência total. Quando comparados os diferentes perfis evolutivos, a bateria neuropsicológica construída provou ser eficaz na identificação de alterações cognitivas nas fases iniciais e permitiu prever níveis de funcionamento cognitivo no longo prazo. Assim abriu espaço para um renovado projeto de intervenção. Embora as ASBC sejam detetadas exclusivamente por exames de imagem, a sua expressão clínica poderá tornar-se identificável através de baterias neuropsicológicas mais sensíveis. A avaliação neuropsicológica permite a definição de um padrão, bem como a determinação do impacto na vida diária para adaptação de programas de intervenção nos estágios iniciais ou em fases mais tardias da doença, assim como introduzir terapias complementares não-farmacológicos, tendo em vista promover a autonomia funcional num maior período de tempo possível. A identificação de alterações no funcionamento cognitivo e o correspondente impacto sobre os pacientes e o seu ambiente, principalmente na família, permite a adoção de estratégias mais amplas de intervenção a transmitir aos cuidadores informais para uso no enfrentamento da carga emocional e física que os atinge.

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1.

INTRODUCTION AND METHODS

I - Introduction

The general decrease in birth rate especially in Western countries and the gradual increase of average life expectancy registered in recent decades, brings with it, as a consequence, an increasingly elderly population. Globally, according to the world population prospects of the United Nations [1], life expectancy at birth is projected to rise from 70 years in 2010-2015 to 77 years in 2045-2050 and to 83 years in 2095-2100, having Europe, Northern America and Oceania a projected gain of 10-11 years. It is also pointed out that the number of persons aged 60 and above is expected to more than double by 2050 and more than triple by 2100. In the same way, the number of persons aged 80 or over is projected to more than triple by 2050 and to increase more than seven-fold by 2100.

These numbers explain and justify the current concerns with the quality of life of elderly population and the increasing interest in the investigation of age-related diseases, being dementia one of the most frequent and disabling.

On the other side, age-related diseases and their respective consequences for the level of autonomy and independence of the elderly led to stress the necessity to investigate how these patients are cared for and who are the caregivers that accompany them throughout the aging process.

Cognitive Decline and Dementia of Vascular Etiology

One of the most studied facts associated with age has been the decline of intellectual capabilities. Descriptions of physical and intellectual loss associated with increasing age are found since the Greco-Roman period and, for some philosophers, such as Plato, Aristotle, Cicero, and Galen considered an inevitability of old age not a disease [2].

The current concept of dementia linked to changes derives from the definition introduced in the early 19th century by Esquirol, disciple of Philippe Pinel, who describes dementia as a "brain disease characterized by weakening of sensitivity, understanding and will", also affecting the capacity of short-term memory, attention,

reasoning, and abstraction [3]. Esquirol identifies three varieties of dementia: the acute, related to an identified cause (fever, hemorrhages) which may be cured; chronic resulting from certain behaviors (alcoholism, masturbation) or from pathology (mania, epilepsy) which is rarely curable; and senile, a form described as “resulting from the advancement of age, beginning as a weakening of memory, specially recent remembrance, and making the act of attention impossible” [2].

New forms of study and approach to mental illness, developed by Emil Kraepelin in the early 20th century, resulted in the distinction between senile and pre-senile forms of dementia and dementia caused by arteriosclerosis. This was based on Binswanger’s and Alzheimer's work correlating anatomical - clinical - pathological facts. These authors appear as pioneers in identifying the earliest forms of dementia with vascular cause, which are grouped into four entities [2, 4]: 1) post-apoplexia dementia or dementia after stroke; 2) cerebral degeneration arteriolosclerosis, characterized by multiple strokes lacunes, étatcriblé and atherosclerosis; 3) cortical vascular senile atrophy characterized by perivascular gliosis and, granular atrophy and laminar necrosis; 4) subcortical atherosclerotic encephalopathy, or Binswanger disease [5]. The latter was initially characterized by Binswanger as subcortical white matter lesions not affecting the U-fibres, ventricles much extended, in particular the horns, and normal brain cortex. Binswanger found in these cases marked atrophy of the white substance, confined to one or more sections of the hemisphere. In the most serious cases, the white substance seemed to have disappeared altogether, more marked changes being in the occipital and temporal lobes. These changes were accompanied by severe cerebral artery atheromatous plaques, so the loss of subcortical fibres was related to poor blood supply caused by atherosclerosis [6].

White Matter Changes: Clinicopathological considerations

The concept of White Matter Changes

The development of new observation techniques *in vivo*, particularly the imaging techniques such as Computerized Tomography (CT) and, later, the Magnetic Resonance Imaging (MRI), allowed that white matter changes (WMC) initially described in anatomical and pathological examinations and related to arteriolosclerosical dementia, could receive imaging correspondence. The term *Leuko-araiosis* (white rarefaction, derived from the Greek), was introduced with the aim of pointing out the signs observed on the CT (as decreased density areas) or MRI (high density areas) scans, which were limited to periventricular areas or encompassing the whole white matter substance, though without indicating a specific clinical or pathogenic meaning [7].

The increasing use of both imaging techniques, allowed the identification of WMC, described as bilateral periventricular or subcortical areas of hypodensity (when observed in CT scans) or hyperintensity (when observed in MRI scans), in a growing number of adults and the association with vascular risk factors, cognitive changes and vascular dementia [7-10]. The anatomical and pathological examinations of these patients have established a correlation between WMC signaled in CT scans and demyelinated areas, white matter infarcts, lacunes or dilated perivascular spaces and, in most cases, arteriolosclerosis. However, some cases have been associated with other types of pathologies such as Alzheimer's disease [11] and the absence of vascular disease and atherosclerosis led to question the diagnosis of Binswanger disease and brought up the question of being confronted by a different pathology.

Indeed, the first studies which used more sensitive imaging techniques such as MRI, revealed that 80% to 90% of healthy subjects with more than 60 years showed changes in white matter substance [12, 13]. However, the relationship between white matter changes (WMC) and cognitive deficits was not clearly identified [14-16]. In the last decades, the clinical impact of WMC have been highly discussed with controversial results being published [17, 18].

The type of imaging technique used proved to be important in identifying the changes in white matter substance and might also explain some of the discrepancies in the studies' results. Correlation studies between images and the changes in post-mortem examinations show that the CT has a sensitivity of 72% and a specificity of 100%, while the MRI has a sensitivity of 100% but a specificity of 88% [19, 20]. The high degree of sensitivity of MRI permits the differentiation of periventricular changes from hyperintensities in deep white matter substance; and to classify different levels of white matter rarefaction severity.

Over these last decades, the title WMC (white matter changes) has been progressively replaced by white matter lesions (WML) or white matter hyperintensities (WMH). The adoption of these terms is directly linked to the increasingly frequent use of MRI, and the resulting description of the neuroimaging findings. Consequently, in the course of the present study, those different terms have been used, corresponding to an effort of appreciating the chronological evolution of the concept and the type of technique used in the mentioned studies

Clinical Significance of White Matter Changes

The occurrence of WMC in healthy individuals varies between 10% and 100% [21, 22], being age an important factor for its increase [21, 23]. Some longitudinal studies reported a prevalence of 11% to 90% in subjects between 65 to 69 years, as well as 54% to 98% in subjects with more than 80 years. The difference of values depends on the design of the studies, the population under study, and the classification scales selected to differentiate severity of WMC. A few authors indicate a significantly greater degree of severity in women [21, 23], while other researches show no relationship with gender [24].

When correlated with cognitive changes, the alterations of white matter substance ceased to be synonyms of dementia, as they could be present in subjects not revealing cognitive defect, as stated above.

The nineties were a decade of intense work in this field (for a revision, Pantoni and Garcia, 1995 [18]). A series of studies revealed that white matter changes were also present among normal individuals with more than 60 years of age [24-26], the same occurring in sick individuals suffering from various degrees of dementia [27]. In patients with dementia of vascular origin, periventricular and subcortical WMC were observed in 80% and 50% of cases, respectively. In patients affected by Alzheimer's disease, 26% to 70% were described as presenting periventricular WML, as well as 20% to 25% presenting subcortical WMC [25, 28].

White Matter Changes: Risk factors and Pathogenesis

Risk Factors

Hypertension seems one of the more important factors associated to WMC, especially in younger subjects [21] and even in subjects under medication without adequate control [24]. Other factors, such as atheroesclerosis, hipercolestrolemia [21], smoking [23], cardiac disease [21, 29] and previous stroke [21, 23, 30] have been associated to WMC, but there is yet little consistency found in data. Diabetes has also been associated with higher risk of WMC, although evidence is lower than for hypertension [31-33].

Pathogenesis

Despite the growth of research in WMC, it is still not clear what are the specific mechanisms related with WMC formation and progression. However, recent studies have provided some evidence that extensive forms of WMC are an expression of small vessel disease [34].

Lesion of small size vessels of the brain (arteries and arterioles) is classically originated by thickening of the arterial media, occlusion of arterial lumen and obstruction of the origins of the penetrating arteries [35].

Localization of the lesions can help as an indicator of etiology. Smooth periventricular hyperintensities, including caps around the ventricular horns, periventricular lining and halos are likely to be of non-vascular origin [36]. They

relate to a disruption of the ependymal lining with subependymal widening of the extracellular space and have to be differentiated from subcortical and deep white matter abnormalities [36]. For the latter, with presumed ischemic origin, a distinction needs to be made between punctate, early confluent and confluent types. Punctate white matter lesions often represent widened perivascular spaces without substantial ischemic tissue damage, early confluent and confluent lesions correspond to incomplete ischemic destruction, although extensive etiology of white matter changes remains controversial [35]. Punctate abnormalities on MRI show a low tendency for progression, while early confluent and confluent changes progress rapidly. Several theories have been proposed, including recurrent ischemia and edema, chronic leakage of fluid related to increased vascular permeability, and contribution of venous pathology [35]. The causative and modifying pathways involved in the occurrence of sporadic age-related white matter changes are still incompletely understood, but recent microarray and genome-wide association approaches can potential help on the pathogenic links [36].

Neuropsychology of White Matter Changes

The presence of white matter changes and lacunar infarcts have been identified as the *in vivo* most detectable consequences of the Small Vessel Disease (SVD) on the brain parenchyma and thus related with cognitive impairment and dementia. For this reason, neuropsychology features of WMC will be explored within SVD findings.

SVD and Global Cognitive Measures

Since SVD is an insidious disease, early subtle cognitive changes are difficult to detect, especially in the absence of other clinical complaints. Some recent longitudinal studies, performed within the general population and reporting data from cognitively intact participants, have demonstrated that increasing volume and extension of WMC are related with lower global cognitive measures, such as Mini Mental State Examination (MMSE) [37], and with conversion to mild cognitive impairment [38, 39]. Nevertheless, in both studies, MMSE mean scores at baseline were over the cut-off point for cognitive impairment (total baseline score

29 and 28, respectively. Global cognitive decline associated with progression of WMC was also found in the Rotterdam Study [40]. Using both MMSE and a composed cognitive score (cognitive index) based on the performance in information processing speed, executive functions and verbal memory tests, the authors found a significant decline with increasing periventricular WMC. Decline on global functioning was mainly caused by impairment in speed (Stroop naming colors) and efficiency of processing (letter-digit substitution test) [40].

Decrease in global cognitive functioning associated with SVD has been more clearly observed in studies reporting the evolution of cognitive status in persons with cognitive complaints or vascular risk factors. In a study that compared the evolution of cognitive decline in three distinctive groups - subjective memory complaints, Mild Cognitive Impairment of amnestic type (MCI-A), and normal controls -, WMC volume was associated with an annual change in the Cambridge Cognitive Examination (CAMCOG) global score [41].

It is to be noted that changes in global cognitive scales are usually associated with the progression and / or severity of the disease, when a global compromise is already installed. For instance, in a cohort of patients with acute lacunar infarcts, MMSE failed to identify 30% of the patients diagnosed with cognitive deficits [42].

The same occurs with other global cognitive scales or batteries such as CAMCOG [43] or Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) [44]. This might be explained by the lack of sensitivity of these instruments in identifying subtle changes or deficits in other cognitive domains either than orientation, memory, language or visual constructional praxis. For instance, memory functioning seems to be less vulnerable to the presence of WML, unless that increasing WML represents a significant loss of brain volume [45].

To decrease the risk of under diagnosing cognitive impairment in the initial phases of the disease, it is generally recommended to add more specific tests to well studied and known batteries in order to improve their sensitivity to executive, attentional and speed processing deficits. An example of such a combination is the Vascular Dementia Assessment Scale-cognitive subscale (VADAS-cog battery)

[46], that resulted from the addition of five tests to assess working memory, psychomotor speed, attention and executive functions (namely, digit span backwards, maze simple task, digit-symbol, digit cancellation and verbal fluency) to the ADAS-Cog battery.

The Montreal Cognitive Assessment scale (MoCA) [47] is another global cognitive screening tool that has been recently developed and recommended by the NINDS-CNS [48] as a more sensitive instrument than MMSE, in detecting Mild Cognitive Impairment (MCI) and vascular cognitive impairment (VCI).The inclusion of executive functioning tasks (such as trail-making B or phonemic verbal fluency), make this screening battery more sensitive to cognitive deficits observed in vascular disease. MoCA has been used in different clinical populations and different countries, where its validity has been explored [49-53]. However, except for one study reporting that MoCA was a useful instrument differentiating a small group of SVD patients from controls [54], there is still a lack of data regarding its sensitivity and specificity to detect subtle cognitive changes in SVD patients.

SVD and Executive Functions

The effect of SVD on the decline of global cognitive measures is mainly due to the compromise and decrease of specific cognitive functions and not, at least in the initial and intermediate stages of the disease, to a diffuse cognitive impairment pattern. Executive dysfunction - mainly characterized by deficits in set shifting, verbal fluency, abstract problem solving and attention -, and decrease on speed of information processing might be detectable even in the initial stages of the disease. Multiple lacunes located in the subcortical structures and confluent and extensive WMC can result in a disconnexion of frontal-subcortical circuits (in particular, the dorsolateral prefrontal circuit) interrupting the central cholinergic pathway [55] and causing this pattern of frontal-lobe dysfunction.

For this reason, tailored instruments should be used in the clinical assessment of patients with SVD. The NINDS-CSN group [48], proposed the use of standard neuropsychological protocols to assess vascular cognitive impairment. The

importance given to measures of executive, attention and speed processing functioning is well established, even in the short-form protocols.

Executive and activation functions are frequently assessed using timed tests with a variety of set shifting, mental flexibility and response inhibition tasks. Both executive functions and speed of processing are frequently impaired in patients with SVD. Lower scores on verbal fluency (both semantic and phonemic), Stroop reading and colour naming tasks [56], and trail making tests[57], have been repeatedly associated with SVD [40, 58-60]. On other non-timed instruments used to assess mental flexibility and conceptualization such as Wisconsin Card Sorting Test [61], changes on scores were also associated to progression of WMC, in a healthy community-dwelling elderly volunteers [45].

When employing a brief assessment battery used to differentiate patients with ischaemic leukoaraiosis from normal controls, the best individual tests identifying cognitive impairment were trail-making and digit-symbol substitution tasks [29]. Also in other studies, a decline in the Symbol-Digit substitution test performance was associated with worse scores of leukoaraiosis [62]. Tests sensitive to reductions in psychomotor speed, mental flexibility, working memory and attention are useful instruments to detect early subtle changes in SVD patients.

Slowing and Motor skills

Decrease on speed of mental processing and attention have been frequently associated with the presence and progression of WMC, either in healthy elderly populations [40, 62, 63] or in elderly population with high risk for vascular disease [64-66]. Changes in attention and processing speed due to SVD are explained by a disruption in brain structures involving the frontal-subcortical pathway circuits causing a frontal lobe related cognitive impairment pattern.

In studies reporting an association between cognitive functions and WMC localization, impairment in speed of mental processing is usually related to WMC located in periventricular regions rather that in subcortical deep areas [40, 63, 66].

A recent study performed by Duering*et. al*. [67], with a cohort of 215 patients with CADASIL – a disease that best reflects the mechanisms of small vessel disease on VCI –, tried to explore the role of strategic lesions, detected for both lacunar and white matter lesions, on different patterns of cognitive decline, including mental processing speed. Using a voxel-based approach the authors were able to report an association between decrease in processing speed and volume of WML and lacunar lesions located on the anterior thalamic radiation and forceps minor. These findings are in accordance with the previously described involvement of these structures in executive functions[68-70], as they are composed by white matter tracts that project between the thalamus, prefrontal cortex and striatum that play an important role in the prefrontal-subcortical circuits.

However, results are still controversial concerning the strategic locations for cognitive symptoms related with SVD. Different results might be explained by differences in imaging techniques, in cohorts of participants and also in the different instruments used in the neuropsychological evaluation. In the majority of the studies, tests used to assess processing speed are usually complex since they require multiple cognitive capacities to perform the task. Instruments such as trail making and symbol-digit modalities are dependent on attention, memory, and motor skills, and require the involvement of different cerebral structures. The role of corpus callosum on processing speed and executive functions was also addressed in previous studies [71].

It is still difficult to identify if slowing is an effect of compromised executive functioning or impairment in sensory motor ability. Wright *et al.* [72], using the Grooved pegboard test, confirmed the association between volume of WMC and poorer performance on sensory-motor tasks. The authors emphasized the use of the Grooved Pegboard as a robust marker of white matter damage since it is sensitive to slow neural transmission or conduction of integrative rostral-caudal pathways. Still, the majority of the studies do not use such specific tests to assess sensoriomotor skills. However, the inclusion of Pegboards tests on the evaluation of patients with SVD, as recommended for the assessment of vascular cognitive impairment [73], would help in differentiating measures of psychomotor speed from those more dependent on executive/activation abilities.

SVD and Memory Performance

Memory deficits observed in SVD are distinctive from those observed in other pathologies such as MCI and AD. Studies comparing patients with MCI, with and without SVD, tried to identify different cognitive profiles [60, 74, 75]. Zou *et al.* [60] reported a non specific profile in non-specified MCI-SVD patients since they found extensive cognitive deficits on these patients. Comparatively, patients with MCI-AD had a more specific pattern characterized by a significantly worse performance on verbal and visual delay recall and recognition measures with a relatively preserved performance on processing speed tasks.

MCI (non defined type) patients with severe WMC were compared with MCI patients with severe hippocampal atrophy using a comprehensive neuropsychological battery [76]. The authors found that patients with hippocampal atrophy exhibited a specific episodic memory impairment while patients with WMC exhibited deficits on episodic memory (assessed by a 36-item object color association task), working memory (were tested on two verbal working memory tasks and a spatial working memory task), and attention control tasks (continuous performance test), suggesting that the episodic memory deficit was secondary to a more general impairment of executive control. In fact, working memory performance requires an ability to hold, manipulate and quickly access information that is dependent on mental flexibility and speed. The mediation effect of executive functions on verbal and visual memory performance of SVD patients was already described [58].

Distinctive patterns can be observed in relation to memory impairment. Ability to storage information is mainly dependent on the limbic and hippocampal structures, while retrieval and short term memory capacities are more related with the integrity of frontal-subcortical structures and temporo-parietal lesions, respectively. In SVD patients, episodic memory impairment is usually absent or mild in the initial phases, being the most frequent deficit characterized by difficulty in recall information that improves in the presence of cues. However, these findings are frequently associated to other variables such as medial temporal lobe atrophy [77] and corpus callosum atrophy [78]. Poorer episodic memory has been associated

with age-related differences in central white matter regions [79]. Recent studies with SVD patients have explored the relationship of microstructural integrity of the hippocampus – not detected with conventional MRI – and verbal memory impairment [80, 81]. These authors found that deficits in verbal memory (immediate, delayed recall and delayed recognition), but not in psychomotor speed, were related with changes in the hippocampus microstructure. These results might lead us into a new perspective in the understanding of memory impairment related with SVD.

Language

Impairment in language functions is not frequent in SVD. Comparing patients with initial dementia, Kertesz *et al.* [82] found that patients with periventricular hyperintensities performed worse on comprehension and attention tasks, compared with those with no hyperintensities that showed worse performances on memory and conceptualization tasks. However, other studies performed within the general population and with high risk non-demented patients with WMH, did not find a relationship between presence of WML or lacunes and language deficits (see Debette *et al.* [83], for a review). Nevertheless, lexical and semantic fluency measures should be included in the assessment of SVD patients. Impairment in lexical tasks is more frequent and prominent than semantic difficulties, showing a different pattern of MCI or AD patients. As occurs in other cognitive functional deficits observed in patients with SVD, the type of impairment found in verbal functions seems to be related with the decrease in speed of processing and access to information which affects word generation tasks.

Visuospatial construction and visuopractical functions

Previous studies with healthy elderly or community-dwelling populations did not find any relationship between visuoconstructional impairment and the presence of WMC [14, 15, 62, 84].

Similar results were also reported in patients with vascular risk factors [64] or initial dementia [82]. On the contrary, in a cohort with more severe dementia, impairment in visuospatial abilities measured by the Wechsler Adult Intelligence Scale-

Revised (WAIS-R) Object Assembly subtest was associated with the volume of WML located on the posterior periventricular regions [85]. Other motor performance subtests were also found to be important contributors to discriminate between groups of severe Vascular Dementia and Alzheimer's Disease [86]. Nevertheless, both WAIS-R subtests used in the two studies are sensitive to constructional abilities and visuospatial organization skills, while they are also time-dependent and highly sensitive to frontal lobe dysfunction.

Results from the Austrian Stroke Prevention Study [45], also show an association between visuopractical skills decline assessed by the Purdue pegboard [87] and the progression of WMC and related loss of brain volume. Again, the performance on this test is highly dependent on the speed of motor response.

More recently, decline in spatial organization and visuo constructional skills, measured by the Benton Visual Retention Test (BVRT) and the Consortium to Establish a Registry in Alzheimer's Disease's (CERAD) geometric design copying test, were found to be uniquely associated with progression of posterior WML [88]. Murray *et al.* [89] investigated the impact of WM hyperintensities (WMH) on cognitive impairment and motor dysfunction in a cohort of neurologically intact elderly subjects. Measuring the percentage of WMH in well-defined cerebral regions (frontal, temporal, parietal, occipital, periventricular and subcortical) and the performance in memory, language, executive functions and visuospatial reasoning domains, the authors found only a trend toward worse performance in visuospatial abilities (measured by the WAIS-R picture completion and block design subtests) with greater percentage of WML. Interestingly, in this study, a higher percentage of WMH in all regions except occipital lobe was associated with worse performance in executive tasks (measured by Trailmaking B and Digit Symbol). No significant relationship was found between WMH and memory or language standard scores. These findings support the importance of the integrity of white matter fibers in anterior brain regions for global cognitive functioning, and might reflect the contribution of executive functions on visual reasoning, as both tests – picture completion and block design – depend also on subjects' abilities of reasoning and judgment about practical and conceptual relevancies, and problem solving techniques.

Different expressions of SVD and its impact on cognition

As previously referred, WML are the most detectable consequences of SVD. However, other forms of SVD, such as lacunes, cerebral microbleeds and brain atrophy [90], may play an important and still not yet completely identified role in cognitive performance.

Lacunes

Lacunes can be detected on MRI T2 and FLAIR sequences and defined as small subcortical infarcts (3 to 20mm of diameter) that occur in cerebral regions supplied by the small perforating arteries [91]. The most frequently affected regions are basal ganglia, internal capsule, thalamus, paramedian and lateral regions of brainstem, corona radiate and centrum semiovale. Depending on the number and localisation, lacunes can be clinically silent or very expressive. Among cognitively normal elderly subjects, the total number of subcortical lacunes was an independent predictor of executive functioning [92], speed and motor control [93]. Thalamic and basal ganglia lacunes were independent predictors of cognitive decline in elderly subjects [94]. Progression of lacunes was also associated with cognitive function, particularly in processing speed and executive functions, along with WMC progression [63, 95].

Among individuals with Alzheimer's disease (AD) a marked influence of thalamic, basal ganglia, and deep white matter lacunes on cognitive function was cleared identified in neuropathological study [96]. However, in other studies, lacunes were present in approximately one-quarter of elderly cases without a relationship with psychiatric or neurological disease [97], or did not predict any of the cognitive tests outcomes when adjusting for age and medial temporal atrophy [98]. Thus, the independent role played by lacunes in cognition and / or progression for dementia is still not well identified.

Cerebral microbleeds

Cerebral microbleeds (CMB) – are small rounded lesions detected on more sensitive MRI sequences (T2*-weighted gradient-recalled echo, GRE, and susceptibility-weighted imaging, SWI) composed of small collection of blood breakdown products [91] - have been recently identified as other forms of SVD, accompanying WML and lacunes [99]. The prevalence of CMB is variable depending on the MRI techniques used [100].
The impact of CMB on cognition has been progressively and consistently reported. A recent meta-analysis [101] evidenced that patients with CMBs had higher incidence of cognitive dysfunction and lower scores of cognitive function. There was also a correlation between the number and specific localizations of CMB (lobar regions, deep areas, basal ganglia, and thalamus regions) with cognitive impairment. Rhian *et al.* [101] did not find evidence of a correlation between infratentorial CMBs and cognitive performance.

However, previous studies have reported associations between deep CMB and motor speed [102], processing speed and executive functions [103]. Infratentorial CMB have been also associated with motor speed, attention [103] and visual memory [104].

Nonetheless, besides an increasing evidence of the influence of other SVD markers on cognitive performance, it is still difficult to identify the direct impact of these different expressions, either because they are consistently associated with each other or because they come with a varied type of vascular risk factors.

WMC: Unsolved issues

In the beginning of this study, and aside the increasing interest and research on white matter lesions and their impact on cognitive performance, there were still a number of unsolved issues to address.

The first one was the most simple and yet the most important: what should we tell an independent elderly person, regarding a neuroimaging examination that

detected the presence of white matter changes, in the absence of other expressive clinical complaints?

It became important to know how WMC would evolve in a medium and long-term period and what cognitive implications they could have. A strong relationship between the presence of WMC and progression to disability had been reported [105], but the long-term evolution of the disturbance and its relationship with cognitive performance along with its impact on the transition to a functionally dependent status, was still not clear.
In the same way, there was still a lack of information regarding the contribution of neuropsychology on detecting predictors of disability and on identifying different profiles of evolution.

At this point, what stood up was the need to better identify those neuropsychological instruments which were most useful in detecting subtle cognitive deficits and changes in the long-term follow-up of elderly subjects with WMC.

Equally important when considering the hypothesis that WMC could have a direct impact on the transition from an autonomous status to a gradual cognitive loss and consequent dependency, is to explore the impact of this outcome on informal caregivers.

Thus, the present thesis took form as an effort to construct and validate a neuropsychological battery to better identify predictors of dementia and non impaired cognitive status in a long-term longitudinal approaches. It further encompassed the study of the impact of the disease on informal caregivers who accompanied patients up to the state of possible full dependency.

II - Objectives and hypotheses under study

The **objectives and hypotheses** under study are summarized as follows:

1. To evaluate the extent to which age-related cerebral white matter changes (WMC) influence cognitive performance and constitute an independent determinant of cognitive decline.
We aimed to identify how cognitive functioning was related with the presence of WMC, which cognitive domains were mainly affected by them, and which are the most sensitive to decline. In order to explore these questions, we had to determine the best instruments to evaluate these cognitive changes to be able to identify neuropsychological predictors of dementia on a long-term follow-up. Considering these purposes, we explored the following hypotheses:

a) A properly designed neuropsychological battery is able to differentiate the cognitive performance of independent elderly subjects with different degrees of WMC, in association with specific demographic variables (age and education);
b) Subtle deficits on global cognitive performance and specific cognitive domains observed at baseline, are predictors of dementia on a 3 year period, in a functionally independent elderly population with WMC.

These hypotheses are studied and discussed in Chapters IV and V of the present thesis.

2. To evaluate the extent to which WMC influence cognitive performance at a 10-year follow-up period and to identify predictors of non-disability.
We hypothesized that:

a) The neuropsychological battery was able to identify different profiles of cognitive performance on a long-term evolution of a sample of initially independent elderly people with WMC. Higher performance in global measures and specific cognitive domains are predictors of no cognitive impairment at 10 years;

b) Progression of WMC was an independent predictor of dementia among elderly people on a long-term follow up.

This study is presented and discussed in Chapter VI of the present thesis.

3. To explore and characterize informal caregivers' burden and needs as they follow the elderly subjects' process of transition from an independent to a condition of disability. For this purpose we established the following hypotheses:

a) Progressive change from an independent and autonomous status to a disabled functioning have an impact on the quality of life of caregivers;
b) The way in which caregivers are affected by the progression of the disease is related with their own coping mechanisms.

The results of this study are presented and discussed in Chapter VII.

III - Methodology

The research here submitted is conceived as a longitudinal, descriptive and analytic observational investigation. The present Chapter is divided in two main parts: A) The first part presents the multinational collaborative study known under the acronym of LADIS (Leukoaraiosis and Disability Study), which attempted to investigate the clinical significance of white matter changes (WMC) as an independent predictor of the transition to disability in initially non-disabled elderly (64 to 84 years). It was supported by the European Union through the 5th European Framework Program 'Quality of life and management of living resources'; B) The second part of the Chapter introduces the long-term follow-up of the Portuguese group of participants in the LADIS study, and identifies the impact of functional and cognitive decline on caregivers.

The LeukoAraiosis and DISability (LADIS) study

The Leukoaraiosis and Disability (LADIS) study was an European multicentre collaborative research established in 2000, with the support of the European Union (5th European Framework Program 'Quality of life and management of living resources'),which aimed to identify the impact of white matter changes (WMC) in the transition from an independent functional status to disability in elderly subjects. It had two main purposes: 1) to assess the role of WMC as an independent predictor of the transition from an autonomous functional status to disability; 2) to identify the role of WMC progression in this transition [106].

The LADIS study was conducted in 11 European centres that were previously involved in the investigation of the clinical consequences of cerebrovascular diseases (Amsterdam, Copenhagen, Florence, Graz, Göteborg, Lisbon, Helsinki, Huddinge, Mannheim, Newcastle-upon-Tyne and Paris, see Appendix 1 for a complete list of participants), and had the staff and structure to carry out this novel multidimensional research [106].

The study was designed to cover a full range of clinical implications and focused 6 main work packages (WP): (1) methodology, (2) disability, (3) neuroimaging, (4) cognition, (5) mood, and (6) gait. Each WP was responsible for the justification and implementation of procedures and harmonization of instruments and techniques of clinical assessment, given the cultural and language differences between groups. Work package's coordination also involved the control of data report and analysis. A handbook was constructed to guide the use of all clinical, cognitive, functional, imaging, behavioural and motor assessment instruments, and several meetings were held in order to validate the procedures before enrolment of participants.

The Lisbon centre was responsible for the coordination of work package 4 (cognition), designed to select the neuropsychological battery, to harmonize cognitive assessment procedures, to plan the statistical approach of cognitive data and to definite parameters of cognitive decline. The construction of the neuropsychological battery and the difficulties related with this task, will be properly explored in Chapter IV.

Participants

Inclusion criteria

Participants in the LADIS study were: a) subjects between 65–84 years of age; b) with WMC of any degree indicated on MRI, according to the revised version of Fazekas' scale [107]; and c) with no disability (no impairment or only 1 item compromised of those included in the Instrumental Activities of Daily Living scale (IADL) [108]; d) with a regularly contactable informant; (e) that agreed to sign an informed consent.

To reduce the impact of cultural differences across countries (for example, gender social roles) in the IADL scale, the protocol included an extra score (score 9, not applicable) to distinguish between activities never performed during her/his lifetime from those that were not done at that moment. It also included a specific question to determine if activities not done at the moment were due to reasons apparently

independent of the subject's willingness or capabilities (e.g. the subject did not have a home phone or never took public transportation because he/she did not need it), the interviewer formulated the question in the following way: 'Suppose that he/she has to make a phone call, take public transportation etc. do you think he/she would be able to do it?' and scored the item accordingly. At least 4 out of the 8 items of the IADL scale had to be applicable to be included in the study.

Reasons for referral in the study were minor neurological, cognitive, mood or motor complaints with no impact on daily activities, and incidental findings on cranial imaging performed for a non-specific event. Some participants were volunteers from other studies or people who came to accompany their relatives or friends, and asked to be included in the study.

Exclusion criteria

Subjects with severe illnesses that might compromise their presence during the follow-up period (cardiac, hepatic or renal failure, cancer or other relevant systemic diseases), severe unrelated neurological diseases, other etiologies for leukoencephalopathy (immunological demyelinating, metabolic, toxic, infectious, other), severe psychiatric disorders, inability to give an informed consent or refusal to undergo cerebral MRI, were excluded.

Procedures and instruments

Participants were submitted to a wide-ranging clinical, functional, motor and neuropsychological examination that was repeated yearly during a 3-year follow-up period. The protocol comprised three main assessment parts: 1) a social background and medical history assessment; 2) a functional and clinical assessment; 3) a Magnetic Resonance Imaging (MRI) Study (see Table 1).

Table 1: Clinical, Functional and Imaging Assessment

Protocol Assessment	Instruments
Social Background and medical history	Standard interview following a comprehensive and structured questionnaire. Registry of demographic data, vascular risk factors, age-related co-morbidities
Functional and Clinical Assessment	1. **Standard cardiovascular and neurological examination**; **2. Functional status and disability** a. Instrumental Activities of Daily Living scale (IADL) [108] b. Disability assessment of dementia scale (DAD) [109] **3. Quality of Life** a. Euro QoL EQ-5D [110] **4. Depression** a. Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria [111] b. Geriatric Depression Scale (GDS) [112] c. Cornell scale for depression in dementia [113] **5. Motor performance** a. Short Physical Performance Battery [114]; b. Single leg stance and gait velocity [115] **6. Neuropsychological assessment** a. Mini-Mental State Examination (MMSE) [37] b. Alzheimer's Disease Assessment Scale (ADAS-Cog) [44] plus delayed recall, symbol digit, digit span, mazes, digit cancellation and verbal fluency (VADAS-Cog) [116] c. Stroop Test [56] d. Trail-Making Test [57] e. Telephone Interview for Cognitive Status (TICS) [117]
Magnetic Resonance Imaging (MRI) Study **MRI Protocol** Axial/coronal T1, T2, PD, FLAIR sequences Diffusion tensor Magnetization transfer techniques	**1. WMC severity grade**: a. Fazekas Scale[107] b. Scheltens Scale [118] c. European Task Force WMC Scale [119] **2. Volumetry** (semiquantitative measurement) [120] **3. Atrophy** a. Scheltens Visual Scale (medial temporal lobeatrophy) [121] **4. Presence of infarcts and lacunes** a. Visual assessment of number and location and side-by-side comparison [122, 123] **5. WMC progression** a. Rotterdam Progression Scale modified [124]

Social background and medical history were assessed with a comprehensive and structured questionnaire performed by the trained practitioner, and designed to obtain the registry of: a) demographic characteristics, that included information on education (years of schooling), occupational status, longest job in life, marital status, living conditions, past and current lifestyle habits (alcohol consumption, smoking), type of leisure and physical activities; b) specific vascular risk factors such as: previous hypertension, determined according to the World Health Organization guidelines for the management of hypertension[125]; diabetes mellitus, defined based on previous diagnosis and/or current treatment with insulin or oral hypoglycaemic medications, or when measured, according to established criteria [126]; hyperlipidaemias defined according to reported criteria [127]; myocardial infarction, documented by history, ECG or cardiac enzymes [128]; angina pectoris [129, 130]; heart failure [131]; atrial fibrillation [132]; lower limb arteriopathy and peripheral vascular disease [133]; history of stroke and/or TIA [134]; cigarette smoking, defined as packs of cigarettes per day multiplied by years smoked; alcohol consumption, expressed as consumed grams per day; c) other age-related co-morbidities, such as: thyroid diseases, head injuries, falls in the last year, hip fractures, visual impairment, hearing loss, recurrent vertigo, any hospital admission over the last 3 years and currently used drugs were registered in a structured way. Participants were specifically asked if they had gait or bladder disturbances, and/or memory complaints. All possible medical information and family history vascular disease or risk factures were also collected (See Appendix 2 with the definition criteria for vascular risk factors and related diseases).

Functional and clinical assessment encompassed: 1) a standard cardiovascular and neurological examination, that included blood pressure supine measurements; 2) the evaluation of functional status and disability, measured by means of the IADL [108] and the Disability Assessment for Dementia scale [109] respectively; 3) the evaluation of health-related quality of life, measured by means of the Euro-QoL 5D [110]; 4) the evaluation of depressive symptoms and depression (presence and severity), using the Geriatric Depression Scale [112] and the Cornell Scale for Depression in Dementia [113], as well as the Diagnostic and Statistical Manual Disorders IV (DSM IV) criteria [111]; 5) the evaluation of

motor performance using the Short Physical Performance Battery [114] and measures of single leg stance and gait velocity [115]; 6) the evaluation of cognitive performance using a neuropsychological battery that included the Mini-Mental State Examination [37], the Vascular Dementia Assessment Scale [116], the Stroop test [56] and the Trail-making test [57].

For patients who could not attend the follow-up clinical visits, a phone interview collecting clinical data and functional status was performed with the patient and the carer. The phone protocol also included the Telephone Interview for Cognitive Status (TICS) [117] performed with the patient, whenever possible. Based on these telephone interviews, and in order to collect information beyond the initial follow-up period, a delayed contact took part in 2008–2009. In this contact, participants performed the TICS and were asked to answer a clinical questionnaire that was also corroborated by the carer.

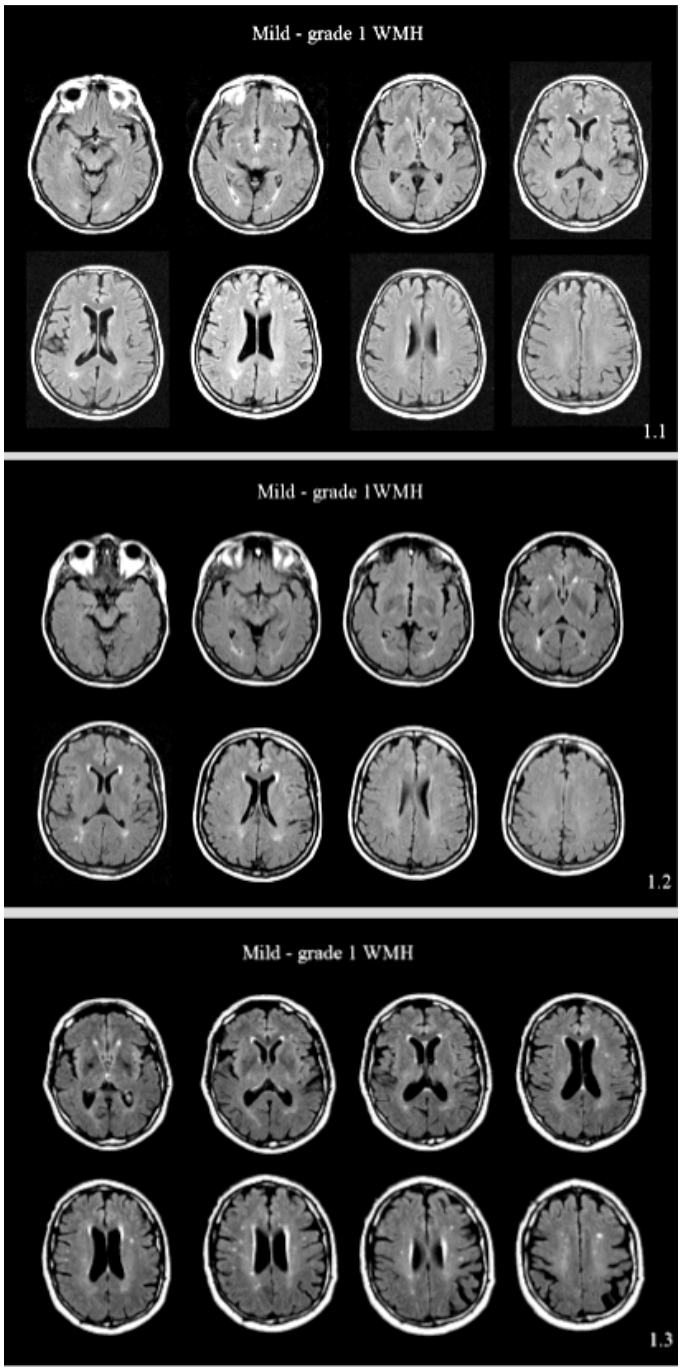
The MRI evaluation was performed at baseline and at the end of the 3-year period, following a standard protocol. MRI studies included T1, T2, proton-density-weighted and fluid-attenuated inversion recovery pulse sequences. The exact sequence parameters were determined at the specific sites to give optimal contrast between the normal brain and WMC. For confirmation, representative images were checked centrally before the study. Diffusion tensor and magnetization transfer techniques were employed by selected centres to further characterize tissue changes [106].

The degree of WMC severity on MRI was rated using the visual scale of Fazekas *et al.* [107] taking into account only deep and subcortical white matter lesions. Presence of WMC is classified as mild, moderate and severe stages (Figure 1). To improve the homogeneity of ratings, centres were provided with an online atlas containing rules and examples for assessing WMC severity. Lesions were classified into 3 categories: mild WMC (single lesions below 10 mm; areas of ‘grouped’ lesions smaller than 20 mm in any diameter); moderate WMC (single lesions between 10 and 20 mm; areas of ‘grouped’ lesions more than 20 mm in any diameter; no more than ‘connecting bridges’ between individual lesions);

severe WMC (single lesions or confluent areas of hyperintensity 20 mm or more in any diameter). The local rating in each centre was used to balance the enrolment across the 3 severity WMC groups. In parallel, WMC severity was determined centrally at the Department of Neurology, Vrije Universiteit Medical Center, Amsterdam, the Netherlands, by raters blinded to the clinical details. This rating is used for all analyses in the context of WMC. The exact rating procedures and the correlation between local and central readings were analysed and the results were good.

Figure 1: Grades of WMC severity according to the Fazekas' Scale

MILD



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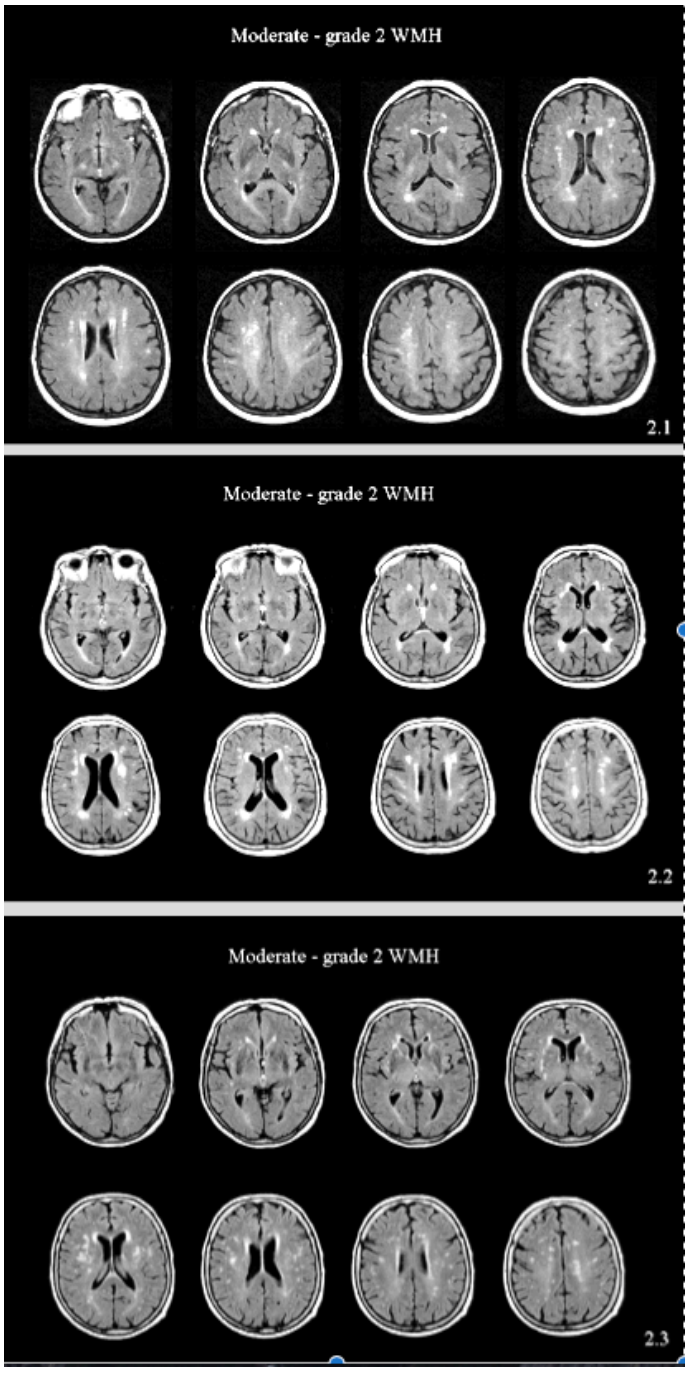
Moderate - grade 2 WMH
2.1
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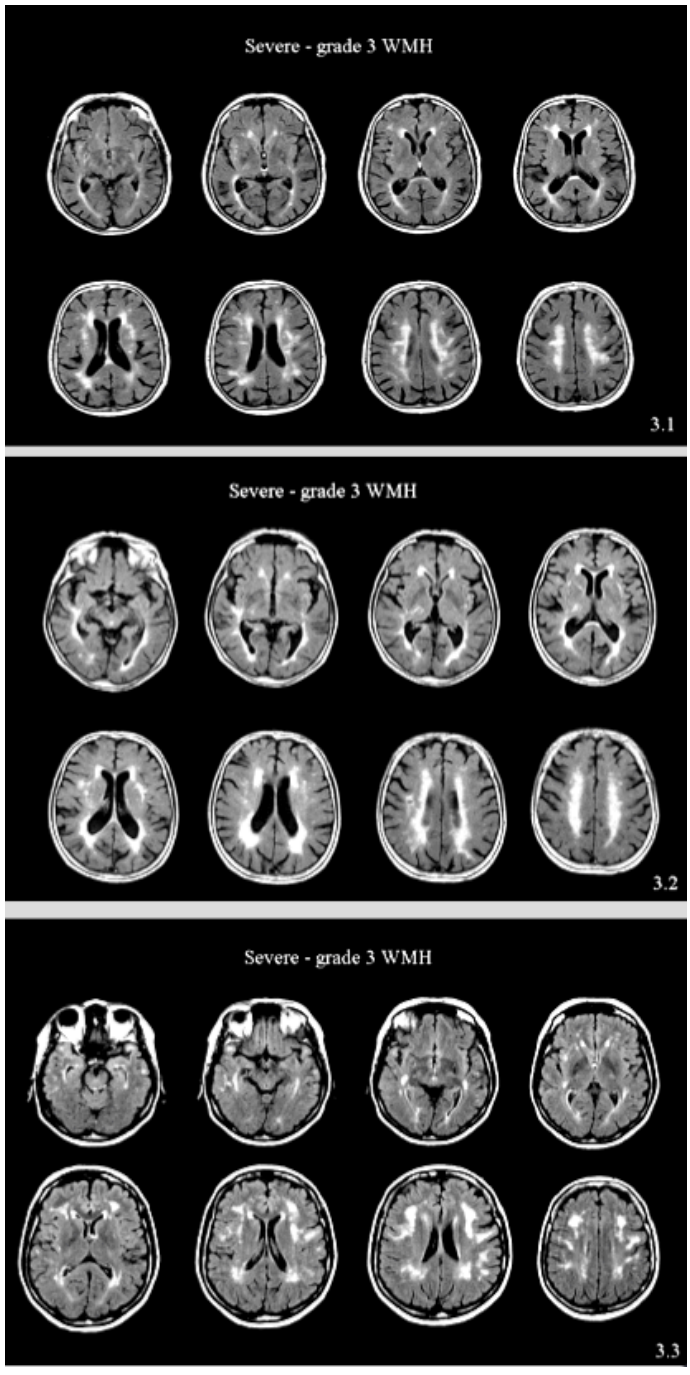
2.2
Moderate - grade 2 WMH
2.3

SEVERE



During the study period, several analyses were developed and performed using MRI data. Volumetric analysis of WMC was performed by a single rater on the same axial FLAIR images, including the infratentorial region [120]. Medial temporal lobe atrophy was assessed on coronal T1 weighted sequences using the MTA

scale [121]. Brain atrophy was evaluated by a single rater at baseline on FLAIR images with a template-based rating scale ranging from 1=no atrophy to 8=severe atrophy separately for cortical (sulcal) and subcortical (ventricular) regions. In case of asymmetry, the side with a more severe atrophy was used for rating. The sum of cortical and sulcal atrophy score was taken as a measure of global atrophy.

Based on the comparison of baseline and follow-up MRI scans, progression of WMC and presence of new lacunes were visually rated in a side-by-side fashion. WMC progression was rated on FLAIR images according to the modified Rotterdam Progression Scale (range 0 to 9) [124], in which "no progression" or "progression" (0 and 1, respectively) was rated in 3 periventricular regions (frontal caps, occipital caps, bands), 4 subcortical white matter regions (frontal, parietal, occipital, temporal), basal ganglia, and infratentorial region. Progression was also classified as "no progression", "mild" (progression in 1 to 3 regions) or "severe" (progression in more than 3 regions) [122]. New lacunes were also visually assessed, according to the number and location in 5 brain regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial). New cortical / lobar infarcts were also identified according to the number and location [122].

All investigators participated in a general meeting to get familiarized with the protocol before they were provided with a specifically developed handbook with guidelines for applying criteria and tools.

Neuropsychological evaluation

The construction of a neuropsychological battery, harmonization of cognitive assessment and data analysis procedures, as well as the definition of cognitive criteria, were the main tasks attributed to the Portuguese centre in the LADIS study. Being such a complex process, with several steps and inherent difficulties, the whole procedure was itself object of study and it is presented in Chapter IV.

Cognitive Status criteria

As previously reported, neuropsychological evaluation was performed at baseline and yearly during a period of 3 years.

In the follow-up visits participant's cognitive status was evaluated clinically and classified into three groups: 1) no cognitive impairment; 2) cognitive impairment no dementia; and 3) dementia, accordingly to established sets of criteria.
Two types of cognitive impairment no dementia were considered: amnestic mild cognitive impairment (MCI), defined as memory complaint, preferably corroborated by an informant; impaired memory function for age and education, preserved general cognitive function, intact activities of daily living and no dementia [135]; and vascular cognitive impairment without dementia (VCIND), defined as evidence of cognitive impairment and clinical consensus to identify significantly related vascular features; exclusion of dementia when impairments were not sufficiently severe to interfere with social or occupational functioning or when impairments were more focal than the global requirement for a diagnosis of dementia [136].

For dementia, the following subtypes and criteria were considered: probable Alzheimer disease, according to the NINCDS-ADRDA Work Group [137]; probable vascular dementia, according to NINDS-AIREN criteria [138]; subtype of subcortical vascular dementia according to Erkinjuntti *et al*. [139]; frontotemporal dementia according to McKhann *et al*. [140] and dementia with Lewy bodies according to McKeith *et al*. [141]. The criteria of Alzheimer's disease with vascular component was made when the investigator judgement considered that the clinical picture presented both aspects of Alzheimer's disease and vascular dementia.

Instruments and criteria were chosen based on the most frequently used and established at the beginning of the LADIS study.

Long-Term Follow-Up of the Portuguese Group of Participants in the LADIS study

The second part of the present Chapter offers an extension of former research, introducing a long-term follow-up of the Portuguese group of participants in the LADIS study. The neuropsychological performance of this cohort in the 10-year follow-up period is evaluated, abiding the former standard protocol. Additionally, data on the impact of the progression of the disease on caregivers and family are reported.

The follow-up of the Portuguese participants of the LADIS study at the end of the 10-years intermission focused: a) survivors of the Portuguese group of participants in the LADIS study; b) attendants or caregivers of those participants. Attendants or caregivers included for assessment were those who had been present for at least three of the five visits made for evaluation of participants, or those who had permanently replaced original caregivers (for example, institution caregivers). Caregivers were interviewed for the purpose of assessment on occasion of the final visit.

Procedures and instruments

The research included the clinical, functional, neuro-radiological and neuropsychological assessments as formerly detailed and described elsewhere [142]. All clinical and neuropsychological assessments were performed by the same neurologist and neuropsychologist, who completed them in the course of the LADIS study. Follow-up MRI was also carried out with the same equipment and following the former protocol so as to ascertain the comparability of results.

For the present purpose, all the Lisbon surviving participants were contacted and invited to come to an extra evaluation at the 10^{th} year of follow-up. This visit consisted of: 1) a clinical and functional evaluation performed by the neurologist, according to the LADIS protocol [106]; (2) a neuropsychological assessment, as included the LADIS battery (the MMSE as a measure of global cognitive status;

the ADAS-Cog, to assess memory, orientation, language, ideational and constructional praxis, with the extension for vascular impairment, or VADAS-cog, that adds the delayed recall of the ADAS's 10 word lists, and a symbol digit test, a digit span backwards, a maze task, a digit cancellation task and an animal naming verbal task; the Trail-Making and Stroop tests to assess executive functions; and the 9-word version of the California Verbal Learning Test, or CVLT-9 to assess memory and learning - see [142], for detailed description of the battery); 3) an MRI scan was performed according to the LADIS protocol, at the same Centre and with the same equipment previously used in the LADIS study.

Severity of WMC was visually rated by the neurologist, who was blind to neuropsychological data, using the Fazekas' scale. CD copies of the MRI scans were sent by mail to the same researcher who rated the follow-up MRI evaluation in the LADIS study and who was blind to clinical details and neuropsychological data. Progression of the WMC and presence of new lacunes were visually rated in a side-by-side fashion, on FLAIR images according to the modified Rotterdam Progression Scale. Procedures and criteria are detailed in Chapter VI

For participants who were unable to come to the hospital for assessment, home visits were conducted for clinical and neuropsychological evaluation. Information concerning non-surviving participants was collected in a face-to-face or telephone interview with the caregivers/informants. This interview included a drop out/death questionnaire used in the LADIS study, which collects clinical and functional data.

Impact of the Progression of the Disease on Caregivers and Family

Caregivers were invited to participate in this research at the same moment that their relatives or patients were contacted. They were informed that the study was conducted by the neuropsychologist and that they had to be interviewed in one-only visit with the aim to identify caregiver's needs. The same information was written and explained when requested, in the consent form (Appendix 3).

Participants in this research were assessed using the following instruments: MMSE [37] to evaluate any cognitive deficit; an open nondirective interview modelled on that used in the Canadian Study of Health and Aging [143], which collects information on the caregiver's sociodemographic and professional identity, on the type of care offered, on the support obtained (institutional, or others), its bearing on professional and social activities and its effect on health and quality of life; The Caregiver Strain Index [144]to assess subjective burden; the MOS SF-36 Index, to assess quality of life [145]; the Brief COPE [146] to identify what coping strategies caregiver uses. In addition to quantitative analysis of data produced with scales applied, content analysis of open interviews, aiming to pinpoint the more frequent complaints / needs reported, were performed.

2.

EXPLORING AND TESTING THE HYPOTHESES

IV - Development of a neuropsychological battery for a multinational study: the LADIS (Leukoaraiosis And DISability) experience and baseline data

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Development of a Neuropsychological Battery for the Leukoaraiosis and Disability in the Elderly Study (LADIS): Experience and Baseline Data

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Key Words
White matter changes · Aging · Cognitive performance · Neuropsychological tests

Abstract
The relationship between age-related white matter changes and cognitive performance in independent elderly people is still not clear. The Leukoaraiosis and Disability in the Elderly study (LADIS) involves 11 European centers. It aims to assess the role of the age-related white matter changes as an independent factor in the transition to disability, and in cognitive performance of an independent elderly population. A comprehensive neuropsychological battery was constructed in order to harmonize the cognitive assessment across countries. Patients were evaluated at baseline and during the 3-year follow-up with the Mini-Mental State Examination, a modified version of the VADAS-Cog (Alzheimer's Dementia Assessment Scale plus tests of Delayed recall, Symbol digit, Digit span, Maze, Digit cancellation and Verbal fluency), Trail making and Stroop test. Six hundred thirty-eight patients (mean age 74 ± 5 years; mean educational level 10 ± 4, F/M: 351/287) were included in this study. Neuropsychological data were analyzed test by test and also grouped in three compound measures (executive, memory and speed/motor control domains). Older subjects (>74 years) performed significantly worse than younger subjects on the ADAS-Mod and on the tests of memory ($t_{631} = 3.25$; $p = 0.001$), executive functions ($t_{581} = 4.68$; $p = 0.001$) and speed/motor control ($t_{587} = 4.01$; $p = 0.001$). Participants with higher educational level (>8 years of school) showed better performances on the compound measures for memory ($t_{631} = 3.25$; $p = 0.001$), executive functions ($t_{581} = 4.68$; $p = 0.001$) and speed/motor control ($t_{587} = 4.01$; $p = 0.001$). Using multiple regression analysis models to study the influence of demographic variables on cognitive performance, age and education remained im-

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Introduction

The relationship between age-related white matter changes (ARWMC) and cognitive impairment has been described in several studies in different population samples [147, 148].

In community-dwelling and independent elderly subjects, some studies reported an association between the presence of ARWMC and deficits in global mental functioning, speed of mental processing and memory [22, 24, 26, 30, 149-151]. However, others failed to find a relationship between the presence of ARWMC and cognitive performance [15, 152, 153].

There are a number of factors that can explain the inconsistency of these results. They may be related to the design of the studies, the type of analysis performed on imaging and the neuropsychological evaluation. Further, regarding cognitive performance, the variability of results can be due to the use of different instruments and measures to assess cognition, the use of different criteria to define cognitively impaired performance, and the use of non-sensitive instruments, such as global measures of cognition, or tests sensitive to memory decline but not to executive functioning.

Despite the recent interest and effort to analyse the impact of ARWMC on cognition, there are still several issues that need to be explored. How is cognitive functioning influenced by ARWMC? Is there a threshold of ARWMC needed to affect cognition? Which cognitive domains are mainly affected by the presence of ARWMC and which domains are more sensitive to decline in parallel to the progression of ARWMC? Is there a neuropsychological profile related to the location of ARWMC?

The LADIS (Leukoaraiosis and Disability) Study aims to assess the role of ARWMC as an independent predictor of disability in the elderly [154], contributing with answers to the above-mentioned issues. The LADIS study involves 11 centres of 10 European countries (Appendix 1).

The assessment of cognitive functions is a difficult task, starting with the selection of the appropriate tests to evaluate specific domains. The difficulty increases in multinational studies since the performance in majority of the tests is dependent on educational, language, cultural and demographic variables.

The aims of the present work are to describe the development of the LADIS neuropsychological battery, to present LADIS neuropsychological baseline data, and to discuss the methodological problems and limitations of the cognitive assessment within the LADIS study.

Methods

LADIS organisation and methodology have already been reported elsewhere [154].

Construction of the neuropsychological battery

The construction of the LADIS neuropsychological battery took in consideration that: 1) selected tests had to be available and familiar in the majority of the centres; 2) the tests had to be sensitive to cognitive decline; 3) the battery had to be innovative, comprehensive, easy to administer, but not too long; 4) all centres had to use the same version of each test; 5) the original English version of tests had to be translated in each local language.

In order to construct the neuropsychological battery for the LADIS study, we performed a review of the studies investigating elderly samples with ARWMC using comprehensive cognitive assessments, published until 2001, and selected the most frequently used instruments. In this review, we also retrieved the criteria for the definition of abnormal performance on the neuropsychological tests used on each study. A list of tests was made according to the frequency they appeared in the studies. All participating centres received a questionnaire in which, for each test of the list, several questions were asked: a) if the test was available at their centre; b) if it was routinely used for cognitive assessment; c) if it had local/national validation norms; d) if the original or other versions were used.

Of the eight tests initially selected, the Mini-Mental State Examination [37] and the Stroop test [56, 155] were the only tests available and in use for assessment in all centres. However, the versions used were slightly different from centre to centre and normative values existed in only 62% (MMSE) and 69% (Stroop) of the countries. Verbal fluency tests were also available in all centres, with normative values for 92% of the countries. Nevertheless, the variability of versions was wide: some centres used semantic fluency (animals, colours, fruits, cities, or supermarket goods), others used only controlled oral word association tests (using different letters such as FAS, PFL or LPS). The Wisconsin Card Sorting Test [156] was available in almost all the centres, but with different versions (original and modified). Further, in half of the centres it was not used on a regular basis.

The following tests were initially selected for inclusion in the LADIS neuropsychological battery: the MMSE to assess global mental status; the Stroop Test and Trail-Making [57] to assess executive functions. In the absence of any frequently used battery, we added the VADAS-Cog [46] which is a recently developed instrument used to assess the cognitive performance of patients with vascular dementia. It is composed by the well-known ADAS-Cog [44], which assesses memory, orientation, language, ideational and constructional praxis, in addition to other specific tests that evaluate memory with interference, attention and executive functions (delayed recall, symbol digit, digit span, maze, digit cancellation, verbal fluency). The psychometric properties of these tests have been previously described with elderly populations [157, 158]. Table 2 tabulates the neuropsychological tests composing the initially LADIS battery and the cognitive domains they assess.

Table 2: LADIS Neuropsychologicalbattery

	MMSE	ADAS-Mod	VADAS					Trail making		Stroop
			Symbol digit	Digit span	Maze	Digit cancellation	Verbal fluency	A	B	
Global mental functioning	+	+								
Orientation		+								
Memory		+		+						
Attention			+	+		+		+		
Language		+								
Constructional abilities		+								
Executive functions			+				+		+	+
Praxis		+								
Speed and motor control					+	+		+		

MMSE = Mini-Mental State Examination; ADAS-Mod = Alzheimer's Disease Assessment Scale, Modified; VADAS = ADAS-Mod plus timed tests.

In order to reduce the time needed to administer the VADAS-Cog, only one trial was used on subtest 1 (word recall) and subtest 8 (word recognition), instead of the original three. On the VADAS-Cog, the translation of the words on subtests 1 and 8 was made according to the frequency of the words in each language [159]. On subtest 5 (naming objects), we used drawings instead of real objects, as it was the best way to reduce the heterogeneity of administration. The subtest "delayed recall" of the words of subtest 1 was also included on the ADAS-Cog. This subtest is scored as the other items of the ADAS-Cog (higher score representing worse performance). Because of these modifications, we will use the designation ADAS-Mod instead of ADAS-Cog. Finally, part B of trail-making (original version) was locally adapted to the alphabet of each country.

The original English version of all tests was collected by the centre responsible for the neuropsychological assessment workpackage and mailed to each centre to be locally translated. A handbook with the instructions of all the tests was also distributed to the centres in order to guarantee that each instrument would be used in the same way.

For the second year of follow-up, two additional tests were included: the 9-Word California Verbal Learning Test [160] and the constructional praxis delayed recall (based on the CERAD battery [161]), in order to improve the assessment of memory decline. Both these tests and the instrument used to assess participants who were unable to come to the visits (the Telephone Interview for Cognitive

Status [162]) will be described and analysed elsewhere, along with the results of the last follow-up.

Analysis of neuropsychological data

Neuropsychological data were analysed as follows: 1) analysis of the test scores distribution; 2) analysis of the differences on the neuropsychological performance related to the demographic variables and centre; 3) analysis of the influence of demographic variables on cognitive performance; 4) analysis of the influence of other potential confounding variables such as visual deficit, previous stroke, or centre of inclusion on the neuropsychological performance.

MMSE was used only as a global measure of cognitive functioning and analysed either as a continuous variable or categorised using the cut-off of ≤ 23 (for dementia), or < 25 (for cognitive deficit) [163]. The Stroop test was considered a measure of executive function, and the analysed measure was time used to perform Stroop 3 minus the time to perform Stroop 2. The Trail-making test was considered a measure of executive functions using the score “time needed to perform part B minus the time to perform part A”. Trail-making/A score was also used as a measure of speed and motor control. Higher scores on both the Stroop and the Trail-making represented worse performance. VADAS-Cog was analysed in two ways: a) as a global measure, consisting of the scores of ADAS-Mod items word recall, commands, constructional praxis, delayed recall, naming, ideational praxis, orientation, word recognition, remembering instructions, spoken language ability, word finding difficulty, comprehension, and concentration / distractibility. Higher scores represented worse performance; b) the 5 additional subtests digit span backwards, maze task, digit cancellation, symbol-digit and verbal fluency were evaluated independently. In all the tests except for maze (where the score is the time to complete the task), higher scores represent better performance.

Depending on the aim of the study performed on the LADIS sample, cognitive variables were analysed as continuous or categorical using specific cut-offs (in the case of MMSE) or the quartiles of the distribution of the LADIS sample (Table 3). For the present paper, all the test scores were analysed as continuous variables.

Table 3: Quartiles of the distribution of the neuropsychological tests scores

		MMSE	Stroop 1	Stroop 2	Stroop 3	Stroop 3 – 2	Trail A	Trail B	Trail B – A	ADAS-TOTAL	Symbol digit	Digit span	Maze	Digit cancel	Verbal fluency
Valid		638	628	626	619	618	633	605	605	633	627	635	632	626	631
Missing		2	12	14	21	22	7	35	35	7	13	5	8	14	9
Mean		27.3	12.0	17.0	50.9	34.1	63.5	177.3	116.8	16.6	26.8	5.4	7.4	19.5	18.9
Median		28.0	11.0	15.0	43.0	27.0	52.0	143.0	91.0	16.0	27.0	5.0	6.0	20.0	19.0
Percentiles	25	26.0	9.0	13.0	32.0	18.0	41.0	106.0	59.0	12.0	19.0	4.0	4.0	14.0	14.0
	50	28.0	11.0	15.0	43.0	27.0	52.0	143.0	91.0	16.0	27.0	5.0	6.0	20.0	19.0
	75	29.0	14.0	19.0	60.0	42.0	72.5	233.5	154.0	20.0	35.0	6.0	8.7	24.0	23.0
Skewness		–1.36	2.44	3.49	3.25	3.66	2.78	2.19	2.93	1.10	0.32	0.31	3.90	0.14	0.22

The distribution of the test scores was analysed for each variable. Non-normal distributions with marked skewness (> 2) were transformed into normal or less skewed distributions using a logarithmic transformation of the scores. Data analysis was conducted using both the raw and the transformed scores. As the results of raw and transformed scores where similar, the results based on raw scores were presented.

To compare performances across tests and by cognitive domain, we used Z-standard scores, using the distribution of the LADIS sample. To analyse performances by domain, compound measures were calculated using standard scores. Three main domains were analysed: 1) memory = z-scores of (Immediate word recall + delayed recall + word recognition + digit span) / 4; 2) executive functions = z-scores of ((Stroop3-2) + (Trail-making/B-Trail-making/A) + Symbol digit + verbal fluency) / 4; 3) speed and motor control = z-scores of (Trail-making/A + Mazes + Digit cancellation) / 3. Z-scores of the tests that had higher scores representing worse performance were inverted (- Z) in order to calculate the compound measure score. A preliminary exploratory factor analysis was performed to evaluate the validity of the neuropsychological battery and the aforementioned compound measures, using Principal Component Analysis as extraction method and Varimax Rotation. The obtained solution was compared with the theoretically derived dimensions.

The degree of ARWMC severity on MRI was rated into mild, moderate and severe using the visual scale of Fazekas *et al.* [164], taking only deep and subcortical white matter lesions into account.

The demographic variables considered for the present analysis were age, education, gender, living conditions (alone or with others), and employment status (retired, working). Age and education were analysed as continuous variables, except for when comparing demographic variables and neuropsychological performance where they were dichotomized using the median of the LADIS sample (74 years and 9 years, respectively).

There were several reasons for referral for the LADIS study, including minor cognitive or neurological complaints, stroke or other neurological disturbances [154]. Therefore, sources of referral were analysed as variables that could influence the performance on neuropsychological testing. Other possible confounders for the analysis of cognitive performance, such as visual or hearing deficits, were also considered in data analysis.

Statistical analysis

Descriptive statistics was performed to analyse the quality and distribution of the neuropsychological data. The distribution of demographic characteristics and test scores among centres was performed using box and whiskers plots. Differences among centres were calculated using one-way ANOVAs with Bonferroni or Tamhane's (equal variance not assumed) post-hoc analyses for multiple comparisons.

The neuropsychological performance in each test and domain was compared across demographic characteristics (age, sex, education, living conditions, employment status) using t-tests. Performance across cognitive tests was also compared according to the sources of referral using one-way ANOVA with Bonferoni post-hoc analysis. In order to study the influence of demographic variables on cognitive performance, linear regression models (including all the significant variables in the previous comparisons, $p<0.05$) were performed for each neuropsychological test and domain. Possible confound variables that could influence the results on neuropsychological performance, such as presence of

visual or hearing deficits, previous stroke or centre of origin, were also included in an additional linear regression model.

Results

Baseline neuropsychological data

Six hundred thirty-nine patients were enrolled in the LADIS study. Baseline demographic and WMC characteristics, as well as the reasons for referral of the patients are shown on Table 4. Neuropsychological examination was performed on 638 (99.8%) patients.

Table 4: Baseline demographic and WMC characteristics and reasons for referral of the patients

Study population (n = 638)	
Demographic factors	
Age, mean ± SD, years	74.1 ± 5
Female/male	351 (55%)/287(45%)
Education, mean ± SD, years	9.6 ± 3.8
Living alone/with other	205 (32%)/434 (68%)
Working/retired	24 (4%)/610 (96%)
Married/not married	401 (63%)/237 (37%)
WMC characteristics	
Mild	284 (44.5%)
Moderate	196 (30.7%)
Severe	158 (24.8%)
Reasons for referral	
Minor cognitive complaints	168 (26.3%)
Minor stroke	122 (19.1%)
Motor complaints	28 (4.4%)
Psychic complaints	13 (2%)
Incidental CT/MRI findings[a]	107 (16.7%)
Other neurological disturbances	129 (20.2%)
Controls in other studies or volunteers	72 (11.3%)

[a] Subjects undergoing a neuroimaging study for nonspecific reasons such as tension headache, dizziness, minor trauma, hearing complaints.

Quality of data and distribution of the test scores:

The highest number of missing values (33 patients, 5%) was observed on trail-making / part B (mental flexibility) and Stroop test / part 3 (3%). Five-hundred seventy-eight patients (91%) had no missing values on the neuropsychological

evaluation. Skewed distributions with a ceiling effect were observed in the subtests command, naming, ideational praxis, orientation, mazes, remembering instructions, spoken language, word finding difficulties, comprehension and concentration, which were transformed using the logarithmic of the scores. There were no differences in the results either using transformed or raw scores (data available when requested).

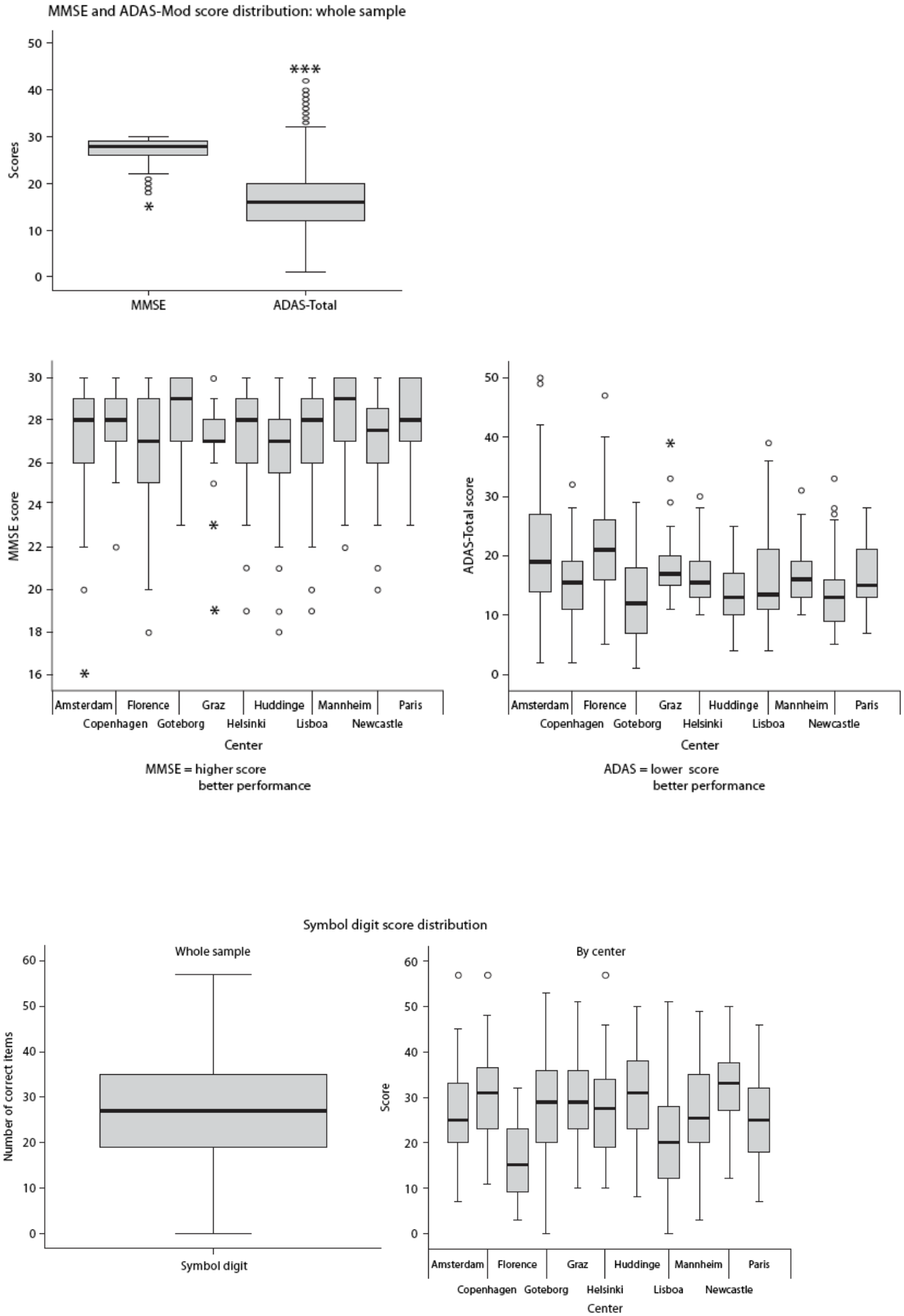
Preliminary exploratory factor analysis:

Factor analysis of principal components with varimax rotation extracted three factors: The eigenvalues for the 3 factors were 5.90, 1.44 and 1.41, explaining 48.6% of the total variance. For Factor I, the most salient tests were trail A, trail B, trail B-A, symbol digit, digit cancellation, maze task and verbal fluency. We denominated this factor as Executive Functions. Factor II was designated as Selective Attention because only Stroop 3 and Stroop 3-2 were loaded saliently. Factor III, was designated as memory as the loadings of the tests of memory as word immediate and delayed recall, word recognition and orientation were the most salient. For the compound measures scores, we excluded the simplest time performed tests as trail A, maze task and digit cancellation from the Executive Functions and added the Stroop test, for theoretical and interpretability reasons. The timed-performed tests were grouped into a Speed / Motor control measure.

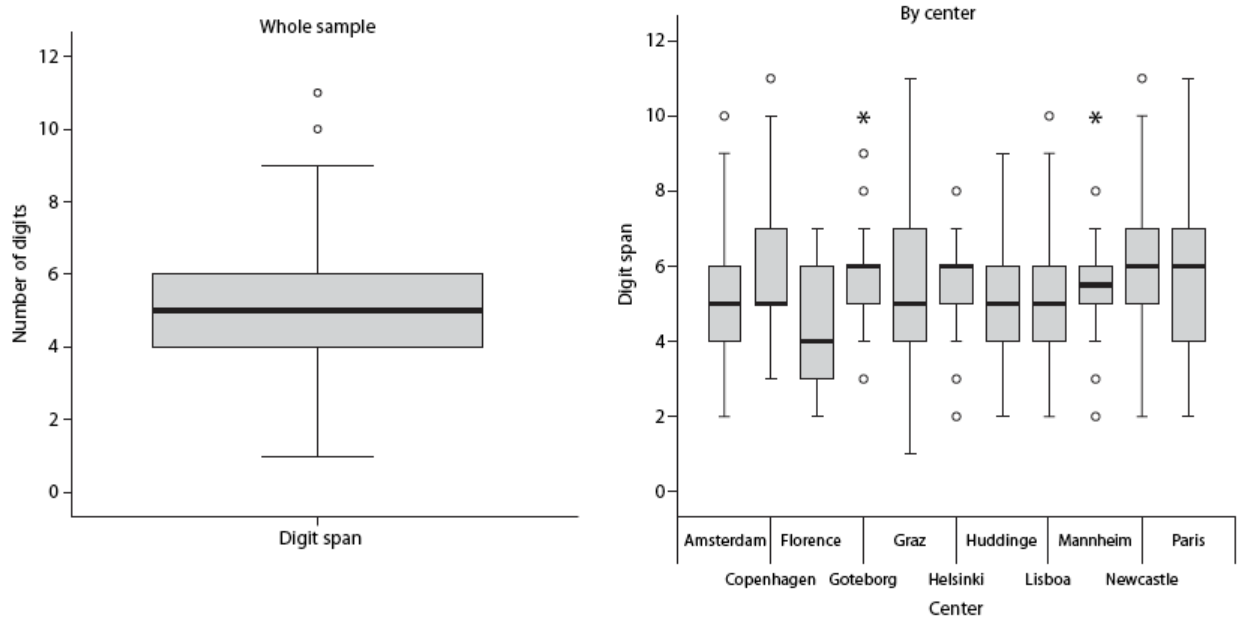
Distribution of the test scores according to centre:

Significant differences among centres were observed for all tests (One-way ANOVAs). Post-hoc analysis (Bonferroni's was employed for all tests, except for symbol digit and verbal fluency which were analysed with Tamanhe's test) showed that differences were randomly distributed, and no consistent pattern was found (there was no centre always better or worse than the others) (Figure 2).

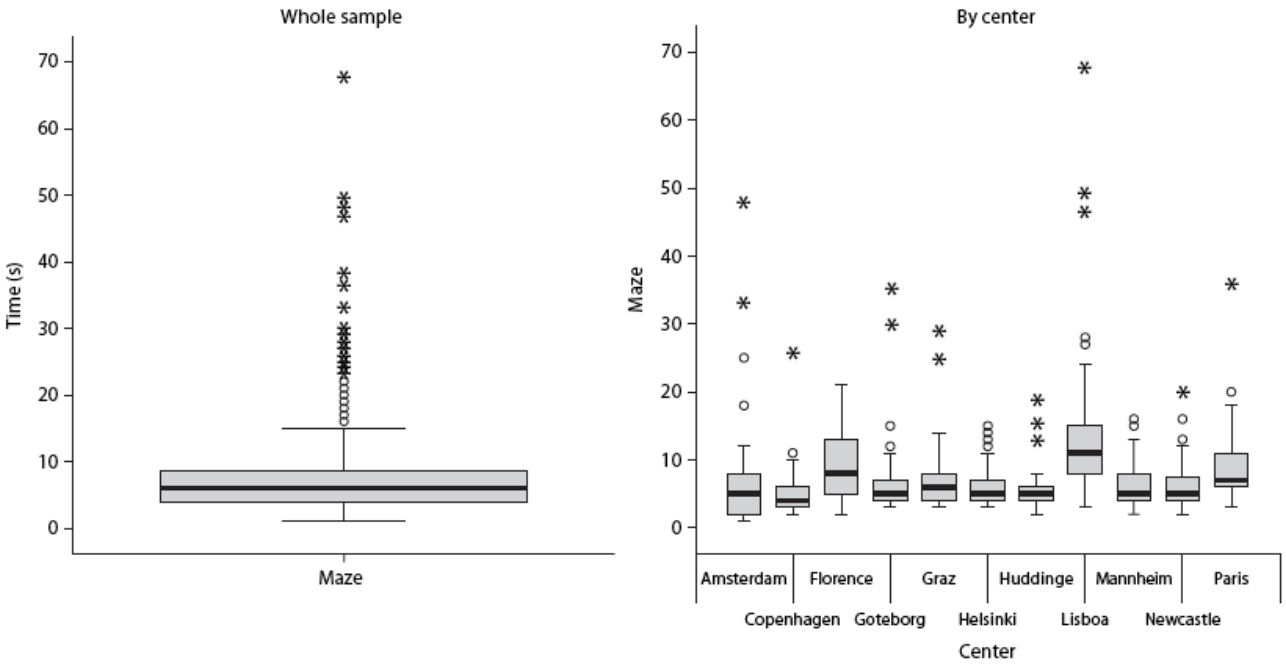
Figure 2: Distribution of the test scores of the whole sample and by center



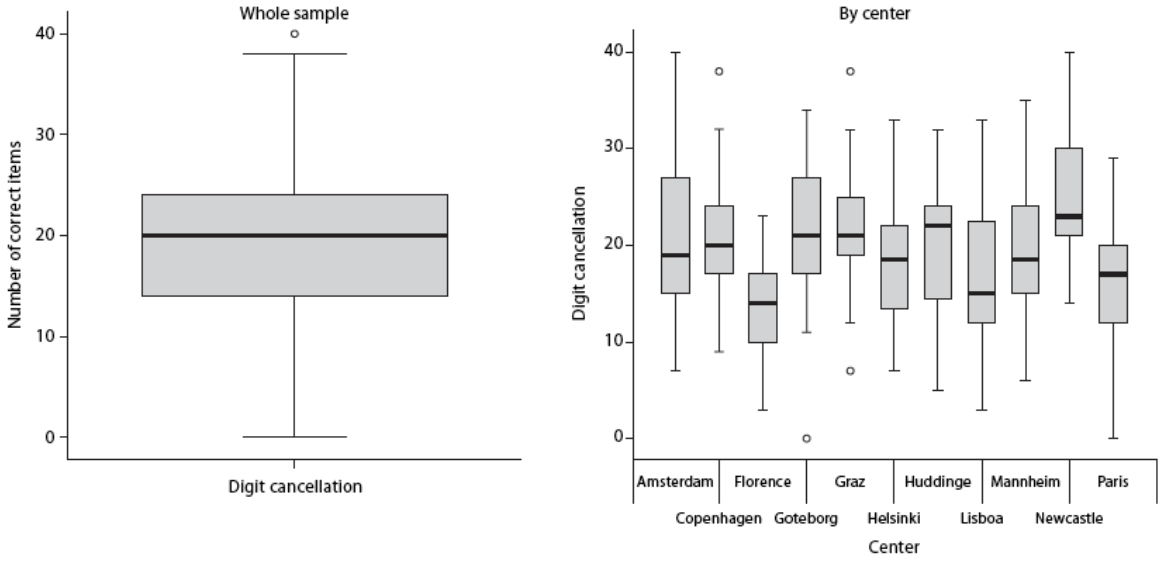
Digit span score distribution



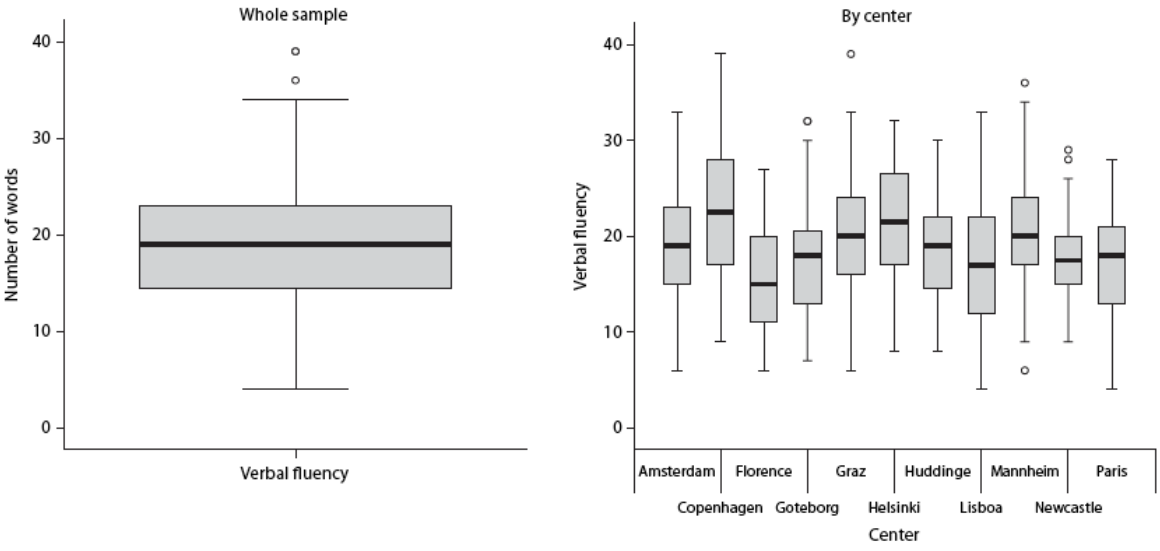
Maze time distribution

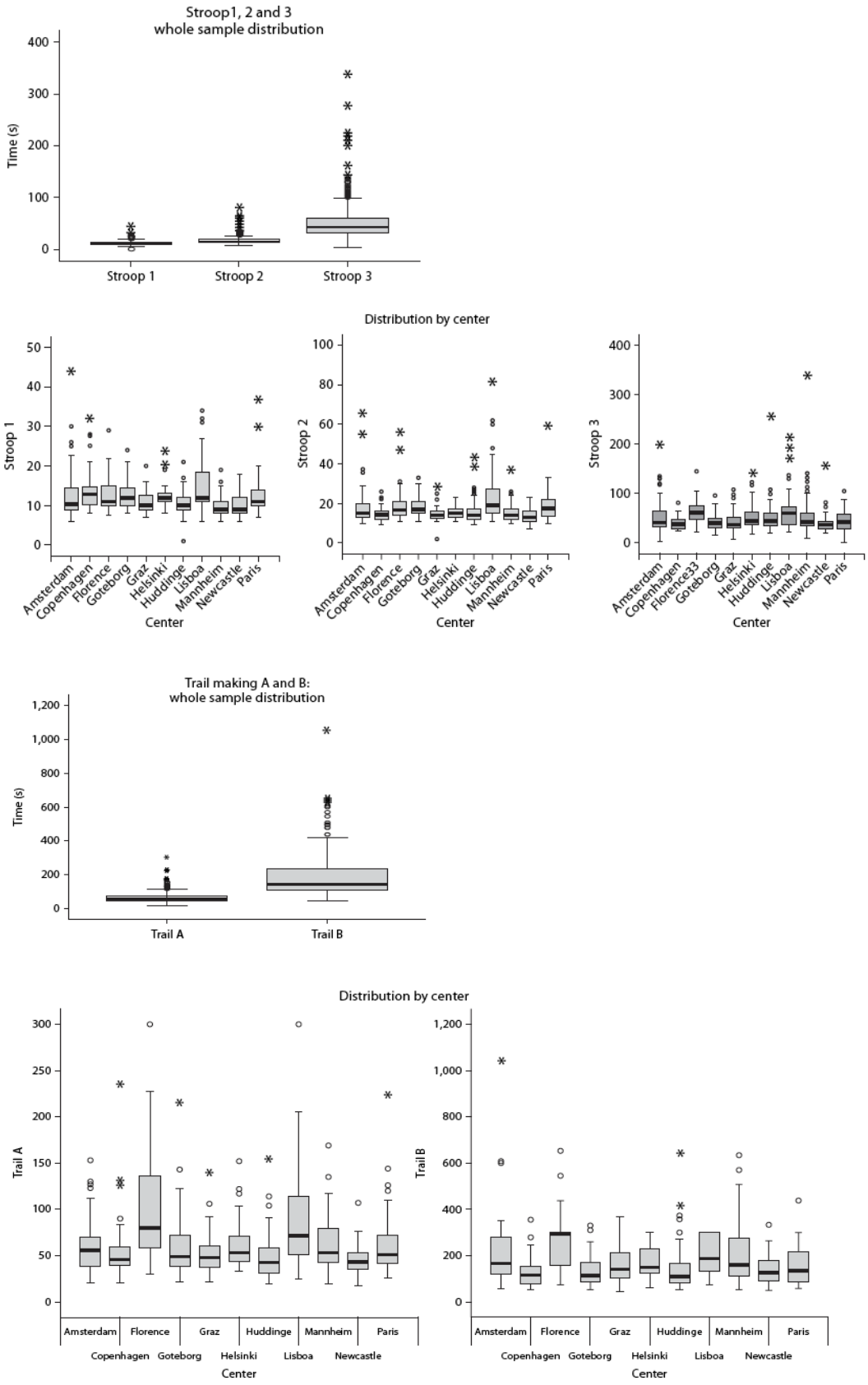


Digit span score distribution



Verbal fluency distribution





Box and whiskers represent the upper quartile (top of the box) and the lower quartile (bottom); bar represents the median; the largest value is on the superior whisker; the smallest value is on the inferior whisker. Open circles and asterisks signify outliers and extreme scores, respectively

The distribution of age and education by centre was analysed, as they are important variables for neuropsychological performance. No significant differences were found among centres with respect to age ($F_{(10,628)}$= 1.27; p= 0.24). Education had a normal distribution with significant differences among centres ($F_{(10,627)}$=11.76; p<0.001). Using Bonferroni post-hoc test, we found that Lisbon and Florence centres differed systematically from the other centres as they had the lowest mean educational levels (for both, p<0.01).

Mean differences regarding demographic variables:

Table 5 shows the differences on neuropsychological performance according to the demographic variables

Age

Older subjects (> 74 years) performed significantly worse than younger subjects on the ADAS-Mod Total based on the differences found on ADAS-Mod subtests constructional praxis ($t_{(513)}$= -3.09; p< 0.01) and delayed recall ($t_{(607)}$= -3.12; p<0.01). Older subjects also showed worse performances on Stroop part 3 ($t_{(617)}$= -2.63; p<0.01), trail making A ($t_{(537)}$= -3,16; p<0.01) and B ($t_{(456)}$= -3,40; p<0.01), symbol digit ($t_{(625)}$= 3,72; p<0.01), digit cancellation ($t_{(631)}$= 4.94; p<0.001) and verbal fluency ($t_{(629)}$=-2.83; p<0.01). Comparing the performance by cognitive domain, older subjects performed worse than younger subjects on executive functions ($t_{(581)}$= 4.68; p<0. 01), memory ($t_{(631)}$= 3.25; p<0. 01) and speed/motor control ($t_{(587)}$= 4.01; p<0.01).

Gender

Women performed significantly worse on the ADAS-Mod subtest constructional praxis ($t_{(635)}$= 3.18; p<0. 01) and maze ($t_{(630)}$= 2.54; p<0.01). There were no gender differences considering the three cognitive domains: executive functions ($t_{(581)}$= -0.99; p=0.31), memory ($t_{(628)}$= -0.18;; p=0.85) and speed/motor control ($t_{(621)}$= -1.46; p=0.14).

Education

Significant differences between subjects with higher (> 8 years of school) and lower educational level (< 9 years) were observed on all tests, except on ADAS-Mod orientation ($t_{(555)}$=1.93; p=0.05, immediate word recall ($t_{(635)}$=1.59; p=0.11), word recognition ($t_{(633)}$=1.93; p=0.05), and commands ($t_{(577)}$=1.94; p=0.05). Considering the compound measures of cognitive domains, subjects with lower educational level had worse performances on executive functions ($t_{(581)}$=-10.74; p<0.01), memory ($t_{(631)}$=-4.99; p<0.01), and speed/motor control ($t_{(381)}$=-8.36; p<0.01).

Living conditions

Participants who lived alone tended to performed better on trail-making A ($t_{(568)}$= 2.19; p<0.05). However, there were no differences on the other tests, nor on the cognitive domains executive functions ($t_{(581)}$=0.52; p=0.60), memory ($t_{(631)}$=0.46; p=0.64) and speed/motor control ($t_{(530)}$=-1.20; p=0.22). As it was not a significant variable, it was not included in the regression models.

Employment status

Participants who were still working performed worse on the ADAS-Mod commands ($t_{(29)}$=-3.28; p<0.01). No differences were found on other tests, nor on cognitive domains of executive functions ($t_{(576)}$=1.48; p=0.14), memory ($t_{(626)}$=1.05; p=0.29) and speed/motor control ($t_{(616)}$=1.02; p=0.31). As participants still working represented only 4% of the LADIS population, this variable was also not included in the regression models.

Sources of referral

Using a one–way ANOVA, we found significant differences in all the cognitive tests, except for the MMSE ($F_{(6,631)}$= 0.72; p= 0.63), ADAS-Mod subtests word recall ($F_{(6,630)}$= 1.93 p= 0.07), commands ($F_{(6,630)}$= 1.33; p= 0.24) and constructional praxis ($F_{(6,630)}$= 1.67; p= 0.12). Post-hoc analysis showed that healthy volunteers performed better in all the cognitive tests compared with patients with previous stroke or other complaints.

Multiple regression analysis

Multiple linear regression models were used to analyse the influence of the demographic variables on the neuropsychological performance. Table 5 shows the analyses performed with model 1, that included the variables age, education and gender; model 2, with added possible confounders, such as previous stroke, and any complaint or visual deficit; and model 3, in which centre origin was added as a covariable. Age remained an important variable influencing the performance of ADAS-Mod Total (R^2= 0.10; $F_{2,630}$ = 35.41; β=0.17; p<0.001) and cognitive domains executive functions (R^2= 0.22; $F_{2,580}$ = 79.99; β=-0.22, p<0.001), and speed/motor control (R^2= 0.16; $F_{2,619}$ = 59.68; β=-0.17, p<0.001).

There was no other significant influence of gender on neuropsychological performance except on ADAS-Mod constructional praxis ($R^{2change}$= 0.004; $F_{6,629}$ = 10.62; ; β= -0.10, p<0.01).

Education remained an important variable influencing the performance on all the tests and domains of executive functions, memory, and speed/motor control (Table 6).

Variables that might work as confounders of cognitive performance, such as “referral for any complaint“ (vs healthy volunteers), and previous stroke and visual problems, were included on the second linear regression model. To have any complaint remained an important variable influencing the performance on trail-making A ($R^{2change}$= 0.02; $F_{6,625}$ = 19.48; β= 0.12, p<0.01), trail-making B-A ($R^{2change}$= 0.10; $F_{16,587}$ = 11.81; β= 0.10, p<0.01), symbol digit ($R^{2change}$= 0.03; $F_{6,619}$ = 44.90; β= -0.13, p<0.001), digit cancellation ($R^{2change}$= 0.06; $F_{6,618}$ = 31.90; β= -0.21, p<0.001), digit span ($R^{2change}$= 0.01; $F_{6,627}$ = 18.62; β= -0.10, p<0.01) and compound measures speed / motor control ($R^{2change}$= 0.03; $F_{6,615}$ = 24.03; β= -0.12, p<0.001) as well as executive ($R^{2change}$= 0.02; $F_{6,576}$ = 30.32; β= -0.10, p<0.01). When visual impairment was included on the linear regression models its influence was observed on the performance of trail-making B-A ($R^{2change}$= 0.10;

$F_{16,587}$ = 11.81; β= 0.10, p<0.01), maze task ($R^{2change}$= 0.03; $F_{6,624}$ = 14.57; β= 0.15, p<0.001) and delayed recall ($R^{2change}$= 0.03; $F_{6,628}$ = 10.34; β= -0.12, p<0.01).

On the third step of the models, centre of origin was included as covariable. We found that centres influenced the performance of all the tests, but again the findings were randomly distributed and there was no centre influencing systematically all the dependent variables in the same way (Table 6).
In all the models, age and education remained important factors for neuropsychological performance.

Discussion

The LADIS neuropsychological battery was constructed with the purpose to evaluate the cognitive performance of a cohort of independent subjects with ARWMC, during a period of three years of follow-up. It is a comprehensive but not too long instrument able to be administered on a single visit, making it less unpleasant and intrusive for older patients. This battery was chosen based on the familiarity of the tests and the validity of the instruments to assess the decline of cognitive functions of patients with vascular disease. The LADIS battery explores a whole range of cognitive functions. Along with widely known and validated instruments (MMSE, Stroop and trail-making tests), it included the recently developed VADAS-Cog, which provides detailed information on cognitive global and selective functioning. Although based on the Alzheimer's Disease Assessment Scale (ADAS), the inclusion of time dependent tasks on VADAS (symbol-digit substitution, mazes tracing, digit cancellation and verbal fluency) complemented the evaluation of attention, speed of mental processing and motor control. These cognitive functions, along with executive functioning, are possibly more likely to be affected by white matter changes [165].

The inclusion of memory specific measures, particularly the 9-word CVLT, during the second and third year of follow-up, was adopted as a way to improve the evaluation of memory decline minimizing the learning effect that might occur if the memory test or the VADAS word recall subtest were administered four times instead of two.

The use of the same version and guidelines for administration of the tests in all the centres reduced the heterogeneity of the cognitive evaluation and allowed the appropriate evaluation of the whole sample of the LADIS cohort.

Nevertheless the neuropsychological battery adopted on the LADIS Study has some limitations: 1) when trying to reduce the time to administer the cognitive battery by using one trial instead of three as described in the original version of VADAS word recall subtest, we did not include any measure of learning memory on the baseline assessment and compromised the possibility of comparing the results of the LADIS sample with other studies that use the same instrument. However, this limitation was minimized by the inclusion of the 9-word CVLT during the second and third follow-up visits; 2) the test versions adopted were not validated in each centre/country and there is no control group to compare the results of the LADIS sample. The absence of a control group is due to fact that it would be necessary to perform MRI on normal volunteers and that would increase enormously the costs of the study; 3) using a handbook with all the administration norms for each test, we tried to reduce the differences concerning the training of the examiners that could lead to differences on the results.

Analysis of data obtained using the LADIS neuropsychological battery shows that differences among centres were observed for almost all the tests except naming and ideational praxis. However, the differences were randomly distributed and no consistent pattern was found. Cultural and educational variables might explain some of the differences between centres. Despite that, when Florence and Lisbon (which had the lowest mean education level) were excluded from the analysis, differences among centres remained. We found that, when compared with younger subjects, older subjects performed significantly worse on trail-making, symbol digit, digit cancellation tests and on executive functions and memory compound measures. Age remained an independent variable influencing the performance on memory and executive functions domains even when controlling for ARWMC severity. The effect of age on neuropsychological performance of healthy subjects with ARWMC was also reported by Ylikoski [30] ,who found that cognitive performance decreased on memory tests, constructional abilities,

language, timed performed tests and speed of mental processing. Our results are similar to those found on this work.

Education was the most consistent factor influencing the performance in all the neuropsychological tests and domains. The association between education and cognitive performance remained significant in the presence of ARWMC. Memory performance seems to be independent of the effect of education. This could be explained by the fact that in the baseline assessment of our study, memory was mainly evaluated verbally (word recall, delayed recall, word recognition, digit span), reducing the influence of education on pencil/paper tests. On the other hand, education seems to play a more important role on complex tasks such as executive functions. One study evaluating mainly speed and executive functions [166] reported the influence of education on the cognitive performance of a sample of elderly subjects with ARWMC. Dufouil *et al*. [167] found no relationship between WMC severity and cognitive performance on participants with a high level of education, and thus reinforced the hypothesis of the cognitive reserve [167]. Independently of the way education influences cognition, it should be considered as a covariate variable on analysing the effect of ARWMC on neuropsychological performance.

On the LADIS sample women performed worse on MMSE, constructional praxis and mazes. Female gender has been associated with difficulties performing visuoconstructional tasks and spatial orientation, which could explain the difficulties performing both constructional praxis and maze task. Although some studies [22, 168] reported a prevalence of earlier and more severe ARWMC on women, in our sample the prevalence and severity of ARWMC was similar for both sexes. In our study, women tended to have less years of education, which might explain the difference on the MMSE. Ott *et al.*, on a large populational study [169], reported a stronger association between low education and dementia in women than in men. However, in a recent study, Ruitenberg *et al.* [170] found that this association was mainly significant among people over 90 years old and that the incidence of dementia was similar for both sexes before this high age.

Conclusion

In our study, the analysis of the baseline neuropsychological data showed a significant influence of demographic variables on cognitive performance. Neuropsychological performance in patients with ARWMC was influenced by age and education. Higher educational level was consistently associated with better performances on cognitive tasks, while older age was associated with difficulties on memory and executive functions. The analysis performed on neuropsychological data on the LADIS study, thus, had to use age and education as modifiers and therefore as covariables.

Table 5: Influence of demographic variables on neuropsychological performance (t-test results) analysis

	MMSE	Executivefunctions						Attention		Speedand motor control			Memory					Language		Praxis		ADAS
		Stroop 3	Stroop 3-2	Verbal fluency	TM B-A	TM-B	EXEC	DC	Sy Dig	TM-A	Maze	Speed	Dig Sp	ImWord Recall	Del Word Recall	Word Recog	MEM	Com	Name	VC Praxis	Id Praxis	ADAS Total
Age	NS.	-2.63*	-2.55*	-2.83*	-2.86**	-3.40*	4.68*	4.94*	3.72*	-3.16*	-2.21**	4.01*	NS	NS	-3.12*	-2.14**	3.25*	NS	NS	-3.09*	NS	-3.84*
Gender	-2.31**	NS	NS	NS	NS	NS	NS	NS	NS	NS	2.54**	NS	NS	NS	NS	NS	NS	NS	NS	3.18*	NS	NS
Education	-6.66*	6.01*	5.14*	-7.37*	6.93*	8.33*	-10.74*	-9.80*	-13.48*	7.84*	5.87*	-8.36*	-9.41*	NS	5.83*	NS	-4.99*	NS	6.7*	5.39*	2.97*	5.69*
LivingConditions	NS	NS	NS	NS	NS	NS	NS	NS	NS	2.19**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Employment Status	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	-3.28*	NS	NS	NS	NS

Values are t-test; *p<0.01; **p<0.05; TM = Trail making; **EXEC** = executive functions compound measure; **DC** = digit cancellation; **Sy Dig** = Symbol-digit; **Dig Sp** = Digit Span; **Im Word Recall**=Immediate Word Recall; **Word Del Recall=** Word Delayed Recall; **Word Recog** = Word Recognition; **MEM** = Memory compound measure; **Com** = commands**; Name** = Naming; **VC Praxis** = Visuo-Constructional Praxis; **Id Praxis** = Ideational Praxis.

Table 6: Influence of demographic variables on neuropsychological performance (linear regression analysis)

	MMSE	Executivefunctions					EXEC	Attention	Speedand motor control		Memory					MEM	Language		Praxis		ADAS
		Stroop 3	Stroop 3-2	Verbal fluency	TM B-A	TM B		DC	Sy Dig	TM-A	Maze	SPEED	Dig Sp	Im Word Recall	Del Word Recall	Word Reco		Com	Name	VC Praxis	Id Praxis	ADAS Total
MODEL 1 (R^2)	.12*	.07*	.05*	.12*	.12*	.18*	.22*	.18*	.27*	.14*	.10*	.16*	.14*	.02*	.06*	.04*	.08*	ns	.09**	.10*	.02**	.10*
Age	ns	ns	ns	-.14*	.15*	.18*	-.23*	-.23*	-.18*	.13**	ns	-.17*	ns		.15*	.11**	-.15*		ns	.10**	ns	.15*
Education	0.33*	-.24*	-.20*	.31*	-.31*	-.38*	.40*	.34*	.49*	-.34*	-.27*	.36*	.38*	-.12**	-.18*	-.15*	.24*		-.30*	-.25*	-.13**	-.27*
Gender	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns		ns			-.10**	ns	ns
MODEL 2 ($R^{2change}$)	ns	.02**	ns	ns	.02**	.03*	.02*	.06*	.03*	.02**	.03*.	.03*	ns	ns	.03*	ns	ns	ns	ns	ns	ns	ns
Age		ns			.15*	.17*	-.22*	-.22*	-.17*	.12**	ns	-.15*			.16*							
Education		-.22*			-.29*	-.36*	.38*	.32*	.46*	-.33*	-.26*	.34*			-.17*							
Gender		ns			ns	ns	ns	ns	ns	ns	ns	ns			ns							
Anycomplaint		ns			ns	ns	-.10**	-.21*	-.13*	.12**	ns	-.12**			ns							
Stroke		ns			ns	ns	ns	ns	ns	ns	ns	ns			ns							
Visual deficit		ns			ns	.10**	ns	ns	ns	ns	.15*	ns			-.12**							
MODEL 3 ($R^{2change}$)	.07*.	.05*.	.05**.	.09*	.10*	.13*	.10*.	.07*.	.08*	.10*	.11*	.10*	.06*	.10*.	.29*	.09*	.14**	ns	.12*	.07*	.06*	.15*
Age	ns	ns	ns	-.16*	.16*	.18*	-.22*	-.22*	-.18*	.12*	.12**	-.17*	ns	.11**	.17*	.11**	-.17*			ns	ns	.16*
Education	.37*	-.20*	-.17*	.29*	-.30*	-.33*	.37*	.26*	.43*	-.25*	-.21*	.27*	.36*	-.17*	-.21*	-.15*	.27*			-.26*	-.11**	-.29*
Gender	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns			-.12**	ns	ns
Anycomplaint	ns	ns	ns	ns	.15**.	.14**.	-.12**	-.12**	ns	ns	ns	ns	ns	ns	ns	ns	ns			ns	ns	ns
Stroke	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns			ns	ns	ns
Visual deficit	ns	ns	ns	ns	.10**	.11**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns				ns	ns
Centre[1]	HU -.18*	CO -.20*; GO -.17**	CO -.14**; GO -.15**	CO .20*; HE .13**	CO -.18*; HU -.13**	CO -.22*; FL .13**; GO -.16**; HU -.20*	AM -.14**; CO .14**; FL -.18**	CO .13**; FL -.12**; GO .13**; NC .21*	CO .19*; HU .16*; NC .15**	CO -.21*; GO -.14**; GR -.14**; HE -.13**; HU -.22*; MA -.15**; NC -.21*	All centres	All except PA and FL	CO .13**; NC .19**; PA .12**	AM .13**; GO -.15**; GR .27*	AM .14**; GO -.19*; GR .29*; HE .14**; HU -.23*; NC -.22*	AM .17**; FL .15**; PA -.15**	AM -.20*; GR -.25*		CO -.20*; FL .15**; GO -.16**; HU -.18*; MA -.21*; NC -.19**	AM .19*; FL .23*; GO .17**; HU .21*; MA .19*; NC .18**; PA .21 *	GO -.14**; HU -.14**; NC -.17**	AM .30*; FL .21*; GR .19*

Values are standardized Beta; *p<0.001; ** p< 0.01; NS = p>0.05; **TM** = Trail making; **EXEC** = executive functions compound measure; **DC** = digit cancellation; **Sy Dig** = Symbol-digit; **Dig Sp** = Digit Span; **Im Word Recall**=Immediate Word Recall; **Word Del Recall**= Word Delayed Recall; **Word Recog** = Word Recognition; **MEM** = Memory compound measure; **Com** = commands; **Name** = Naming; **VC Praxis** = Visuo-Constructional Praxis; **Id Praxis** = Ideational Praxis.

Centres: AM = Amesterdam; CO = Copenhagen; FL = Florence; GO = Goteborg; GR = Graz; HE = Helsinki; HU = Huddinge; LS = Lisbon; MA = Manheim; NC = Newcastle; PA = Paris,

V - Neuropsychological predictors of dementia in a 3-year follow-up period: data from the LADIS study

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Neuropsychological Predictors of Dementia in a Three-Year Follow-Up Period: Data from the LADIS Study

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Key Words
Neuropsychological predictors, dementia · LADIS · White matter changes

Abstract
Background: White matter changes (WMC) are related to cognitive deficits and dementia. Our aim was to determine the extent to which the performance in neuropsychological tests would be able to predict the clinical diagnosis of dementia. ***Methods:*** The LADIS (Leukoaraiosis and Disability) is a prospective study that evaluates the impact of WMC on the transition of independent elderly to disability. The subjects were evaluated at baseline and yearly during 3 years with a comprehensive clinical, functional and neuropsychological protocol. At each visit, dementia was classified according to clinical criteria. The performance in the neuropsychological batteries was compared according to the clinical diagnosis of dementia. ***Results:*** From the initially enrolled 639 subjects, 480 were evaluated at year 3. Dementia was diagnosed in 90 participants. The demented subjects had worse performance in almost all the baseline cognitive tests. Using receiver operating characteristic curves, we found that the Vascular Dementia Assessment Scale (VADAS) battery had higher sensitivity and specificity rates (area under the curve = 82%) to identify dementia compared with the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale. Worse performance on baseline MMSE ($\beta = 0.33$; $p < 0.001$) and VADAS ($\beta = -0.07$; $p = 0.02$) were predictors of dementia (regression analyses). ***Conclusion:*** Performance on the MMSE and the VADAS battery were important predictors of dementia at a 3-year period.

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Introduction

Age-related white matter changes (ARWMC) have been associated with cognitive impairment and dementia, and represents a form of cerebrovascular disease. However, the relation between severity of ARWMC and progression to dementia or other forms of vascular cognitive impairment, which include vascular dementia and other cognitive impairment without dementia, is still not completely understood.

The LADIS study is a large multinational three-year longitudinal study [106, 171] that aims to identify the importance of the presence of ARWMC on the transition to disability in a non-disabled elderly population. For this pan-European study, a specific neuropsychological battery was constructed in order to include instruments sensitive to changes related with the presence of ARWMC, mainly executive and speed of mental processing functions [172, 173].

The importance of the use of sensitive measures for the cognitive evaluation of this specific population was described by Ylikoski *et al.* [173]. Their results showed that the inclusion of tests reflecting mental speed and executive functions, the VADAS-cog extension of the ADAS-Cog [46], was an important tool differentiating patients with mild to moderate and severe ARWMC. Although several instruments have been used in the assessment of cognitive dysfunction (including VADAS-Cog in clinical trials), it is important to validate sensitive tools for specific populations as it is the case of vascular patients, since different patterns of neuropsychological functioning are expected.

In addition, in a previously reported cross-sectional analysis of the neuropsychological baseline LADIS data, we identified the importance of other demographic (older age, lower educational level) and clinical (presence of diabetes, hypertension, previous stroke) factors on cognitive performance [172, 174] along with the presence of ARWMC.

Several studies performed with patients and healthy elderly have also associated specific cognitive deficits with ARWMC, such as speed of mental processing and

executive functions [30, 175, 176]. However, there is less information regarding the way these deficits progress over time.

Recent studies [177, 178] tried to identify neuropsychological predictors of vascular cognitive impairment (VCI), differentiating them from those frequently associated with Alzheimer's disease (AD). Ingles *et al.* [177] reported that low baseline scores on tests of free recall, similarities, comprehension, block design, and verbal fluency were associated with incident VCI 5 years after the inclusion. Also a trend toward an association between low baseline scores on the similarities subtest and incident VCI was found, in comparison with incident AD.

The aim of this paper is to determine the extent to which in the LADIS population, baseline performance in specific neuropsychological tests was able to predict the clinical diagnosis of dementia three years later.

Methods

Participants and methods

The rationale and methodology of the LADIS study have been extensively reported elsewhere [171, 172]. Briefly, the LADIS is a longitudinal multinational study involving 11 centres from 10 European countries (see Appendix 1) which aims to evaluate the impact of white matter changes on the transition to disability. Inclusion criteria were: a) age 65 to 84 years, b) white matter changes of any degree according to the modified Fazekas' visual rating scale [179], c) no or mild impairment (none or one item affected) on the instrumental activities of daily living (IADL) scale [108], and d) presence of a contactable informant and agreement to sign an informed consent. We excluded participants with: a) severe illness likely leading to drop out, b) severe unrelated neurological disease, c) leukoencephalopathy of non-vascular origin, d) severe psychiatric disorders, and e) inability or refusal to undergo brain MRI. Patients were enrolled due to minor neurological, cognitive or motor complaints or incidental finding on cranial imaging due to non-specific reasons (incidental finding in brain imaging) [171].

Participants were submitted to a comprehensive clinical, functional, motor and neuropsychological examination that was repeated yearly during a three year follow-up period. Clinical and functional assessment included: 1) standard cardiovascular and neurological examination; 2) functional status measured by means of the IADL scale and the Disability Assessment for Dementia scale [109]; and 3) health-related quality of life measured using the Euro-QoL 5D [180].
MRI was performed at baseline and at the 3rd year follow-up visit using a standard protocol [171]. White matter rating and volumetric analysis was performed by a single centre (Amsterdam) [181].

Six-hundred and thirty nine participants were included at baseline and 638 performed the complete baseline assessment. At the 3rd year of the study, 475 (75%) came to the last follow-up visit.

Neuropsychological evaluation

Participants were submitted to a standardized cognitive evaluation every year. The construction of the neuropsychological battery was described in detail in a previous paper [172]. The battery included: the Mini-Mental State Examination (MMSE)[37, 182] as a measure of global cognitive status; the Alzheimer's Disease Dementia Scale (ADAS-Cog) to assess memory, orientation, language, ideational and constructional praxis [44, 183] used in the original version (except on the words list recall item where we used one trial instead of 3); the Vascular Dementia Assessment Scale-cognition (VADAS-cog) extension, which includes delayed recall of the ADAS's 10 words list, a symbol digit test, a digit span backwards, a maze task, a digit cancellation task and a verbal fluency task (animal naming); the Trail-Making [57] and Stroop test [56] used to assess executive functions. The VADAS-cog total score was calculated accordingly to Ylikoski *et al.* [173]. The scores used as measures of executive functions were "time used to perform Stroop part 3 minus the time to perform Stroop part 2" and "time needed to perform Trail-making part B minus the time to perform trail-making part A". As described in detail in a previous paper [172], compound measures were calculated in order to analyse performances by domain. Three main domains were analysed: 1) memory, using the z-scores of Immediate word recall, delayed recall, word

recognition and digit span; 2) executive functions, using z-scores of Stroop3-2, Trail-making/B-Trail-making/A, Symbol digit and verbal fluency; 3) speed and motor control, using z-scores of Trail-making/A, Maze and Digit cancellation.

Criteria of dementia and cognitive impairment no dementia

At each follow-up visit, a questionnaire for the clinical diagnosis of dementia and dementia subtypes included in the LADIS protocol was filled by the clinician.

Criteria used to define dementia, dementia subtypes and cognitive impairment no dementia (CIND) are described in detail in a previous paper [171]. For the current study, we used the clinical diagnosis of dementia defined according to the DSM-IV criteria [111] and CIND according to Wentzel *et al.* [184].

When analysing the participants according to the clinical diagnosis, we used the Last Observation Carried Forward (LOCF) method to classify the participants who did not come to the 3rd year follow-up visit. The diagnosis observed on the last visit of the participant was then considered as the final diagnosis and analysed accordingly. The LOCF method was used to reduce the number of missing values.

Statistical analysis

Reasons of referral, demographic (age, gender, years of education), clinical (WMC severity) and cognitive (scores on neuropsychological tests) baseline characteristics were compared between participants who came to the 3rd year follow-up visit with those who did not, using bivariate analysis (T- test and Qui-square). The same procedure was used to compare participants with and without the diagnosis of dementia at the last follow-up.

When comparing baseline characteristics of participants with dementia, CIND, and no cognitive impairment, we used ANOVA with multiple comparisons analyses.

In order to ascertain the sensitivity and specificity of each neuropsychological test to predict diagnosis of dementia and CIND at the 3-years period, we used Receiver Operating Characteristic (ROC) analyses.

Multinomial logistic regression models adjusted for the confound variables were then used to identify the neuropsychological baseline predictors of dementia at the last follow-up visit.

In order to reduce the chance of Type I error, Bonferroni post-hoc analyses were used for ANOVA comparisons. A more conservative p-level of 0.01 was used for single tests.

Results

Descriptive and comparative analysis

Baseline demographic and clinical characteristics of the LADIS population have been described elsewhere [172].

From the 639 participants enrolled in the LADIS study, 480 (75%) could be evaluated in the last follow-up visit 3 years later. Patients who came to the last evaluation were younger (t = 3.68; p < 0.001), had a higher level of education (t = -2.94; p = 0.004) and presented better performance in the baseline MMSE (t = -4.30; p < 0.001), ADAS-Cog (t = 4.24; p < 0.001) and VADAS-Cog (t = 5.80; p < 0.001), Stroop test (t = 4.53; p < 0.001) and Trail-making (t = 6.17; p < 0.001) tests, when compared to those who were not able to come to the last follow-up. No differences were found considering WMC severity (X^2 = 5.39; p= 0.07) and reasons of referral (X^2 = 7.44; p= 0.28).

Four-hundred and eighty participants had the clinical diagnosis at the third-year visit of follow-up. Using the LOCF method we obtained a total of 588 participants with clinical diagnosis. A total of 90 (14%) out of these 588 participants had a clinical diagnosis of dementia: 12 participants with diagnosis at the 1st year follow-up visit; 7 with diagnosis at the 2nd year visit and 71 with the diagnosis on the 3rd year visit.

When comparing demographic and clinical characteristics of participants diagnosed with dementia and those without dementia on the last follow-up (Table7), we found that patients with dementia were older (t = 3.71; p < 0.001), had lower educational level (t = -2.38; p <0.02), more severe WMC (X^2 = 39.07; p < 0.001) and higher volume of WMC (t = 4.73; p < 0.001).

Table 7: Comparisons between participants with dementia and those with no dementia concerning demographic and clinical data

Demographic and clinical characteristics	Dementia		No dementia		t test	p value
	n	mean ± SD	n	mean ± SD		
Age, years	90	75.9 ± 4.7	498	73.7 ± 5.0	–3.71	<0.001
Education, years	90	8.8 ± 3.5	497	9.8 ± 3.9	2.57	<0.002
WMC						
Severe grade (χ^2)	90	47%	498	20%		<0.001
Volume	88	34.1 ± 2.9	480	18.7 ± 2.0	–4.73	<0.001

Concerning baseline cognitive performance (Table 8), participants with dementia had had lower scores in all the neuropsychological tests, except for the ADAS-Cog following command subtest (t = 2.56; p < 0.02). Participants with dementia had also had significantly lower scores at executive functioning (t = - 8.21; p < 0.001), memory (t = -9.68; p < 0.001), speed and motor control (t = -9.55; p < 0.001) than participants without dementia at the end of follow-up (Table 8).

Table 8: Comparisons between participants with dementia and those with no dementia concerning neuropsychological baseline performance

	Dementia		No dementia		t test	p value
	n	mean ± SD	n	mean ± SD		
Performance						
MMSE	90	25 ± 3	497	28 ± 2	–8.57	<0.001
ADAS-Cog total[1]	88	23 ± 8	496	15 ± 6	8.50	<0.001
Word recall	89	6 ± 1.8	497	5 ± 1.6	6.01	<0.001
Command	89	0.5 ± 0.7	498	0.3 ± 0.6	2.23	<0.03
Construction	89	0.8 ± 0.7	498	0.5 ± 0.7	3.49	<0.001
Naming	89	0.3 ± 0.6	498	0.1 ± 0.4	2.67	<0.001
Ideational praxis	89	0.4 ± 0.8	498	0.1 ± 0.5	2.98	<0.001
Orientation	89	1.1 ± 1.6	498	0.2 ± 0.8	5.43	<0.001
Word recognition	88	4.3 ± 2.8	498	2.5 ± 2.2	5.48	<0.001
Remembering instructions	89	0.5 ± 6.9	498	0.2 ± 0.6	3.24	<0.001
Spoken difficulties	89	0.3 ± 0.8	498	0.1 ± 0.4	2.28	<0.001
Word finding	89	0.5 ± 0.9	497	0.2 ± 0.5	3.28	<0.001
Comprehension	89	0.6 ± 0.9	498	0.2 ± 0.6	4.16	<0.001
Concentration	89	0.7 ± 1.1	498	0.3 ± 0.7	3.20	<0.001
VADAS-Cog total[1]	78	57 ± 11.6	483	41 ± 12.5	10.38	<0.001
Delayed recall	89	7.3 ± 2.1	497	5.5 ± 2.3	6.68	<0.001
Digit span	89	4.6 ± 1.6	497	7.3 ± 2.1	–5.15	<0.001
Verbal fluency	87	14.4 ± 5.6	495	20 ± 6.1	–8.25	<0.001
Symbol digit	84	18.2 ± 9.2	495	28.7 ± 10.5	–8.68	<0.001
Digit cancellation	84	15.2 ± 7	495	20.5 ± 6.5	–6.91	<0.001
Maze	84	11.9 ± 10.9	495	6.6 ± 4.6	4.36	<0.001
Stroop (3 – 2)[1]	84	51 ± 40	487	31 ± 23	4.47	<0.001
Trail-Making (B – A)[1]	85	144 ± 64	485	99 ± 59	5.93	<0.001
Compound measures						
Memory	88	–0.6 ± 0.6	496	0.1 ± 0.6	–9.52	<0.001
Executive functions	68	–0.6 ± 0.6	472	0.2 ± 0.7	–8.16	<0.001
Speed and motor control	80	–0.7 ± 1	490	0.2 ± 0.7	–7.10	<0.001

t test: non-parametric analysis was also conducted due to the skewness of the distribution of some tests. The results were similar. [1] Higher scores represent worse performance.

Demographic and Neuropsychological predictors of Dementia

We performed ROC analyses to ascertain the sensitivity and specificity of each neuropsychological test and battery to identify participants with dementia following a 3-year period. On the single tests analyses, we identified (Table 9) symbol digit and verbal fluency as having the higher scores of sensitivity and specificity (AUC 78% and 75% respectively) although fair.

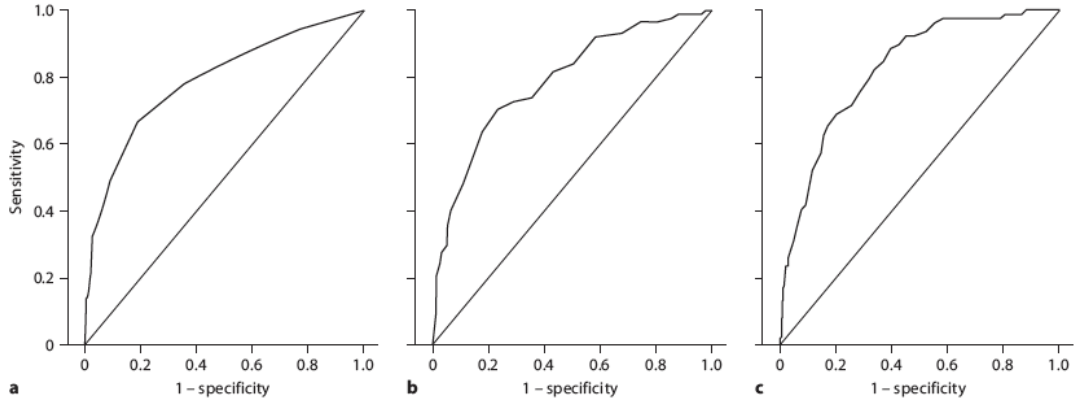
Table 9: ROC analyses, sensitivity and specificity of neuropsychological batteries and single tests

Batteries and tests	AUC %	Sensi-tivity, %	Speci-ficity, %
Batteries			
MMSE	79	29	87
ADAS-Cog	79	20	84
VADAS	82	25	88
VADAS extension	79	8	82
Single tests			
Trail making (part B – A)	70	–	86
Stroop (part 3 – 2)	69	62	86
Word immediate recall	68	71	85
Delayed recall	71	20	85
Word recognition	69	54	85
Constructional praxis	62	–	85
Ideational praxis	59	40	85
Naming	56	–	84
Orientation	70	65	84
Symbol digit	78	68	87
Digit span	64	50	85
Digit cancellation	73	55	86
Maze	71	58	86
Verbal fluency	75	45	86

– = No positive cases were identified.

Concerning the neuropsychological batteries, MMSE and ADAS-Cog obtained the same rate (79%) but VADAS-Cog had a good rate (82%) of sensitivity and specificity on identifying dementia at 3 years (Figure 3). VADAS-extension alone obtained 79% of sensitivity and specificity for dementia at 3 years.

Figure 3: ROC Curves of the three batteries



a MMSE total (AUC = 79%). **b** ADAS-Cog total (AUC = 79%). **c** VADAS Cog (AUC = 82%).

Using logistic regression analyses to identify neuropsychological predictors of dementia while controlling for age, education and WMC severity (as they are known predictors; see Table 10), we found that worse performance on MMSE (B =.33; OR = 1.39, 95%CI 1.19 -1.62; p<.001) and VADAS-cog (B = -.07; OR =.93, 95%CI 0.88 -1.0; p = 0.02) were independent predictors of dementia. In order to know which component of the VADAS (ADAS or the VADAS extension) was the stronger predictor of dementia, we repeated the logistic regression model separating the ADAS score from the VADAS-extension total score (data not shown). In this model, VADAS extension was an independent predictor of dementia (B =-.08; OR = 1.09, 95%CI 1.02-1.15; p<.01).

Table 10: Baseline neuropsychological predictors of dementia at a 3 years period (logistic regression analysis)

	β	p value	OR
Age	−0.069	0.03	0.93 (0.88–0.99)
Education	−0.116	0.01	0.89 (0.81–0.98)
WMH grade	−0.264	n.s.	0.77 (0.53–1.11)
MMSE total	0.328	<0.001	1.39 (1.19–1.62)
ADAS total	0.020	n.s.	1.02 (0.93–1.11)
VADAS total	−0.070	0.02	0.93 (0.88–0.99)
Trail B – A	−0.002	n.s.	1.00 (0.99–1.00)
Stroop 3 – 2	−0.002	n.s.	1.00 (0.99–1.01)

$R^2 = 0.34$. Figures in parentheses are 95% CI.

Concerning the neuropsychological baseline compound scores, both memory (B = 1.2; OR =3.33, 95%CI 1.9-5.9; p < 0.001) and executive functions (B =.69; OR = 2.0, 95%CI 1.15-3.46; p<.01) were independent predictors of dementia at the third year (Table 11).

Table 11: Baseline compound measures predictors of dementia at a 3 years period (logistic regression analysis)

	β	p value	OR (95% CI)
Age	−0.07	0.02	0.93 (0.87–0.99)
Education	−0.09	0.03	0.91 (0.84–0.99)
WMH severity	0.87	0.03	2.36 (1.10–5.07)
Executive functions	0.69	0.01	2.00 (1.15–3.46)
Memory	1.20	0.001	3.33 (1.88–5.90)
Speed and motor control	0.47	0.04	1.61 (1.01–2.55)

Figures in parentheses are 95% CI.

Demographic and neuropsychological predictors of cognitive impairment (dementia and cognitive impairment no dementia)

We compared participants who were diagnosed with dementia (DEM) (N= 90) with those diagnosed with CIND (N= 147) and those with no cognitive impairment (NCI) (N= 351) as clinically classified. Using ANOVA's with Bonferroni's multiple comparisons analyses (data not shown), we found that age was significantly different when comparing NCI participants with those with DEM (mean age NCI =73.4 ± 5, DEM = 75.8 ± 5; p<.001) but not when comparing NCI with CIND patients (mean age NCI = 73.4 ± 5, CIND = 74.2 ± 5; p = 0.41) not CIND with participants with DEM (p=0.05). Differences in educational level were significant when comparing NCI with CIND (mean educational level NCI = 10.3 ± 4, CIND = 8.8 ± 4; p< .001) and DEM (mean 8.8 ± 4¸p=.003), but not when comparing CIND with DEM (p> .05). Volume of WMC was significantly different in the 3 groups (mean WMC volume NCI = 16.5, CIND = 23.9; DEM = 33.8; p< .001).

Concerning baseline scores of the neuropsychological tests, there were significant differences between the three groups in the global measures (Figure 4), compound scores (Figure 5) and in all the single tests, except for ADAS-Cog's subtest following command. Multiple comparisons analyses (data not shown) allowed us to conclude that for ADAS-Cog subtests' word recall, delayed recall, word recognition, orientation, construction, naming, ideational praxis, remembering instructions, spoken, word finding, comprehension and concentration, the differences were significant only when participants with DEM were compared with those with NCI. In these tests, in the MMSE and in the Stroop "time to perform part 3 minus time to perform part 2", participants with NCI did not differ significantly from the group with CIND. When comparing the group of CIND with DEM we found significant differences in all the tests except ADAS-Cog's subtest construction, naming and ideational praxis.

Figure 4: Comparisons between participants with no impairment, CIND and dementia concerning baseline neuropsychological batteries (mean scores)

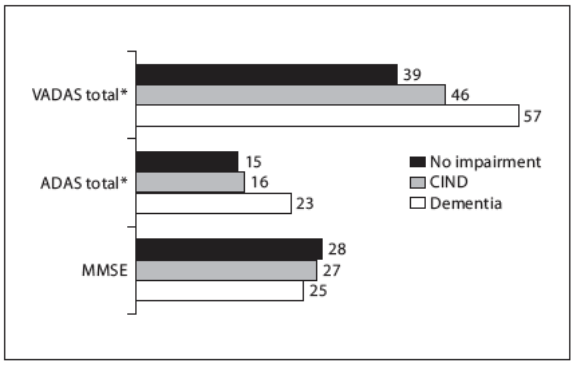
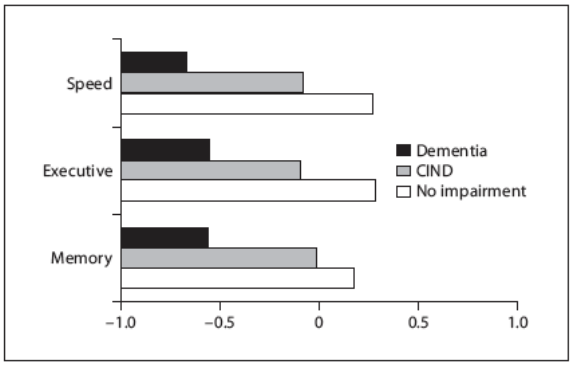


Figure 5: Comparisons between participants with no impairment,CIND anddementia concerning baseline neuropsychological compound scores (mean Z-scores)



* Higher scores represent worse performance; **All differences were significant (t test with $p < 0.001$)

When using ROC analyses to assess sensitivity and specificity of the neuropsychological tests and batteries in identifying participants with CIND at the third year (excluding participants with DEM), we found that none of the tests, batteries or compound measures had good rates (data available when requested). In the multinomial logistic analysis model (R^2 = .28), we included baseline global measures of MMSE, ADAS-Cog, VADAS-Cog, the Stroop and Trail-making test,

and used age, education and WMC (categorized) as covariates (Table 12). MMSE (B -.311; OR 1.36 (1.16- 1.60); p =.001) and VADAS-Cog (B -.093; OR .911 (.858-.968); p =.003) were independent predictors of dementia at a 3 year period of follow-up.

Table 12: Baseline NP tests predictors of no impairment, cognitive impairment no dementia (CIND) and dementia (multinomial logistic regression)

	β	p value	OR
No impairment			
Age	−0.076	0.02	0.93 (0.87–0.99)
Education	−0.101	0.04	0.90 (0.82–0.99)
WMH grade	−0.36	0.06	0.70 (0.48–1.02)
MMSE total	0.311	<0.001	1.37 (1.16–1.60)
ADAS total	0.037	0.40	1.04 (0.95–1.13)
VADAS total	−0.090	0.01	0.91 (0.86–0.97)
Trail B – A	−0.001	0.66	1.00 (0.99–1.00)
Stroop 3 – 2	−0.003	0.68	1.00 (0.98–1.01)
CIND			
Age	−0.054	0.12	0.95 (0.88–1.01)
Education	−0.144	0.01	0.87 (0.78–0.96)
WMH grade	−0.121	0.55	0.89 (0.59–1.32)
MMSE total	0.36	<0.001	1.43 (1.20–1.70)
ADAS total	0.023	0.62	0.97 (0.89–1.07)
VADAS total	−0.023	0.48	0.97 (0.90–1.07)
Trail B – A	−0.004	0.25	0.99 (0.99–1.00)
Stroop 3 – 2	−0.002	0.73	1.00 (0.98–1.01)

The reference category is dementia. Accuracy rate: 63% (>57%).

Discussion

Participants included in the LADIS study were followed during a 3 year period and assessed with a complete clinical and neuropsychological evaluation each year. At each visit, a clinical diagnosis of the mental status was made, which was defined as “dementia”, “cognitive impairment no dementia” and “no cognitive impairment”, for the purpose of this study. When we analysed the baseline results of these 3 groups, and despite the fact that participants were all functionally independent at the time of inclusion, we found that those clinically diagnosed with dementia at the

end of the 3-year follow-up period had had lower scores in almost all the baseline neuropsychological tests, when compared with participants without dementia. This is consistent with the understanding of dementia as a progressive disease that starts insidiously, usually without evident signs besides subtle differences of cognitive tests scores. In the LADIS study, the differences were observed in all the baseline tests and not only in those previously reported as sensitive enough to predict cognitive decline in normal individuals, such as episodic memory, executive functions or abstract reasoning and verbal fluency [177, 185]. Differences were also observed on the total scores of MMSE, ADAS-Cog and VADAS-Cog batteries between participants who developed dementia during a three-year period and those who did not, showing that general cognitive capacities are also affected by ARWMC.

Participants with dementia were also older, had lower educational levels and more severe ARWMC than participants without the diagnosis of dementia. These results are in line with previous reported data on the LADIS study. Increasing age and low educational levels have been identified as risk factors for lower cognitive performance even in the presence of ARWMC [172].

Besides older age and lower educational levels, baseline scores in the MMSE were important predictors of the diagnosis of dementia at the end of follow up. These were also reported in previous studies that tried to identify preclinical markers of VD and AD [177, 178]. Backman and Small [178] described a research program to identify preclinical markers of VD and AD. When reviewing the data from a community-based, longitudinal study, they reported the presence of preclinical deficits 3 years before the diagnosis of VD in the total score, delayed recall and orientation of the Mini Mental State Examination (MMSE), being used as an outcome measure. MMSE is a common instrument assessing global functions and detecting cognitive impairment. However, its sensitivity and specificity decrease when used to assess mild cognitive impairment, at least when using the original cut-off values. Nevertheless, in the LADIS study, the median baseline score for MMSE of participant who developed dementia during the 3 year period (median = 26) was higher than the original MMSE proposed cut off for dementia (< 25). This is also consistent with the reports of the importance of using different cut

off scores for the MMSE according to age and level of education. In a recent paper [186], it is proposed that a higher cut-off score should be used for detecting dementia among patients with higher educational levels. This change might also increase the rates of sensitivity and specificity of the MMSE for mild cognitive impairment.

Concerning sensitivity and specificity rates, we found MMSE to have lower scores compared with the VADAS-Cog battery. VADAS-Cog was previously reported that it was a more sensitive instrument to evaluate patients with WMC when compared with ADAS-Cog[173]. The authors identified that 5 (out of the 6) tests that compound the VADAS-Cog extension (namely, delayed recall, symbol-digit, maze, digit cancellation and verbal fluency), were able to differentiate among mild, moderate and severe WMC. Most of these 5 tests are used to assess speed of mental processing and executive functions, cognitive capacities shown to be impaired in patients with vascular disease or WMC [175]. However, in the LADIS population, none of the specific tests used to assess executive functions (Stroop and Trail-making tests) were baseline predictors of dementia at the end of follow-up. Some studies have found no relationship between ARWMC and specific tests for the assessment of executive functions [187, 188]. Nevertheless, in our study, the compound score of executive functions that, besides the Stroop and trail-making, includes scores on symbol-digit and verbal fluency tests, was an independent predictor of dementia at the end of follow up. Similarly, both symbol-digit and verbal fluency were the single tests with higher rates of sensitivity for dementia at 3 years. Semantic category fluency was seen to be an independent predictor of VCI [177].

Memory and executive baseline compound scores were independent predictors of dementia. An association between WMC and memory impairment has been previously reported [175]. Jokinen *et al.* found that memory impairment was mediated by executive functions and mental speed. They suggest that executive dysfunction causes secondary deficits such as memory impairment. In the LADIS population, dementia at the end of follow-up might be related with other causes rather than a direct effect of ARWMC. The heterogeneity of the type of dementia

(VD, AD with vascular component, others) might explain this multidomaine pattern of cognitive impairment.

In this paper we also compared participants with no impairment (NI) with those with CIND and Dementia at the end of follow-up. We found that performance on the baseline neuropsychological tests was distinctively different for the 3 groups clinically diagnosed at the end of the follow-up period, showing a consistent relation between clinical criteria and neuropsychological assessment.

We found that patients with CIND were older than patients with NI and younger than those with dementia. This group of patients had also a lower educational level when compared with participants with NI, but did not differ from those with dementia. Concerning cognitive performance at baseline, patients with CIND differed from patients with dementia in almost all the tests and global measures. When compared with those with NI, patients with CIND had no significant differences on the baseline performance of MMSE, Stroop and ADAS-Cog. These findings show the heterogeneity of this particular group, which seems to be in the continuous line between the “no impairment” and “dementia”. In the CIND group, we found participants with similar performances to those with no impairment but also with those with dementia, along with more risk factors for dementia such as older age. These results illustrate the difficulty of identify predictors in the CIND group, since it is very heterogeneous.

A possible limitation of this study is related to the use of dichotomized or categorized variables such as dementia/no dementia or NCI/CIND, including patients with different types of dementia in the same group. However, splitting these groups would reduce the statistical power and compromised the results. Also the absence of sensitive measures of memory, such as verbal learning and cued recall, limits our interpretation of the baseline results. However, the introduction of these tests during the follow up of the LADIS study will permit us to analyse the evolution of memory performance over time in further studies.

Conclusion

The present study contributes to the identification of sensitive measures to assess participants with ARWMC and to evaluate the risk of progression for dementia in a population with no functional or major cognitive impairment in initial evaluations. It also enhances the importance of the neuropsychological assessment to the study of subtle changes on progression to dementia.

In the LADIS study, baseline scores of MMSE and memory and executive compound scores were predictors of dementia at the end of the 3 year follow-up period.

VI - White matter changes and cognitive decline in a 10 year follow-up period: a pilot study from a single centre cohort from the LADIS study

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Original Research Article

White Matter Changes and Cognitive Decline in a Ten-Year Follow-Up Period: A Pilot Study on a Single-Center Cohort from the Leukoaraiosis and Disability Study

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Key Words
Cognition · Neuropsychological predictors · White matter lesions · Dementia

Abstract
Aims: To describe the contribution of white matter lesions to the long-term neuropsychological profiles of different groups of clinical diagnoses, and to identify neuropsychological predictors of cognitive impairment in a 10-year follow-up. ***Methods:*** The Lisbon subcohort of the Leukoaraiosis and Disability (LADIS) study was re-evaluated performing a clinical, functional and cognitive evaluation [including Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog) and ADAS-Cog with the extension for vascular impairment (VADAS-Cog), the 9-word version of the California Verbal Learning Test (CVLT-9), the Trail-Making test and the Stroop test] as well as an MRI scan. Using clinical diagnostic criteria, participants were identified as having no cognitive impairment (NI), cognitive impairment but no dementia (CIND) or dementia (DEM), and the effect of time on clinical diagnosis and neuropsychological profiles was analyzed. ***Results:*** From the initial group of 66 participants, 37 out of 41 survivors (90%) were re-evaluated (mean age 81.40 years, 57% women). Fifteen patients (41%) had DEM, 12 (32%) CIND and 10 (27%) NI. Over time, the three groups presented distinct profiles in the MMSE [$F_{2, 62} = 15.85$, $p = 0.000$], ADAS [$F_{2, 62} = 15.85$, $p = 0.000$] and VADAS [$F_{2, 48} = 5.87$, $p = 0.008$]. Logistic regression analysis identified higher scores on MMSE ($\beta = 1.14$, $p = 0.03$, OR = 3.13, 95% CI 1.09–8.97) as predictors of NI after 10 years of follow-up. ***Conclusion:*** Higher scores on baseline MMSE were the only neuropsychological predictors of NI after 10 years.

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Introduction

Longitudinal studies in the general population of cognitively intact participants, have demonstrated that increasing volume and increased progression of white matter lesions (WML) are related to lower global cognitive performance and conversion to mild cognitive impairment and dementia [38, 39]. In the 3 year follow-up of the Leukaoaraiosis and Disability (LADIS) study, WML and lacunes were found to progress over time appearing mostly in the subcortical white matter. Progression was related to more severe WML and higher number of lacunes at baseline, and to several vascular risk factors [122]. The impact of diabetes and severity of WML on decline of cognitive performance was also reported by Verdelho *et al*. in the LADIS study [174]In the same sample, neuropsychological predictors of dementia and cognitive impairment no dementia (CIND) were both identified, above and beyond clinical and demographic factors [189]. Patients who developed CIND or dementia 3 years after the inclusion, already presented lower scores on cognitive baseline performance in global measures such as Mini-Mental State Examination (MMSE) and Vascular Dementia Assessment Scale (VADAS), compared with those who had no cognitive impairment or CIND at three year follow-up, despite the fact that they were all functionally independent at baseline. Very long-term follow-up studies on the impact of WML for the transition to dementia are still rare [190-192] and none of them had followed a group of initially non-dependent participants with WML. Furthermore, prediction of no impairment is particularly less common in the literature and, hence, it is one of our foci using both global batteries and subtests scores.

In the present study we aimed to evaluate a subcohort of the LADIS study who had been functionally independent at baseline, after 10-year of follow up, in order to: 1) locate the cognitive evolution of different groups of cognitive clinical diagnosis; and 2) identify neuropsychological predictors of non impairment, cognitive impairment and dementia.

Methods

Participants and Methods

For the purpose of this study, we included all the 66 participants of the Portuguese Lisbon Centre who were previously enrolled in the longitudinal European multinational LADIS study. The rationale and methodology of the LADIS project had been extensively reported in other papers [106, 142]. Briefly, the LADIS study started in 2001 and aimed to evaluate the impact of WML in the transition to disability, during a follow-up of 3 years. Each of the 11 European centers involved, had to include participants with: (a) age 65–84 years, (b) WML of any degree according to the modified Fazekas' visual rating scale [107], (c) no or mild impairment (none or 1 item affected) on the instrumental activities of daily living scale [108], and (d) presence of a contactable informant and agreement to sign an informed consent. Patients were enrolled due to minor neurological, cognitive or motor complaints or incidental finding in brain imaging due to nonspecific grounds (controls on other studies and volunteers) [106]. The participants were submitted to a comprehensive clinical, functional, motor and neuropsychological examination that was repeated yearly, and an MRI was performed at baseline and at the end of the 3-year period.

For the current study, all the Lisbon surviving participants were contacted by a neuropsychologist (SM) and invited to come to an extra evaluation at the 10th year of follow-up. This visit consisted of: 1) a clinical and functional evaluation performed by a neurologist (AV), according to the LADIS protocol [106]; 2) a neuropsychological assessment, which included the LADIS battery consisting of the Mini-Mental State Examination (MMSE) [37] a measure of global cognitive status; the **Alzheimer's Disease Assessment Scale-Cognition** (ADAS-Cog) to assess memory, orientation, language, ideational and constructional praxis [44, 193] with the extension for vascular impairment (VADAS-cog) [116], that adds the delayed recall of the ADAS's 10 word lists, a symbol digit test, a digit span backwards, a maze task, a digit cancellation task and an animal naming verbal task; the Trail-Making [57] and Stroop tests [56] to assess executive functions; and the 9-word version of the California Verbal Learning Test (CVLT-9) [160] to assess memory and learning (for a more detailed description of the battery, see [142]; 3)

an MRI scan was performed according to the LADIS protocol [106], at the same Centre and with the same equipment which were previously used in the LADIS study. Severity of WML was visually rated by a neurologist (AV), who was blind to neuropsychological data, using the Fazekas' scale [107]. CD copies of the MRI scans were sent by mail to the same researcher who rated the follow-up MRI evaluation in the LADIS study (AG) and who was blind to clinical details and neuropsychological data. Progression of the WML and presence of new lacunes were visually rated in a side-by-side fashion and the entire procedure is described elsewhere [122]. Briefly, WML progression was rated on FLAIR images according to the modified Rotterdam Progression Scale (range 0 to 9) [124], in which "no progression" or "progression"(0 and 1, respectively) was rated in 3 periventricular regions (frontal caps, occipital caps, bands), 4 subcortical white matter regions (frontal, parietal, occipital, temporal), basal ganglia, and infratentorial region. Progression was also classified as "no progression", "mild" (progression in 1 to 3 regions) or "severe" (progression in more than 3 regions) [122]. New lacunes were also visually assessed, according to the number and location in 5 brain regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial). New cortical / lobar infarcts were also identified according to the number and location [122].

For participants who were unable to come to the hospital for assessment, home visits were conducted for clinical and neuropsychological evaluation. Information concerning non-surviving participants was collected in a face-to-face or telephone interview with the caregivers/informants. This interview included a drop out/death questionnaire used in the LADIS study, which collects clinical and functional data.
The study was submitted and approved by the Ethical Committee of the university hospital (Faculdade de Medicina, Hospital de Santa Maria).

Neuropsychological data and cognitive status

For the purpose of this study, neuropsychological battery scores were analyzed as previously described in detail [142]. Briefly, we used both subtests scores and total raw scores of ADAS and VADAS-Cog, the last one calculated according to Ylikoski *et al*.[194]. We considered 'time used to perform Stroop part 3 minus the time to perform Stroop part 2' and 'time needed to perform Trail-Making part B

minus the time to perform Trail-Making part A (raw scores), as measures of executive functions. CVLT-9 scores used for the purpose of this study were the total raw score of the 5 learning trials and the raw score of both short and long delayed free recall tasks, as measures of verbal learning and retrieval.

Cognitive status of participants was evaluated clinically and classified into three groups by a Neurologist (AV), who had access to MRI results but was blinded to neuropsychological data, 1) no cognitive impairment (NI); 2) cognitive impairment not demented (CIND); and 3) demented (DEM), accordingly to previously established sets of criteria[195]. Briefly, for CIND two types were considered: 1. amnestic mild cognitive impairment (MCI) [135]; and 2. vascular cognitive impairment without dementia (VCIND)[136]. For dementia were considered the following subtypes: probable Alzheimer disease (AD) [137],probable vascular dementia (VD) [138], frontotemporal dementia [140] and dementia with Lewy bodies (DLB) [141].

Statistical analyses

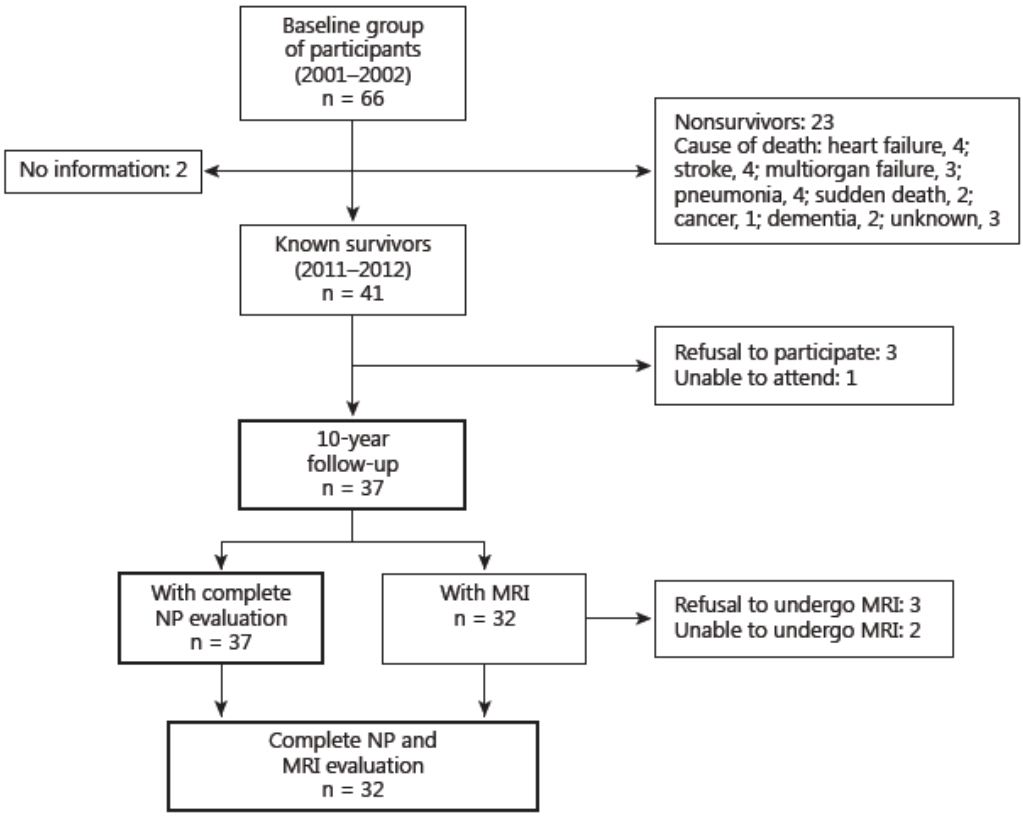
To test associations between clinical diagnosis or progression of WML with different variables, and differences among participant groups, bivariate analyses were used: a) comparing survivors and non-survivors and, b) those who came to the follow-up evaluation at 10 years with those who did not, to assess potential selection bias, using non-parametric tests (Mann-Whitney test, Chi-Square test); c) comparing groups of diagnosis (NI, CIND, DEM) concerning neuropsychological performance using non-parametric statistics such as Mann-Whitney test and Kruskall-Wallis test for multiple groups. ANOVAs with repeated measures were performed in order to study how test scores changed across the 3 time points (baseline, 3rd and 10th years of follow-up), exploring the effect of time, clinical diagnosis group and the interaction between them. In these series, time and clinical diagnosis at 10th year (NI vs CIND vs DEM) were used as independent variables. We also performed regression analyses (linear and logistic) to identify predictors of clinical decline using the most significant demographic, clinical and neuropsychological data as independent variables. For each analysis age and education were included in step 1 as independent variables, since they are known to influence cognitive performance. Baseline WMC severity (mild, moderate or

severe) was added in step 2 and cognitive baseline performance was included in step 3. No more than 4 variables were included in each model to avoid Type I errors. Specifically we tested the effects of known clinical predictors (diabetes and stroke) and global neuropsychological measures. A 0.05 level of significance was used except when comparing multiple tests with multiple variables, where a more conservative level of 0.01 or 0.001 (Bonferroni's correction) was adopted. Data analyses were performed using the SPSS 21.0 software.

Results

From the initial group of 66 Portuguese elderly participants who had been enrolled in the LADIS study in 2001-2002, 41 (62%) were still alive at the 10 year-follow up visit (Figure 6). Twenty-three participants died during the 10-year period (1 during the first year of the study, 1 in 2004 and 21 between 2005 and 2012). The most frequent cause of death was stroke (4 patients) and heart failure (4 patients). Two participants were lost for this follow-up and we were unable to obtain any further information. One of them was lost during the first year of the study.

Figure 6: Schematic representation of participants assessed at year 10th



There were no significant differences between survivors (n=41) and non-survivors (n= 23) concerning sex ($X^2(1)=0.03$, p=0.88), educational level (U=368, p=0.11) and WML severity ($X^2(2)=2.56$, p=0.28) or WML volume (U=590, p=0.10) at baseline. Non-survivors (mean age at baseline = 74.7±4.8) tended to be older than survivors (mean age at baseline = 72.1±5.1; U = 691, p=0.04). Concerning the cognitive clinical diagnosis at the third year of evaluation, survivors and non-survivors had no significant differences ($X^2(2)=4.66$, p=0.10).

Of the 41 participants who were alive 10 years after the enrollment in the LADIS study, 4 refused to participate and 1 was living in a nursing home far from Lisbon and it was not possible to evaluate him in the new residence. Thus 37 (90%) could be evaluated at the 10th year of follow-up. Participants who came to this evaluation (n=37), when compared with all those who did not come (n= 29), had a higher level of education (U=377; p=0.02), but were not different concerning sex, age, baseline WMC severity, or clinical diagnosis at the 3rd year. There were also no differences concerning MMSE scores at baseline (U=434, p=0.18) and at the 3rd year of follow-up (U=275, p = 0.08), as illustrated in Table 13. Of the 37 participants who came to the 10th year of follow up, 5 refused (n=3) or had contraindications (n=2) to repeat the MRI scan. Thus, a final group of 32 (78%) participants conducted complete neuropsychological and also had MRI evaluation at 10 years of follow-up.

Table 13: Comparisons between participants who conducted the 10th year follow-up and those who did not

	Participants who attended (n = 37)	Participants who did not attend (n = 29)	p value
Mean age at baseline, years[a]	72.35	74.28	n.s.
Mean age at 10-year follow-up, years	81.30	–	–
Mean education, years[a]	8.2	5.6	0.02
Sex[b]			
Female	21	17	n.s.
Male	16	12	n.s.
Baseline WMLs[b]			
Mild	20	14	n.s.
Moderate	9	6	n.s.
Severe	8	9	n.s.
Mean baseline WML volume, ml[a]	19.11	18.65	n.s.
Third-year clinical diagnosis[b]			
NI	16	10	n.s.
CIND	17	11	n.s.
DEM	4	7	n.s.
Mean MMSE score[a]			
Baseline	27.57	26.69	n.s.
Three-year follow-up	27.28	25.81	n.s.

n.s. = Nonsignificant. [a] Mann-Whitney test. [b] χ^2 test.

WMC = white matter changes; MMSE = Mini-Mental State Examination; CIND = Cognitive Impairment No Dementia;

In the sample at the 10th year follow-up there were 37 participants (21 women; 57%), with a mean age of 81 years old (ranging from 74 to 92 years old) and a mean educational level of 8.2 years (ranging from 4 to 26 years of education). Of those who underwent a MRI, severe WML at follow-up were observed in 16 (43%) patients, moderate in 7 (19%) and mild in 9 (24%) of the participants.

Fifteen patients (41%) were clinically diagnosed with dementia (Vascular Dementia =10; Alzheimer's Disease =4; Dementia with Lewy Bodies (DLB) =1), 12 (32%) with CIND, and 10 (27%) showed no cognitive impairment (NI).
Compared to the clinical diagnosis of the 3rd year of follow-up, 14 participants had cognitively declined: 6 participants (16%) changed from NI into CIND (MCI= 2; VCIND=1) and DEM (VD = 1; AD= 1; DLB=1), and 8 participants (22%) changed from CIND to DEM (VD=6; AD=2).
At the 10th year follow-up, cognitive performance for the total sample as well as for the groups of participants with NI and participants with any impairment (CIND or dementia) is presented in Table 14. Overall, data showed that, as expected,

neuropsychological performance after 10 years was statistically better for participants without any cognitive impairment than for those who had CIND or Dementia.

Table14: Neuropsychological performance at the 10th yearfollowup (raw test scores)

Neuropsychological performance	No impairment		Any impairment		Total		Mann-Whitney U value
	n	mean ± SD	n	mean ± SD	n	mean ± SD	
MMSE	10	28.20±1.62	27	21.19±7.98	37	23.08±7.52	214**
ADAS-Cog							
Total[a]	10	17.00±5.67	25	28.92±12.78	35	28.77±17.47	51**
Word recall[a]	10	5.00±1.41	26	6.69±2.21	36	6.22±2.14	n.s.
Command[a]	10	0.20±0.63	26	0.69±1.26	36	0.56±1.13	n.s.
Construction[a]	10	0.70±0.95	25	0.96±1.21	35	0.89±1.13	n.s.
Naming[a]	10	0.30±0.48	25	1.52±1.61	35	1.17±1.48	52.5**
Ideational praxis[a]	10	0.80±1.03	26	1.96±1.48	36	1.64±1.46	n.s.
Orientation[a]	10	0.10±0.32	26	2.31±2.43	36	1.69±2.29	47.0**
Word recognition[a]	10	3.00±2.26	25	6.24±3.92	35	5.31±3.79	n.s.
Remembering instructions[a]	10	0.00±0.00	27	1.37±1.90	37	1.00±1.72	75.0*
Speaking difficulties[a]	10	0.00±0.00	27	1.07±1.71	37	0.78±1.53	n.s.
Word finding[a]	10	0.00±0.00	27	1.04±1.63	37	0.76±1.46	n.s.
Comprehension[a]	10	0.10±0.32	27	0.81±1.50	37	0.62±1.32	n.s.
Concentration[a]	10	0.10±0.32	27	0.63±1.15	37	0.49±1.02	n.s.
VADAS-Cog							
Total[a]	10	49.30±11.10	22	66.72±16.44	32	61.28±16.92	40.5**
Delayed recall	10	6.90±2.28	26	8.23±1.90	36	7.86±2.07	n.s.
Digit span	10	4.00±2.11	25	3.24±1.86	35	3.46±1.93	n.s.
Verbal fluency	10	19.60±4.14	26	11.23±6.31	36	13.56±6.88	224.5**
Symbol digit	10	18.40±9.83	23	10.57±9.71	33	12.95±10.27	n.s.
Digit cancellation	10	16.60±7.30	24	10.00±6.74	34	11.94±7.46	n.s.
Maze[a]	10	12.20±6.34	23	16.00±11.05	33	14.85±9.92	n.s.
Stroop							
Stroop 3-2[a]	10	34.00±31.78	19	47.79±29.14	29	43.03±30.25	n.s.
Stroop 1[a]	10	10.70±4.30	21	27.76±16.63	31	22.26±15.99	20.5**
Stroop 2[a]	10	18.20±4.24	21	37.05±30.02	31	30.97±26.20	41.0**
Stroop 3[a]	10	52.20±32.93	20	77.50±34.69	30	69.07±35.67	n.s.
Trail-Making							
Trail-Making B-A[a]	10	124.7±55.16	19	143.50±73.63	29	137.00±67.42	n.s.
Trail-Making A[a]	10	67.90±35.46	23	150.43±90.89	33	125.42±86.70	44.5**
Trail-Making B[a]	10	192.60±77.25	19	273.63±47.32	29	245.69±69.96	24.0**
CVLT-9							
Total	10	36.20±6.70	27	21.63±10.73	37	25.57±11.7	236.5**
Short delay	10	7.30±1.8690	27	2.70±2.63	37	3.95±3.18	241.0**
Long delay	10	6.80±2.15	27	3.11±2.47	37	4.11±2.88	232.0**
Recognition	10	7.80±2.82	27	6.93±2.95	37	7.16±2.90	n.s.

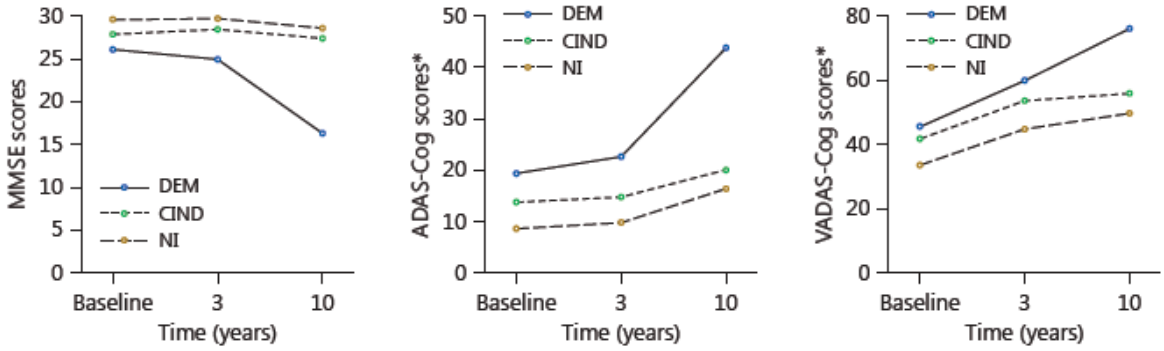
[a] Tests in which higher scores indicate worse performance. * $p < 0.01$; ** $p < 0.001$.

Changes in cognitive performance across the 10-year period

Regarding general scores of neuropsychological measures, we used ANOVA repeated measures to evaluate the main effect of time and group in each battery or test. For MMSE scores (Figure 7), the main effect of time was significant [$F(2,66)=21.52$, $p=0.000$], with performance decreasing after the 3rd year; the main

effect of participant group (NI, CIND, DEM) was also significant, [F(2,66)=17.65, p=0.001], with the group of patients with dementia demonstrating the lowest results; and the interaction effect of time x group was significant [F(4,66)=14.24, p=0.000]. The steeper decline was found among participants with dementia even though the three groups decreased performance over time.

Figure 7: MMSE, ADAS-Cog and VADAS-Cog scores over 10 years for participants with no cognitive impairment (NI), with cognitive impairment no dementia CIND and with Dementia (DEM)



A similar analysis was performed for ADAS-Cog in which we also found a significant main effect of time [F(2,62)=37.88, p=0.000], of group [F(2,62)=15.85, p=0.000], and of the interaction between time x group [F(4,62)=8.97, p=0.000]. Given that high scores represent worse performance, the Graph (Figure 7) reveals that performance also decreased with time, especially after year 3 and that the group whose results worsened the most was the group with dementia.

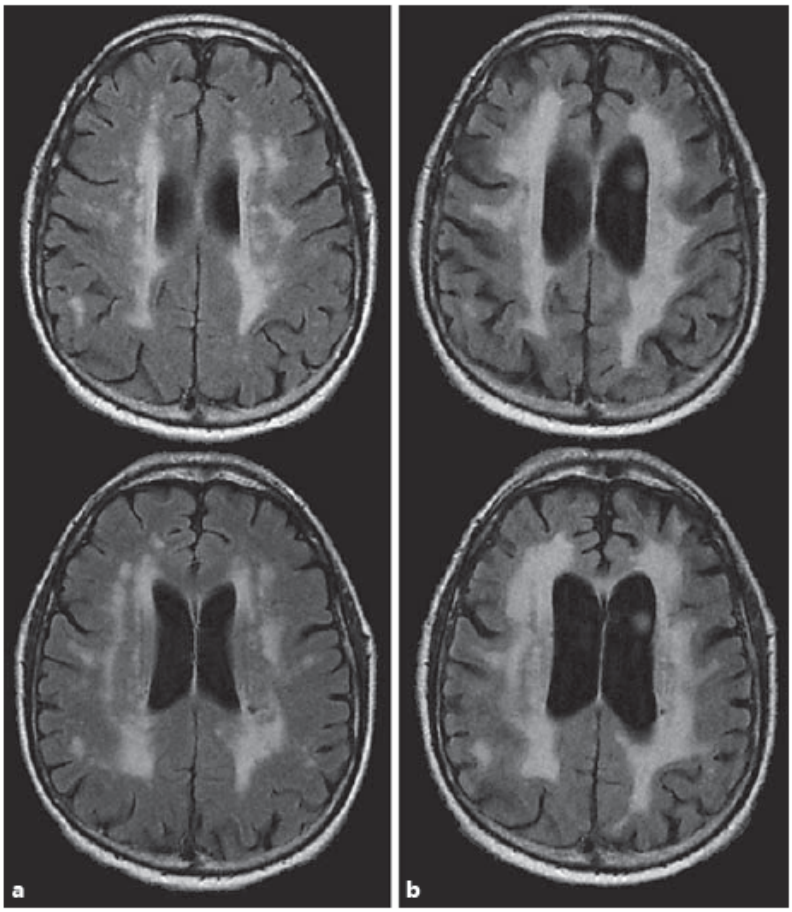
The VADAS-Cog was also explored in terms of the change across the 10-year period. The main effect of time [F(2,48)=41.35, p=0.000], the main effect of group [F(2,48)=5.87, p=0.008], and the interaction effect [F(4,48)=3.430, p=0.018] were significant as well (Figure 7).

When changes across time were explored for the executive measures of both trail-making and Stroop, only a significant effect of time [F(2,46)=6.95, p=0.002] and group [F(2,46)=5.98, p=0.008] were found for TM B-A, but the interaction time x group was not significant.

WML progression, cognitive performance and clinical diagnosis

Four (13%) out of the 32 participants who performed the MRI, showed no WML progression from the baseline assessment. Mild WML progression was observed in 11 (34%) participants, and 17 (53%) had severe WML progression (Figure 8 illustrates an example of WML progression from baseline to the 10th year of follow up). Presence of, at least, one new lacune was identified in 9 (28%) participants. Participants with severe WML progression had a tendency to have lower education comparing with those who did not progress or had a mild progression (U=178.5, p=0.05). No other differences were found concerning age (U=170, p=0.11) or WML volume at baseline (U=142, p=0.58). There were no significant differences between participants with NI and those with any impairment concerning WML progression (U=102.5, p=0.96) or presence of new lacunae (U=90, p=0.47). Concerning WML severity at 10th year, participants with NI had less severe WML than participants with any impairment (X^2(2)=9.21, p=0.01).

Figure 8: MRI axial FLAIR images of one patient at baseline (a) and 10 years after (b), show a clear progression of WMC in the frontal caps and bands of the periventricular region (b)



Predictors of Clinical Diagnosis at 10-years follow-up

Participants with NI at 10 years had also no significant differences concerning volume of WML at baseline, when compared with participants with CIND or DEM (U=72; p=0.031), presence of medial temporal lobe atrophy (MTA) (U=86, p=0.08), or WML progression rated at year 3 (U=104, p=0.60).Regarding the presence of new stroke (N=4) or lacunes (N=9) during the long-term follow up, its effect also failed to reach statistical significance comparing participants with NI or any cognitive impairment.

A logistic regression was performed in order to determine the ability to predict non impaired participants (NI) after 10 years, based on the cognitive measures that appeared to distinguish participants with NI from those with any cognitive impairment. For each analysis, step 1 included the demographic variables of age and education, given their known association with cognitive performance, in order to control for their effect. Step 2 entered the baseline WML and in step 3 were included cognitive scores as dependent variables. Only MMSE (β = 1.14; p=0.03; OR=3.13 (95% CI 1.09 - 8.97) and ADAS (β = 0.61; p=0.02; OR=.54 (95% CI .32 - .91) scores at baseline were found to be significant predictors of NI after 10 years of follow-up, with both models (MMSE X^2=14.66, R^2 = 0.48; ADAS X^2 = 21.20, R^2 = 0.63) able to correctly predict 87% of the participants. No effects were found for age and education.

Discussion

In this study, the Lisbon group of functionally independent elderly people with age-related WML, who had been included in the multinational pan-european LADIS study, was followed during a period of 10 years. The long-term follow-up allowed the identification of different profiles of evolution of the three groups of clinical diagnosis. As expected, the group of participants with dementia showed more prominent decline all over the time, while the group with a clinical diagnosis of CIND revealed a profile closer to non impaired participants, even after such a long period of time. Differences between groups of diagnosis were observed in the main batteries MMSE, ADAS-Cog and VADAS, but not in executive measures when composed scores (Stroop 3-2 and Trail-making B-A) were used: in both

Stroop and Trail-Making tests, only the effect of time was significant. The absence of differences in composed executive measures could be explained 1) by the fact that age-related decline in processing speed might contribute for an increase of time to perform the task in less complex parts (reading words, naming colors and connecting ordered numbers), reducing the magnitude of the difference between both tasks [196]; b) by the increasing number of persons who performed the first part of the tests but are not able to perform the more complex parts. Considering these findings, the best discriminative measures in long-term follow-up evaluations seemed to be the individual scores of each task and not the differences between them.

When baseline clinical and neuropsychological variables were analysed, we found that the only predictor of NI at the end of the decade was baseline MMSE score. MMSE baseline scores were already identified as predictors of dementia in a sample of independent elderly participants with WML after a 3-year follow up period [189]. Moreover, MMSE mean scores were relatively high and suggestive of the importance of establishing high cut off scores for early identification of CIND. Another study has also reported the importance to use higher cut off scores on MMSE to detect people at risk of dementia in highly educated elderly [197].

More than half of the participants showed progression of WML in more than 3 regions which is consistent with what was previously described in a similar group of patients [122]. However, in our cohort, we did not find an association between severe progression of WML and any demographic, vascular risk factors or baseline severity of WML. It has already been described that some factors related with progression of WML on a medium follow up period might disappear in longer periods[198], which might explain the absence of these associations in our study. On the other hand, in the visual rating of some MRI scans obtained in the 10^{th} year of follow-up, white matter atrophy with prominent ventricular enlargement could be seen in absence of an expressive WML increase. This could lead us to the hypothesis that the disease might have a different expression of progression after such a long-term process.

The interpretation of these results might be limited by some aspects of the present research. Such long-term periods of follow-up in elderly populations are associated with high rates of attrition, either due to death or the presence of other diseases that might interfere with the WML natural progression. Moreover, the small number of patients did not allow more specific analysis, for instance of what type of dementia could be better predicted. Nevertheless, we were able to evaluate a group of older adults with severe vascular risks or/and vascular disease for a period of 10 years. The small sample, an intrinsic risk in long-term follow-up studies performed in elderly populations, contributes to a loss of statistical power in some analyses. The use of a conservative level of significance in order to reduce type I error can also explain the absence of associations regarding some variables that are consistently reported as related with cognitive decline in this population (eg. age or educational level). Still, this procedure allowed us to identify some significant findings such as the identification of a global battery, the MMSE, as a potential predictor of non-impairment on this very long period of follow up. However, these findings as well as the absence of a clear association between WML progression on cognitive performance, reflect the importance of the present data and replication of the study with a larger population.

Conclusion

In this study we presented different longitudinal profiles of cognitive performance in a cohort of independent elderly participants with WML, and identified higher scores on baseline MMSE cognitive performance as the strongest predictor of long-term clinical diagnosis of no cognitive impairment. Higher cut-off points on global batteries such as MMSE should be used to identify participants at risk of cognitive decline on long-term periods.

VII - Informal caregivers' burden and needs on a long-term follow-up study of independent elderly patients with WMC: an exploratory study

Introduction

Loosing autonomy during the aging process is inevitably related with the need of a caregiver. Frequently, this process occurs in the context of the family, becoming an element of this system the first care-provider, assuming the informal care. The impact of being an informal caregiver, especially if dealing with chronic and progressive diseases (eg. dementia), on mental and physical health has been consistently reported [199-202]. Factors such as caregiver's age and co-morbidities, type of relationship with the patient, time spent on providing care, degree of dependency [203], seem to play a role on the perceived burden. Also factors related with personality traces and coping styles of the caregivers are being explored as mediators on the relationship between caregiving experience and physical and psychological health [204, 205].

Some studies have also explored differences between caregivers of patients with Alzheimer's Disease or Vascular Dementia and identified length of time care, severity of symptoms and stage of the disease as factors associated with caregivers burden [206, 207]. The onset and course of the disease that differentiate these two types of dementia, seems to play an important role on caregiver's perceived burden and adaptation during the different stages of both diseases.

White matter changes (WMC), frequently present in elderly subjects, are a recognized marker of small vessel disease[208], and have been associated with a higher risk of transition from a state of autonomy to disability and dementia [209]. In this population, disability can be due to multiple factors such as motor difficulties, urinary incontinence, depression or cognitive impairment [210]. Elderly people with severe WMC are at risk to decline on global functional performance even counting from just one year [210, 211]. An important issue which has not yet been sufficiently explored is the impact of this transition on caregivers.

During the follow up of the LADIS study[106, 212], it was possible to study the cognitive decline and consequent loss of autonomy of a group of initially independent elderly people. We intend to explore and characterize informal

caregiver's burden and needs as they followed the elderly subjects with WMC's process of transition to a condition of disability. We aim to i) describe the subjective burden and physical and psychological health status of caregivers of those patients who became dependent; ii) evaluate to what extent the degree of dependency predicted subjective burden; and iii) explore the possible mediating role of coping strategies on this relationship.

Methods

Participants and Methods

For the purpose of this study, we included the attendants of the 66 Portuguese participants of the European multinational LADIS study. The rationale and methodology of the LADIS had been extensively reported elsewhere [106, 142]. Briefly, the LADIS was a longitudinal study that aimed to evaluate the impact of WMC in the transition to disability during a follow-up of 3 years. Criteria for inclusion of participants had been: (a) age 65–84 years, (b) WML of any degree according to the modified Fazekas' visual rating scale [107], (c) no or mild impairment on the instrumental activities of daily living scale [108], and (d) presence of a contactable informant and agreement to sign an informed consent. Participants were submitted to a comprehensive clinical, functional, motor and neuropsychological examination that was repeated yearly. In each visit were accompanied by an informant who was interviewed in order to complete the information and to evaluate the functional status of the participant.

An extra evaluation at the 10^{th} year of follow-up of the LADIS participants was made for the Lisbon group of participants [212] intending to explore and characterize informal caregivers' burden and needs as they followed the elderly subjects' process of transition from an independent state to a condition of disability. Caregivers were defined as subjects delivering or being directly involved in providing care. In the course of this extra evaluation, each elderly subject's attendant, often a relative was directly contacted by a neuropsychologist (SM), on occasion being invited to contribute to the research, in the position of informant and caregiver. They were all told that this study was to be conducted by the neuropsychologist and that they had to be interviewed in one-only visit, with the

aim of identifying caregiver's needs during the evolution of the disease. The same information was written in the consent form, and explained when requested. Informants, or caregivers, considered for assessment were those who had been present for at least three of the five visits made for evaluation of LADIS participants, or those who had permanently replaced original caregivers (for example, institutional caregivers).

Caregivers who accepted to participate in the study were submitted to an open nondirective interview modelled on that used in the Canadian Study of Health and Aging (CSHA) [143], which collected information on the caregiver's sociodemographic and professional identity, on the type of care offered, on the support / resources obtained (institutional, or others), and on how informed they were about the diagnosis of the care recipient. They were also assessed with the Caregiver Strain Index (CSI) [144] to identify subjective burden; the Medical Outcomes Study Short Form-36 Index (MOS SF-36), to assess quality of life [145]; and the Brief COPE inventory [146] to identify what coping strategies caregiver uses. Participants older than 65 years old, were also screened with the Mini Mental State Examination (MMSE) [37] to exclude any cognitive deficit. For informants, or caregivers, of non-surviving LADIS patients, scales were adopted and they were asked to refer to the last year they accompanied or provided care. For participants who were unable to come to the hospital for assessment, home visits were conducted. All self-administrated scales were reviewed with the participant and questions/items clarified whenever needed.

Our study included attendants of LADIS participants who were dependent or presenting any functional limitations when compared to baseline.
The study was submitted and approved by the Ethical Committee of the university hospital (Faculdade de Medicina, Hospital de Santa Maria).

Caregiver Burden, Quality of Life and Coping strategies

After collecting socio demographic data, informants were asked if they were involved (in the present or past) in providing care to their relatives and, if not, if this was because they did not need assistance, or if there were other formal care

providers. Type of external assistance and classification (on a 5 points Likert scale) were also identified. Only informants who were, or had been, directly involved in providing care were considered for this study and included as caregivers.

Quantitative measures of burden were obtained using the CSI[213], a brief, easily to administrate scale. In its original form is consisted of 13 negative statements on which participants are asked to agree or disagree (yes/no). Following what was used in previous studies [214], we determined substantial subjective burden a total score higher than 6 points (7 to 13).

Caregiver's health related quality of life was assessed with the Portuguese version of the MOS-SF-36 [145]. Briefly, it is a self-administrated scale, consisted of 36 items covering 8 health concepts, grouped in two main components (mental and physical). Items are designed to evaluate the presence of limitations in these different concepts: physical functioning (intend to evaluate limitations in performing usual physical activities from the lighter to the heaviest), physical role functioning (type and quantity of work that might be limited); bodily pain, general health (global perception of health status), mental health (anxiety, depression, emotional and behavioral control, and well being), emotional role functioning, social functioning and vitality. An extra scale is obtained by asking the respondent to identify the quantity of change in her/his health during a one-year period. These scales can be grouped in two main components: physical and mental [215]. Raw scores were transformed and calculated according to the Portuguese norms and presented in terms of percentage [145].

Caregiver's coping strategies were identified using the Brief COPE inventory [146]. It is a self-administrated instrument that consists of 28 items organized in 14 dimensions (2 items for each dimension): Active Coping, Planning, Positive Reframing, Acceptance, Humor, Religion, Emotional Support, Instrumental Support, Self-Distraction, Denial, Venting, Substance use, Behavioral Disengagement, Self-Blame. Participants were asked to choose from a 4-points Likert scale (1 ="*I haven't been doing this at all",* to 4 = "*I have been doing this a lot*") in what extent those activities were performed by them. Again, for those

caregivers that were no longer providing care, an adaptation of the questionnaire was made, asking them to report how they have dealt with the situation. The items were grouped into 3 main types of coping styles, based on what was found in previous studies [216, 217]: problem-focused, emotion-focused and dysfunctional coping.

Functional status and clinical diagnosis

Care recipient's degree of dependency was assessed using a questionnaire based on the caregiver's questionnaire of the Canadian Study of Health and Aging [143](www.csha.ca).

Caregivers were asked to describe how their relative managed her/his daily life. Fourteen common activities were listed and participants were asked to tell if the relative was able to manage it "without help" (0 points); "with some help" (1 point)or "could not do it at all" (2 points). We classified as "not applicable" activities that were never performed by the relative. For example, patients who had never prepared their own meals were classified as "item not applicable". Scores range from 0 (functional autonomy status) to 28 (complete functional dependency).

Data from the LADIS study

Functional status of the care recipient, measured by the IADL scale [108] as a part of the LADIS protocol, was also analyzed. For the purpose of this study, IADL was rated in number of items with any impairment (raging from 0 to 8).

Care recipient's cognitive status was evaluated clinically at the 10^{th} year follow-up evaluation and classified into three groups accordingly to previously established and described in the LADIS study [195]. For those who did not survive, cognitive diagnosis was obtained by the information collected with the informant using a death form questionnaire. Whenever possible, information was also collected with the patient's general practitioner. All the information obtained in this way was also compared with the previous data from the LADIS study. Presence of behavioral

symptoms, mood disorders, gait disturbances and loss of sphincter control were registry according to the LADIS protocol [106].

Statistical Analyses

Descriptive analyses were performed using raw scores, means and percentages. In exploring significant differences, non parametric statistics were used due to sample size. Bivariate linear regression analyses were performed to identify predictors of subjective perception of burden. We used the most significant demographic variables (age, educational level and sex), functional status and coping strategies as independent variables. Categorical variables were dummy coded. Due to the small size of the sample, initial data analyses were conducted to ensure relevant assumptions to perform regression analyses.

A p-value of <0.05 was used to determine statistical significance. Analyses were performed using SPSS, version 20.0 for Windows.

Results

The initial sample was composed by the group of 66 informants who consented to accompany their relatives or friends during the whole period of the LADIS study. From this initial group, 58 informants (87%) were contacted and invited to participate in this study. Ten refused to come to a visit or to be interviewed by phone. Forty-nine informants (74%) of the initial group were included in this study. From these, 17 informants were not caregivers: participants who were accompanied by them were completely autonomous (16 persons); or were not directly involved in care giving (1 person). One participant did not allow her informant to participate, and one participant lived in a religious community where all the activities were shared.

As in our study we included caregivers of LADIS participants who became dependent along the follow-up period of the study, this inclusion/exclusion criteria resulted in a sample of 31 caregivers (23 women; 74%), with a mean age of 65 years old (ranging from 43 to 86) and a mean educational level of 9,7 years of schooling (ranging from 4 to 21). Concerning the relationship with the patient,

almost all the caregivers had a family connection: 14 were daughters or sons (46%); 14 were spouses (43%); 2 (6%) were a nephew and niece; and only 1 (3%) was a friend. Eighteen participants (58%) lived in the same residence (Table 15). Eighteen care recipients (58%) had a clinical diagnosis of dementia and this was the main reason for care need. Reasons for care need not related with the clinical diagnosis of dementia were gait impairment and incontinence (n= 6; 21%).

Table 15: Socio-demographic characteristic of caregivers (N=31)

Age (mean, minimum, maximum)	64.89 (42-86)
Education (years of schooling)	9.7 (4-21)
Female sex (number/%)	23 (74%)
Kinship ties (number/%)	
Wife/Husband	13 (42%)/1(3%)
Daughter/Son	8 (26%)/6 (19%)
Friend	1 (3%)
Common residence (number/%)	18 (58%)
Care recipient clinical diagnosis (N=24)*	
No cognitive impairment	1[1]
CIND (MCI/VCIND)	5[2](2/3)
Dementia (AD/VD/FTD/LBD)	18 (4/10/1)

*based on the LADIS evaluation using the LOCF; [1]patient with post-stroke severe motor deficit; [2] patients with gait impairment and/or incontinence; CIND=Cognitive impairment no dementia, MCI=Mild Cognitive Impairment, VCIND=Vascular Cognitive Impairment Alzheimer's Disease, VC=Vascular Dementia, FTD=Fronto Temporal Dementia, LBD= Lewy Body Dementia;

Subjective burden and coping strategies

Substantial subjective burden (CSI >6) was identified in 14 participants (45%). Caregivers with substantial burden did not differ significantly from those with no substantial burden, in terms of socio-demographic characteristics such as age, gender, educational level, place of residence and kinship ties.

Concerning the coping strategies used by caregivers, acceptance, planning, active, emotional and instrumental support were the most reported dimensions by the whole group, with emotional-focused coping type the most frequent. None of the caregivers reported the use of substances. When comparing participants with substantial burden with those with no to mild burden, caregivers with substantial burden used a higher number of active ($U = 59$, $p=0.03$, $r=0.40$), and denial ($U = 71$, $p= 0.03$, $r=0.39$) strategies. Concerning the type of strategies used (problem-

focused, emotional-focused or dysfunctional), no differences were found between both groups of caregivers (see Table 16).

Caregivers with substantial burden had care recipients with more severe functional impairment, (U= 26, p=0.05, r=0.34) when compared with the group of no substantial burden (Table 16). Caregivers of 21 patients had also evaluated their relatives with the IADL scale, as part of the 10th year follow-up visit, and the difference between groups was the same, with care recipients of caregivers with substantial burden, being more dependent than the others (U=26, p=0.05, r=.42).

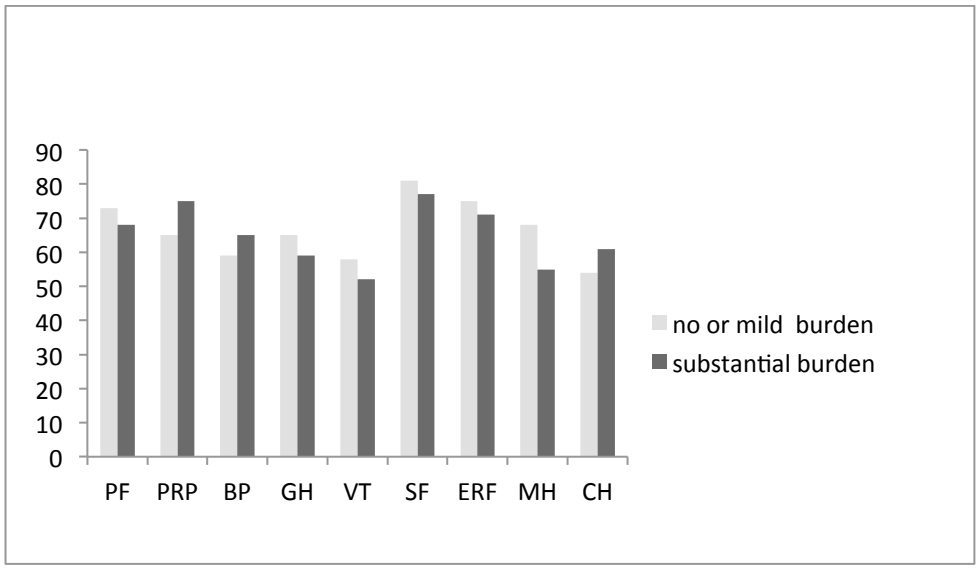
Table 16: Coping strategies, health related quality of life, and care recipient functional status

Variables	All group (N=31) (mean±SD)	No substantial burden (n=17) (mean±SD)	Substantial burden (n=14) (mean±SD)	Test Mann-Whitney
COPING STRATEGIES (Brief COPE)				
Problem-focused	7.8±2.7	7.2±2.7	8.9±2.4	*n.s.*
Active	2.8±1.0	2.5±1.0	3.2±0.9	**U = 59, p=0.03, r=0.40**
Planning	2.9±1.1	2.7±1.2	3.2±1.1	*n.s.*
Instrumental support	2.2±0.9	2.1±1.0	2.5±0.7	*n.s.*
Emotion-focused	11.3±2.3	11.6±2.4	11.0±2.2	*n.s.*
Positive reframing	2.4±0.9	2.7±0.9	2.1±0.8	*n.s.*
Acceptance	3.4±0.8	3.4±0.9	3.4±0.5	*n.s.*
Emotional support	2.3±0.9	2.2±0.9	2.5±1.1	*n.s.*
Humor	1.1±0.2	1.1±0.3	1.0±0.1	*n.s.*
Religion	2.13±1.2	2.2±1.2	2±1.1	*n.s.*
Dysfunctional coping	**8.2±2.0**	**7.9±1.7**	**8.7±2.5**	***n.s***
Venting	1.4±0.5	1.4±0.4	1.3±0.6	*n.s*
Denial	1.3±0.6	1.1±0.3	1.5±0.8	**U = 71, p= 0.03, r=0.39**
Self-Blame	1.6±0.6	1.7±0.7	1.6±0.6	*n.s.*
Behavioral disengagement	1.3±0.7	1.1±0.5	1.6±0.9	*n.s.*
Self-distraction	1.6±0.8	1.5±0.9	1.6±0.8	*n.s.*
Substance use	1.0±0	1.0±0	1.0±0	*n.s.*
CARE RECEIVER FUNCTIONAL STATUS				
CSHA (total)	13.5±9.8	9.12±8.9	18.7±8.5	**U=49.5, p=0.006, r=0.50**
IADL (N=21)*	4.4±2.3	3.7±2.3	5.5±2	**U=26, p=0.05, r=.42**

*IADL only available for participants who were reevaluated at 10th year

When health related quality of life of both groups was compared (Figure 9), caregivers with substantial burden reported relatively more limitations on physical role functioning (physical role functioning 75±41 vs 65±30), although had less physical functioning complaints (physical functioning = 68±33 vs 73±27).

Figure 9: Health related quality of life (MOS SF-36)



PF-physical functioning; PRP-physical role functioning; BP-bodily pain; GH-general health; MH-mental health; ERF-emotional role functioning; SF-social functioning; VT-vitality

Needs and Resources used

Nineteen caregivers (61%) reported the use of an external aid for care providing. The most frequent type of aid referred was the assistance of an housemaid (42%), either on full or part-time. Home care assistance (palliative care or non differentiated teams) was also frequent (26%). Nursing home was referred as a choice for severe or terminal states (26%).

Predictors of burden

Bivariate regression analyses were performed in order to examine the predictive value of dependency on experienced substantial burden of caregivers.

Initial data analyses were conducted to ensure relevant assumptions to perform regression analyses. No significant outliers were detected and independence of observations was ensured (Durbin-Watson statistic= 2.21). Score distributions did not significantly differ from a normal curve – skewness and kurtosis values, and P-P plots and Q-Q plots appeared to approximate normal distribution. Similarly, standardized residuals approached normality (histogram with superimposed normal curve and Normal P-P plot). When also taking into account coping styles, data did not show multicollinearity (VIF's close to 1) (data not shown).

Bivariate linear regression analyses showed that the degree of dependency, measured by the CSHA, was a predictor of the intensity of the burden (R^2=34.5%; $F_{(1,29)}$ = 14.75, p<0.01; β=0.59, p<0.01). This effect maintained statistical significance even after controlling the effect of demographic variables ($F_{(7,29)}$ = 2.97, p<0.05; β=0.65, p < 0.01), with age as the only additional marginal effect (β=-0.63, p = 0.05) with younger caregivers reporting less burden.

When clinical diagnoses were added to the model, as dummy coded variables, having dementia was a predictor of the intensity of burden (R^2=19.6%, $F_{(1,22)}$=5.12, p=0.03; β=0.44, p = 0.03). Gait disturbances, incontinence or memory and behavior complaints did not predict intensity of burden.

Finally, in order to test the possible role of the mechanisms of coping as mediators of the relationship between dependence and perceived burden, a set of multiple regressions was performed. "Active coping" was the only mechanism of coping that was found to be a predictor of level of burden (R^2=22.4%, $F_{(1,29)}$=8.10, p=0.01; β=1.64; p=0.008). However, when the extent of dependency of the patient (measured on the CSHA scale) was added to the model, the latter variable fully absorbed all related variance in respect to the burden of caring (R^2=45.0%, $F_{(1,30)}$=5.33, p=0.003; β=0.38; p=0.05). Thus, coping did not seem to contribute as an independent variable to the degree of experienced burden.

Discussion

To our knowledge this is the first study that aimed to evaluate the characteristics of burden in caregivers of this elderly population with WML who evolved from a complete independent functional status to a loss of autonomy. Caregivers were, with one exception, family members of participants of the LADIS study, who became the main care providers during the follow-up period. It is well recognized that relatives, usually spouses or adult children, are the most frequent type of care providers of home living elderly people and the most long lasting support for patients with dementia [218, 219]. In our study, for more than half of care recipients, the need for caring was due to a dementia diagnosis, being the high degree of dependency associated to the substantial burden, reported by nearly half of the caregivers.

Caregiver burden is a concept that is being explored for some decades and related with the physical and psychological well-being of informal care providers [220]. It is a complex response to the act of care that involves a multiplicity of factors that goes from those directly related with patients characteristics (such as presence of behavioral and psychiatric symptoms or lack of self-care/need of support), to those determined by caregivers (such as personality traits, coping style or social functioning) [204].

Caregivers burden, as an expression of stress response, can be explained based on the model of Lazarus and Folkman [221] , that assumes that the stress reaction is not immediately related with the life event, but rather with the individual's appraisal of the situation as harmful. This immediate perception (defined by "primary appraisal") could be aggravated by the self-evaluation of own capacities as unable to cope with the potential threat ("secondary appraisal"). Therefore, and adopting this model to the caregiver's process [222], burden response, as a result of this dual appraisal process, can be mediated by a set of variables including personal, illness-related, social and material factors.

Based on this assumption, we expected that in this sample, substantial burden would be mediated by both caregivers' determinants (coping mechanisms, health related quality of life), and illness/care recipient related characteristics (clinical

diagnosis, degree of functional impairment). In our sample, the perception of substantial burden was associated with the degree of functional impairment - measured both as number of compromised instrumental activities (IADL) and degree of impaired basic activities (caregivers' questionnaire) -, presence of active and denial coping strategies, and lower health status perception in almost all the dimensions except in physical role functioning (type and quantity of work that might be limited), with higher percentages revealing less complaints. Considering health related quality of life, main results are consistent with what is being reported in the literature, where complaints of depressive symptoms and poor perceived health among caregivers associated to higher care needs have been previously reported [223-226]. In our sample, however, there were lower rates of physical role functioning complaints among caregivers with more substantial burden. This could be explained by the fact that caregivers with substantial burden tend to consider their physical performance as good, based on what they consider to be possible in terms of their job as care providers.

An association of substantial burden with some caregiver's approaches, namely active and denial coping strategies, was found in our study. Although the use of such different type of strategies (problem-focused and dysfunctional coping, respectively) could be seem as a paradox, it can be also be revealing of the psychological effort and conflict associated to caregiver's role. It can also explain the fact that no predominant main type of coping style (problem-focused, emotion-focused or dysfunctional), was found in association with substantial burden.

Previous studies, that included patients with different types of dementia, have reported a clear relation between loss of functional ability in daily living activities and high rates of caregivers perceived burden, being factors related with functional decline, predictors of caregivers burden [227-230]. As previously reported [229], care recipient loss of capacities in daily living management of basic or instrumental activities, requires a higher level of involvement of care providers with direct impact in the time need to care. In our sample, dementia was the main reason of care need but its role as predictor of burden was fully absorbed by impairment in functional activities, which became the only independent variable able to predict perceived burden. Therefore, loss of capacities in performing instrumental and

basic activities in daily living became the only predictor of burden on this caregiver-patient dyad.

Our study has some limitations that might constrain the generalization of results. The first is related with the small size of the sample of caregivers-patient dyads. Although obeying a cross-sectional design, this study emerged from a longitudinal approach of 10 years of length. Hence, attrition during this period is understandably high, especially it being a case of research with elderly populations. A second limitation stems from the high number of variables involved, as a result of the complex response that we aimed to understand, combined with a heterogeneous sample of participants, this leads to a great number of possible confounders. In addition, comparisons between groups (e.g. dementia type) were compromised due to sample size.

However, the fact that we were able to evaluate caregivers of such a specific group of patients is a clear strength of this study. Besides, the long-term follow-up of this group of care recipients enables us to have a more comprehensive characterization of this population. Last, despite the low statistical power, we were able to establish a strong effect of functional impairment on perceived burden.

Conclusion

The importance of this result in this particular population - initially independent elderly people with WMC who became functionally disabled through time -, relies on the fact that small vessel disease have specific clinical symptoms that might contribute to a loss of functional capacities, even in very mild stages of the disease [231]. Gait and balance disturbances, as well as incontinence, are disabling conditions directly associated to white matter changes [210, 232, 233], that contribute to a more functional dependent state, and higher care need. Therefore, more attention should be payed to the evaluation of these conditions and caregiver support throughout the disease process.

3.

DISCUSSION AND CONCLUSIONS

Discussion of the hypotheses under study

The present thesis constitutes an effort to characterize the long-term neuropsychological performance of elderly subjects with WMC, who were functionally independent at the baseline. We aimed to evaluate the extent to which age-related WMC influence cognitive performance and determine the transition from a healthy status to disability as well as to explore the impact of this change in caregivers.

Cognitive Functioning and WMC

Our first aim was to identify how cognitive functioning was related with WMC, which cognitive domains were mainly affected and which were more sensitive to decline. This goal was operationalized in the following hypotheses.

A properly designed neuropsychological battery is able to differentiate the cognitive performance of independent elderly subjects with different degrees of WMC, in association with specific demographic variables (age and education)

It was clearly demonstrated that the present neuropsychological battery, chosen based on the familiarity of the tests and the validity of the instruments to assess the decline of cognitive functions of patients with vascular disease, but also incorporating innovative assessment proposals (the VADAS-Cog), constitutes a sensitive instrument to differentiate levels of cognitive performance [142]. Preliminary exploratory factor analyses were performed in this study and confirmed later by longitudinal data, as described in Moleiro *et al.* [234]. Results showed that executive functioning, memory and speed of motor abilities were valid latent variables of neuropsychological performance among older adults, and that this structure was relatively consistent longitudinally.

This aforementioned hypothesis was confirmed in a cross-sectional study which demonstrated that the use of both global measures of mental status and specific measures for individual domains assessment, was able to determine different

levels of cognitive performance [142]. Furthermore, the analysis of the baseline neuropsychological data showed a significant influence of demographic variables on cognitive performance. Complementary data presented in a different study [235] have also confirmed that neuropsychological performance is influenced by demographic factors (age, education) and also by severity of WMC and vascular risk factors.

Higher educational level was consistently associated with better performances on cognitive tasks. Education was the most consistent factor influencing the neuropsychological performance in this sample of elderly subjects with WMC, with higher impact in complex tasks involving executive functioning. At the time of our cross-sectional study, only one study reported the relationship between education and cognitive performance associated with WMC [236]. Nevertheless, the idea of a cognitive reserve, that encompasses the ability to resist brain disease without developing signs or symptoms of the same, and acting as a mediator of cognitive decline in dementia, was being explored as an explanation for the inter-individual differences on the course of the diseases [167, 237, 238]. The importance of education, while a measure of cognitive reserve as a mediator between the severity of brain small vessel disease and the clinical expression of the pathology, has been recently reported [239-241]. This factor has been pointed as a possible explanation for the high rates of variability in the outcome of this population and may constitute a buffer against the negative effects of having WMC.

Long-term influence of WMC on Cognitive Functioning

Subtle deficits on global cognitive performance and specific cognitive domains observed at baseline, are predictors of dementia on a 3 year period, in a functionally independent elderly population with WMC

This hypothesis was explored and confirmed in the first longitudinal study performed in the LADIS sample [189]. In this study, participants were followed during 3 years and a clinical diagnosis was made in each follow-up visit, every

year. Participants were diagnosed as having “dementia”, “cognitive impairment no dementia” (CIND) and “no cognitive impairment”.

In this sample of functionally independent elderly population with WMC, subtle deficits on cognitive performance were predictors of dementia on a 3 year period, even after controlling for age and educational level. Participants clinically diagnosed with dementia at the end of the 3-year follow-up period had had lower scores in almost all the baseline neuropsychological tests, when compared with participants without dementia. This is consistent with the understanding of dementia as a progressive disease that starts insidiously, usually without evident signs besides subtle differences of cognitive tests scores.

In our sample, memory and executive functioning baseline compound measures were predictors of dementia at 3 years. Executive functioning measured by trail-making or Stroop tests individually, were not predictors of dementia. The absence of relationship between specific tests for the assessment of executive functions and WMC, was also reported in other studies [188, 242]. What we found was that, using a combination of more complex tests, such as verbal fluency and symbol-digit, in a compound measure of executive functioning, could increase the sensitivity to detect preclinical changes of the disease.

These cognitive performance differences could be considered a marker of preclinical stage and are observed either in tests that are proven to be more sensitive to cognitive change in cerebrovascular patients [243, 244], either in global measures that are usually considered to be less sensitive, such as the MMSE. This is in accordance to previous studies that also identify lower global cognitive scores, as preclinical markers of dementia [178]. In the LADIS sample, scores on MMSE were higher than those reported as cut-off scores for dementia, which enhances the importance of using different cut off scores among patients with higher educational level.

In this second study, we were also able to identify that patients with CIND were older and had lower educational levels when compared with participants with no cognitive impairment, independently of the severity of WMC. Again, these results

reflect the influence of demographic variables on cognitive decline that act beyond the pathology. However, except for demographic factors, we did not find neuropsychological variables that could predict the transition from no impairment to CIND, since baseline cognitive performance did no differ between these two groups. This also reflects the heterogeneity of this group of patients and the importance of develop more sensitive cognitive measures to detect subtle differences of performance.

The neuropsychological battery was able to identify different profiles of cognitive performance on a long-term evolution of a sample of initially independent elderly people with WMC. Higher performance in global measures and specific cognitive domains are predictors of no cognitive impairment at 10 years.

In the third study of the present thesis, a long-term 10-year follow-up research effort, the Lisbon group of participants in the LADIS study was evaluated in order to identify long-term neuropsychological predictors of non-impaired cognitive functioning. In this study we presented different longitudinal profiles of cognitive performance in a cohort of initially independent elderly participants with WMC. The average cognitive scores of the participants, in the three groups of clinical diagnosis (no cognitive impairment, CIND and dementia), declined during the follow-up period, the steeper decline being found in the group of participants with dementia. Differences between groups of diagnosis were observed in the main batteries MMSE, ADAS-Cog and VADAS, but not in the individual tests used to evaluate executive functioning (trail-making and Stroop). Combined scores in outcomes on trail-making and Stroop tests (resulting from the difference between time to perform both tasks) did not differentiate participants with no cognitive impairment from those with any impairment. These results could be related with a) the fact that age-related decline in processing speed might contribute for an increase of time to perform the task in less complex parts (reading words, naming colors and connecting ordered numbers), reducing the magnitude of the difference between both tasks [196], or b) by the increasing number of persons who

performed the first part of the tests but are not able to perform the more complex parts. Considering these findings, we identified that the best discriminative measures in long-term follow-up evaluations should to be the individual scores of each task and not the differences between them.

When baseline clinical and neuropsychological variables were analysed, we found higher scores on baseline MMSE were the strongest predictor of long-term clinical diagnosis of no cognitive impairment. These results are consistent with what was previously found at the third year of follow-up of the same population [189].

It became clear that, for participants with WMC, higher cut-off points on global batteries such as the MMSE, should be used in future to identify participants at risk of cognitive decline. The importance of using high cut off scores on MMSE to determine highly educated subjects at risk of decline was also discussed in a previous study[197]. There is some criticism to the use of MMSE to detect mild cognitive impairment and the newly adapted Montreael Cognitive Assessment Battery (MoCA) [47], has been pointed out as a better screening instrument for subtle cognitive changes of vascular origin [47, 245, 246]. However, results are still not consistent, with some studies presenting MMSE with equal discriminant [247] and predictive characteristics [248] than MoCA. Only two relevant studies have compared both instruments strictly in a sample of participants with SVD [54, 249] and report MoCA as a more suitable instrument for detecting mild cognitive impairment. However, more studies are needed to provide extensive support for its future use in this population.

Progression of WMC was an independent predictor of dementia among elderly people on a long-term follow up

The third hypothesis of this study was not confirmed. In our 10 years follow-up study, severe progression of WMC was observed in more than half of the participants, which is consistent with what was previously reported [122]. Previous long-term studies [45, 250, 251] have described the same or higher rates of progression of white matter lesions, correlating them with loss of brain volume [45] and establishing an association between progression of WMC and deterioration of

cognitive functioning [45, 251, 252]. In the LADIS sample [251], deterioration of cognitive functioning was only moderately associated with progression of WMC and attenuated in subjects with severe WMC grade at baseline. In the referred study, only subjects with severe grade at baseline and progression of WMC showed marked cognitive decline [251].

However, in the present study, we found no relationship between WMC progression and dementia. We also did not find differences between participants with no impairment or any cognitive impairment concerning progression of WMC. WMC progression was also not found to be associated to any demographic, vascular risk factors or baseline severity WMC.

Some factors associated with long-term progression of WMC, such as brain parenchymal volume loss, have been associated to cognitive decline, rather than WMC progression [45]. In our study brain volume loss associated to WMC progression loads was not evaluated, which might explain the absence of these associations in our study. On the other hand, in such a long-term evaluation, the expression of the disease could change, being the contribution of other variables. In our study we add an unique opportunity to compare MRI data in a very length period of time, by using the same MRI protocol, as well as the same equipment (or similar) and even, the same person, who rated all the scan images of the LADIS study. However, the use of the same protocol and techniques, limited the exploration of other measures and identification of other variables, such as mesial lobe atrophy, normal appearing white matter anisotropy or cerebral microbleeds that could play, in this long-term period, a more prominent role than white matter lesions itself [198]. As suggested in a recent study [219], periventricular white matter changes might be an indirect consequence of the Alzheimer-related brain atrophy, subsequent ventricular dilatation and ruptures of the ependymal lining with increased leakage of CSF into the surrounding periventricular white matter, or alternatively, might result directly from hippocampal and neocortical neurodegeneration and subsequent loss of axons in fibre tracts, which run near the lateral ventricles. Amyloid burden has also been associated with white matter microstructure changes [220]. Finally, it has also been demonstrated that WMC

differ according to the technique used, and that macrostructural and microstructural studies are complementary [218].

Impact of transition to disability in informal caregivers

The final part of this thesis was committed to the effort to offer a more efficient treatment to the elderly with WMC, by exploring the impact of transition to a dependent status on family and caregivers. It was designed to evaluate how this transition was perceived by caregivers and what possible factors would mediate this relationship.

To explore and characterize informal caregivers and needs as they follow the elderly subjects' process of transition from an independent to a condition of disability, we established two hypotheses:

Progressive change from an independent and autonomous status to a disabled functioning has an impact on the quality of life of caregivers

This hypothesis was explored and confirmed in the last study of this thesis. In our sample of caregivers of the LADIS participants who became dependent during the 10 year follow-up period, almost half reported substantial burden. In more than half of care recipients, the need for care was due to a diagnosis of dementia, with high degree of dependency, measured by a functional questionnaire, associated to the substantial burden.

The perception of substantial burden was associated with 1) the degree of functional impairment; 2) presence of active and denial coping strategies; and 3) lower health status perception in almost all the dimensions except in physical role functioning (type and quantity of work that might be limited).

Functional impairment, measured both as degree of impaired basic activities (caregivers' questionnaire) or number of compromised instrumental activities (using the IADL), was the most prominent factor associated with subjective burden.

Loss of functional ability in daily living activities associated with high rates of caregivers perceived burden have been previously reported [227-230].

An association of substantial burden with some caregiver's approaches, namely active and denial coping strategies, was found in our study. The way caregivers' coping styles affect the perception of burden and / or health related quality of life, is still not clear. Based on the Transactional Stress Theory model [221] several theories have been used to explain caregivers' stress response. Several factors have been identified in the stress response of caregivers, such as background and context of caregiving, objective stressors (care demands and care provided), subjective primary stressors (role overload and relational deprivation), secondary stressors (role strains and intrapsychic strains) and mediators such as social support and coping [253]. A recent systematic review [205], found some evidence for a positive association between avoidance coping and subjective burden in home caregivers of older relatives with cognitive impairment. Avoidance coping strategies, in which denial can be included, are strategies oriented to avoid problems and engage in indirect attempts to reduce distress [254]. However, the direction of this relationship was not identified. Is still not clear if coping mediates or moderates subjective burden or if it is the cause of it [205].

In our study, both avoidance strategies, such as denial, and approach strategies (coping strategies oriented for the resolution of the problems) such as active strategies, were found to be related with subjective burden. Although the use of such different type of strategies could be seen as a paradox, it can be also be revealing of the psychological effort and conflict associated to caregiver's role. It can also explain the fact that no predominant main type of coping style (problem-focused, emotion-focused or dysfunctional), was found in association with substantial burden.

Considering health related quality of life, main results are consistent with what has been reported in the literature, where complaints of depressive symptoms and poor perceived health among caregivers are associated to higher care needs [223-226].

Results lead to the conclusion that the degree of dependency was the only predictor of the intensity of the burden. Despite the fact that 'active coping' appeared as a predictor of level of burden, the extent of dependency of the patient (measured on the CSHA scale) fully absorbed all related variance in respect to the burden of caring.

The way in which caregivers are affected by the progression of the disease is related with their own coping mechanisms

This hypothesis was not confirmed in our study. As above stated, based on the model of stress response of Lazarus and Folkmann [221] and adapting it to caregiver's process [222, 253], we assumed that burden response would be mediated by both caregivers' determinants (coping mechanisms, health related quality of life), and illness/care recipient related characteristics (clinical diagnosis, degree of functional impairment).

An association of substantial burden with some caregiver's approaches, namely active and denial coping strategies, was found in our study. However, as mentioned, when other objective stressors, such as care recipient degree of dependency, were included, the only independent predictor of substantial burden was the degree of functional impairment.

Previous studies have reported a clear relation between loss of functional ability in daily living activities and high rates of caregivers perceived burden, being factors related with functional decline, predictors of caregivers burden [227-230]. Care recipient loss of capacities in daily living management of basic or instrumental activities, requires a higher level of involvement of care providers with direct impact in the time needed to care [229]. In our sample, dementia was the main reason of care need but its role as predictor of burden was fully absorbed by impairment in functional activities, which became the only independent variable able to predict perceived burden. Therefore, loss of capacities in performing instrumental and basic activities in daily living became the only predictor of burden on this caregiver-patient dyad.

Main results

In the attempt to characterize the long-term neuropsychological performance of elderly subjects with WMC, who were functionally independent at the baseline, and were followed during a period of 10 years, we found that:

1. There is a significant influence of demographic variables on cognitive performance. Neuropsychological performance in patients with ARWMC was influenced by age and education. Higher educational level was consistently associated with better performances on cognitive tasks, while older age was associated with difficulties on memory and executive functions.
2. In an elderly population with WMC and no functional or major cognitive impairment in initial evaluations, comprehensive neuropsychological assessment detected subtle changes in cognitive performance associated with progression for dementia.
3. Concerning cognitive performance at baseline, there is a clear distinction between the three groups of clinical diagnosis (no cognitive impairment, CIND and dementia). Patients with CIND differed from patients with dementia in almost all the tests and global measures. The neuropsychological distinction between participants with no cognitive impairment and with CIND is less prominent, reflecting the heterogeneity of this particular group, which seems to be in the continuous line between the "no impairment" and "dementia".
4. Baseline scores of MMSE and memory and executive compound scores were predictors of dementia at the end of the 3 year follow-up period.
5. It was possible to identify different longitudinal profiles of cognitive performance in a cohort of independent elderly participants with WMC. As expected, the group of participants with dementia showed more prominent decline all over the time, while the group with a clinical diagnosis of CIND revealed a profile closer to non-impaired participants, even after such a long period of time. We identified higher scores on baseline MMSE cognitive performance as the strongest predictor of long-term (10 years) clinical diagnosis of no cognitive impairment.

6. More than half of caregivers of participants who became dependent during the follow-up study, showed substantial burden. Although an association between coping strategies and perception of burden could be noted, the high degree of dependency was the only predictor associated to the substantial burden.

Strengths and limitations of the study

Strengths of the study

The study here presented was carried out in the context of the LADIS project that consisted in a rare opportunity to study a specific pathology, i.e. age-related white matter changes in an elderly population, based on data taken from a large heterogeneous multinational sample. Exhaustive and rigorous information was to be collected allowing a better understanding of the impact of the disease on cognitive functioning. The cultural and socio-economic characteristics which differentiate the various participating countries, had to be accepted as a challenge in constructing a battery of neuropsychological assessment.

The balanced combination of neuropsychological measures, using both long validated tests (e.g. MMSE, Trail-making), as well as recently developed proposals (VADS-Cog), and the multicentre harmonization work based on the use of the same version of chosen tests for all the countries (adapted only for national language specificities), accompanied by strict guidelines of application, made it possible to improve the cognitive assessment of this population.

Cultural and social differences across countries contributed to a great heterogeneity of the sample. The impact of these differences on cognitive performance was explored and identified cross-national variables were controlled in several analyses and did not interfere with the results [142].

The longitudinal design of this study also made possible to evaluate the evolution of the disease and its impact in the transition from a healthy to a disabled functional state. The medium (3 years) and long (10 years) follow-up of this sample, enabled us to identify demographic, clinical and neuropsychological predictors of impairment which would not be possible in a cross-sectional design. Using data from the Lisbon Center, we were able to register and rate the progression of white matter changes in a 10 year follow-up period, in a smaller sample of initially independent elderly participants, which constitutes a unique study.

Furthermore, the 10th year follow up of this small sample of Lisbon centre participants made it possible to evaluate the impact of progressive disability on caregivers. Although this last study was constrained in the interpretation of the results, it enabled the characterization of the burden on this group of caregivers and the exploration of some possible predictors.

Finally, it is rare to have such long periods of follow-up with this amount of data, which included demographic, clinical, and vascular risk factors, as well as MRI studies. Although it was not possible to extend the extra 10th year follow up to other LADIS centers - mainly due to organizational difficulties (changes in the researcher's staff, for instance) and to the fact that there was no funding for this study -, we were able to registry and rated the progression of white matter changes in a 10 year follow-up period in a small sample of initially independent elderly participants. We used exactly the same criteria and imaging techniques, and scans were rated by the same person who classified the entire sample during the LADIS follow-up. This constitutes a rare or, to our knowledge, maybe a unique achievement.

Limitations of the study

Longitudinal studies, especially very-long term ones, have always some limitations in the interpretation of data. One important limitation has to do with the high attrition rates that are due to a diverse number of factors, but especially important in the case of older adults in a long-term follow-up. Higher attrition, death and co-morbity rates are inherent to this type of study design and population, and may limit some conclusions. Whenever possible, we tried to decrease this impact by obtaining all the information we could concerning clinical and mental status, by using structured phone interviews (e.g., TICS), contacting relatives or friends, and getting clinical information from general practitioners.

Another limitation results from the continuous technological and methodological changes occurring during the period of the study. In a decade, it is natural and desired to witness some improvement in measures, parameters, instruments, etc.

These adaptations may constrain comparability of results. For instance, during the 10 year follow-up period, imaging techniques changed considerable. Time susceptibility-weighted imaging (SWI) and T2 * and perfusion/diffusion MRI sequences became more frequently used but were not included at the beginning of our study. Again, due to some technical constraints, diffusion tensor imaging (DTI) and magnetisation transfer ratio (MRT) techniques were not available in all the centres and were left optional [106]. As DTI has been reported as able to detect changes in normal-appearing white matter [238], the impact of white matter changes was probably underestimated. Concerning imaging analyses, the LADIS study did include hippocampal volumetry evaluation and cerebral atrophy was conducted in a sub-sample of subjects. These measures would be important contributors to understand and differentiate neuropsychological profiles and clinical outcomes. In order to compare results between baseline and the 10^{th} year follow-up period, we had to use exactly the same equipment and protocol, even knowing that more sensitive measures had been developed since the beginning of the study.

The same reasoning is also applicable to the construction of the LADIS neuropsychological battery. At the beginning of the study, we tried to use the most familiar and easy to administer instruments (such as MMSE, trail-making, Stroop) in order to decrease possible differences between centres. Recent proposals of screening tests for vascular impairment, such as the MoCA battery, did not exist at the moment. The inclusion of specific measures to improve the assessment of vascular impairment (such as delayed recall, symbol-digit, digit span, maze, digit cancellation and verbal fluency that make up the VADAS-Cog) increased the time needed to administer and would increase the risk of patient's withdrawal. For this reason, we reduced the number of memory trials (only one trial was used on word recall and word recognition tests), which limited the assessment of verbal learning and thus might have limited the interpretation of baseline results.

Another possible drawback of our study is related to the use of dichotomized or categorized variables such as dementia/no dementia or NCI/CIND, including patients with different types of dementia in the same group. However, splitting these groups into subsamples would have reduced statistical power and

compromised the analysis of the results, given that certain types of dementia had very low frequencies.

Finally, there are a number of contributors for cognitive functioning, directly or indirectly related with small vessel disease, that were not controlled in this study, limiting the interpretation of some results. For instance, global atrophy was not controlled in this study. However, in other study [77], medial temporal and subcortical atrophy were identified as predictors of global cognitive decline, and decline in psychomotor speed, executive functions, and memory, potentiating the effect of WMC. Moreover, the presence of microbleeds, that have been related with cognitive decline, mainly non-memory functioning [103, 255, 256], was not analysed in our study, since at the time of beginning of the LADIS study, there was no evidence of the impact of cerebral microbleeds in cognitive functioning.

Implications for clinical practice

After a decade of work in evaluating the impact of WMC on cognitive performance, we hope to have contributed with some evidence on this field. It became clear that WMC, as one of the most detectable expressions of small vessel disease, can interfere in cognitive performance of elderly subjects, even before they have functional complaints. Still, even before the onset of these complaints, subtle changes in cognitive performance are detectable through sensitive neuropsychological evaluation.

These results enhance the importance of neuropsychological assessment in clinical practice as a form of detecting subtle changes in very initial phases of brain diseases. The use of adequate cut-off scores and sensitive measures in the neuropsychological evaluation can lead to the detection of people at risk of cognitive decline and dementia. Earlier neuropsychological diagnosis of elderly people with WMC leads to more efficacious implementation of non-pharmacological approaches that aim to compensate cognitive deficits, and therefore, to the maintenance of their maximum autonomy. In the same way, knowing the impact of the progression of the disease in the patients and their families, early interventions with caregivers should also be used.

Implications for future research

Although the knowledge acquired during the last years considering the neuropsychological assessment of WMC, there is still work to be done on the development of more sensitive cognitive measures. Instruments more able to distinguish neuropsychological profiles among patients with CIND and to identify predictors of long-term decline and dementia, are needed. Similarly, it is still needed to identify early neuropsychological profiles able to predict the progression for different types of dementia.

In the same line, it is also needed to identify other SVD manifestation markers, such as mibrobleeds, lacunes and regional or global atrophy, on the impact of cognitive performance. In order to do that, future research must include imaging sensitive tools for the measure of cerebral WMC. Recent MRI diffusion, perfusion

and spectroscopy sequences, that allow the visualization of tissue changes in areas of white matter that appear normal using conventional MRI, should be used.

It is also important to address the impact of pharmacological and non-pharmacological therapies on neuropsychological performance. Programs of cognitive stimulation in early stages of the disease, comparing patients with and without structured interventions, should be evaluated. Three types of non-pharmacological programs could be evaluated in this population: 1) cognitive stimulation and rehabilitation programs in early stages of the disease; 2) implementation of physical activity programs for patients; 3) programs directed to caregivers of patients in moderate to severe stages of the disease. To perform these types of studies, we need to increase the number of included subjects, to allow the control of multiple concomitant factors that can confound the interpretation of results and interfere with statistical power. Multi-national clinical trials may provide the frame and resources for such studies.

Conclusion

The thesis here presented aims to have a say in further identifying clear profiles of cognitive functioning in patients with WMC, and to underline the existence of subtle deficits independent of the degree of severity of the WMC which are to be found in autonomous and independent subjects (1st study).

As detailed, when comparing different evolutionary profiles, the battery constructed proved to be effective in detecting deficits appearing in early stages (2nd study). While identifying predictors of good cognitive functioning (MMSE > 28) in lengthy follow-up research efforts, the battery gives support in establishing intervention programs for a population identified as at risk.

Though WMC are almost exclusively detected by imaging markers, the clinical expression of those changes, particularly as related to cognitive function, should become possible to assess through sensitive batteries adapted to this population.

Neuropsychological assessment allows the definition of the impairment, as well as the determination of its impact on daily life and adaptation of intervention programmes either in early or later stages of progression of the disease. This approach allows the introduction of non-pharmacologic complementary therapies in view of promoting functional autonomy for the longest period of time possible.

Similarly, the identification of changes in cognitive functioning and the corresponding impact on patients and their environment, mostly in the family, allows the adoption of broader intervention strategies, potentiating the maximum autonomy, involving future informal caregivers in terms of decreasing their load.

Regarding caregivers, and considering the evolutionary character of this disease, a fact which becomes more prominent each day, it is important to develop research projects focusing on larger groups of patients and their relatives, using sensitive measures of assessment and resource strategies over time.

This would lead to identify determinants of subjective overload and, more importantly, it would produce wellness indicators associated with the function of care which, in turn, would be enhanced as mediators of psychological and emotional well-being.

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Appendix

Appendix 1

- List of participating centers and personnel

Appendix 2

- Definition Criteria for Risk Factors and Diseases under Study

Appendix 3

- Consent form

Appendix 4

Madureira, S., Verdelho, A., Ferro, J., Basile, A. M., Chabriat, H., Erkinjuntti, T., etal.(2006). Development of a Neuropsychological Battery for the Leukoaraiosis and Disability in the Elderly Study (LADIS): Experience and Baseline Data. *Neuroepidemiology*, 27(2), 101-116.

Appendix 5

Madureira S,Verdelho A, Moleiro C, Ferro JM, Erkinjuntti T, Jokinen H, Pantoni L, Fazekas F, Van der Flier W, Visser M, Waldemar G, Wallin A, Hennerici M, Inzitari D (2010). Neuropsychological Predictors of Dementia in a Three-Year Follow-Up Period: Data from the LADIS Study. *Dementia and Geriatric Cognitive Disorders*, 29(4), 325-334

Appendix 6

Madureira S, Verdelho A, Moleiro C, Santos C, Scheltens P, Gouw A, Ferro J (2016). White matter changes and cognitive decline in a 10 year follow-up period: a pilot study from a single centre cohort from the LADIS study *Dementia and Geriatric Cognitive Disorders* 41:303-313 (DOI:10.1159/000447121)

Appendix 1: List of participating centers and personnel

Helsinki, Finland (Department of Neurology, Helsinki University Central Hospital and Department of Neurological Sciences, University of Helsinki, Finland): Timo Erkinjuntti, MD, PhD, Tarja Pohjasvaara, MD, PhD, Pia Pihanen, MD, Raija Ylikoski, PhD, Hanna Jokinen, PhD, Meija-Marjut Somerkoski, MPsych, Riitta Mäntylä, MD, PhD, Oili Salonen, MD, PhD;

Graz, Austria (Department of Neurology and Department of Radiology, Division of Neuroradiology, Medical University Graz): Franz Fazekas, MD, Reinhold Schmidt, MD, Stefan Ropele, PhD, Brigitte Rous, MD, Katja Petrovic, MagPsychol, Ulrike Garmehi, Alexandra Seewann, MD;

Lisboa, Portugal (Serviço de Neurologia, Centro de Estudos Egas Moniz, Hospital de Santa Maria): José M. Ferro, MD, PhD, Ana Verdelho, MD, Sofia Madureira, Psy, Carla Moleiro, PhD;

Amsterdam, The Netherlands (Department of Radiology and Neurology, VU Medical Center): Philip Scheltens, MD, PhD, Ilse van Straaten, MD, Frederik Barkhof, MD, PhD, Alida Gouw, MD, Wiesje van der Flier, PhD;

Goteborg, Sweden (Institute of Clinical Neuroscience, Goteborg University): Anders Wallin, MD, PhD, Michael Jonsson, MD, Karin Lind, MD, Arto Nordlund, PsyD, Sindre Rolstad, PsyD, Ingela Isblad, RN;

Huddinge, Sweden (Karolinska Institutet, Department of Neurbiology, Care Sciences and Society; Karolinska University Hospital Huddinge): Lars-Olof Wahlund, MD, PhD, Milita Crisby, MD, PhD, Anna Pettersson, RPT, PhD, Kaarina Amberla, PsyD;

Paris, France (Department of Neurology, Hopital Lariboisiere): Hugues Chabriat, MD, PhD, Karen Hernandez, psychologist, Annie Kurtz, psychologist, Dominique Hervé, MD, Sarah Benisty, MD, Jean Pierre Guichard, MD;

Mannheim, Germany (Department of Neurology, University of Heidelberg, Klinikum Mannheim): Michael Hennerici, MD, Christian Blahak, MD, Hansjorg Baezner, MD, Martin Wiarda, PsyD, Susanne Seip, RN;

Copenhagen, Denmark (Memory Disorders Research Group, Department of Neurology, Rigshospitalet, and the Danish Research Center for Magnetic Resonance, Hvidovre Hospital, Copenhagen University Hospitals): Gunhild Waldemar, MD, DMSc, Egill Rostrup, MD, MSc; Charlotte Ryberg, MSc, Tim Dyrby MSc, Olaf B. Paulson, MD, DMSc; Ellen Garde, MD, PhD; Kristian Steen Frederiksen, MD;

Newcastle-upon-Tyne, UK (Institute for Ageing and Health, Newcastle University): John O'Brien, DM, Sanjeet Pakrasi, MRCPsych, Mani Krishnan MRCPsych, Andrew Teodorczuk, MRCPsych, Michael Firbank, PhD, Philip English, DCR, Thais Minett, MD, PhD.

The Coordinating centre is in **Florence, Italy** (Department of Neurological and Psychiatric Sciences, University of Florence): Domenico Inzitari, MD (Study Coordinator); Luciano Bartolini, PhD, Anna Maria Basile, MD, PhD, Eliana Magnani, MD, Monica Martini, MD, Mario Mascalchi, MD, PhD, Marco Moretti, MD, Leonardo Pantoni, MD, PhD, Anna Poggesi, MD, PhD, Giovanni Pracucci, MD, Emilia Salvadori, PhD, Michela Simoni, MD.

The **LADIS Steering Committee** is formed by Domenico Inzitari, MD (study coordinator), Timo Erkinjuntti, MD, PhD, Philip Scheltens, MD, PhD, Marieke Visser, MD, PhD, and Peter Langhorne, MD, BSC, PhD, FRCP who replaced in this role Kjell Asplund, MD, PhD beginning with 2005.

Appendix 2: Definition Criteria for Risk Factors and Diseases under Study

Myocardial Infarction

Myocardial infarction, documented by history, ECG or cardiac enzymes, was defined according to the Consensus Document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction [28]. Criteria were the following:

Criteria for Acute, Evolving or Recent Myocardial Infarction
Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischemic symptoms; (b) development of pathological Q waves on the ECG; (c) ECG changes indicative of ischemia (S–T segment elevation or depression), or (d) coronary artery intervention (e.g. coronary angioplasty). Pathological findings of an acute myocardial infarction.

Criteria for Established Myocardial Infarction
Any of the following criteria satisfies the diagnosis of established myocardial infarction:
Development of new pathological Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed. Pathological findings of a healed or healing myocardial infarction.

Angina pectoris

Angina pectoris was defined according to the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [29, 30] as follows.
A clinical syndrome typically characterized by a deep, poorly localized chest or arm discomfort that is reproducibly associated with physical exertion or emotional stress and relieved promptly (i.e. 15 min) with rest or sublingual nitroglycerine. The discomfort of angina is often hard for patients to describe, and many patients do not consider it to be ‘pain’. Patients with unstable angina may have discomfort with all the qualities of typical angina except that episodes are severer and prolonged and may occur at rest with an unknown relationship to exertion or stress.

Cardiac Valvulopathy
Cardiac valvulopathies were classified according to the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [31]. Information was available from history and/or clinical records and the best clinical judgment was used to determine whether the valvulopathy was relevant in terms of cardiac function. (Leukoaraiosis and Disability Neuroepidemiology 2005; 24:51–62 59)

Heart Failure
Heart failure was defined according to the Task Force on Heart Failure of the European Society of Cardiology [32]. The definition was the following: symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed toward heart failure.

Cardiac Arrhythmias
Diagnosis of cardiac arrhythmias was based on history and/or available clinical records. Atrial fibrillation was defined according to Falk [33], as characterized electrocardiographically by the presence of rapid, irregular, fibrillatory waves that vary in size, shape and timing, usually associated with an irregular ventricular response.

Cerebrovascular Diseases
Stroke and TIA were defined according to the World Health Organization [34]. The Rankin scale [35] was used as a functional measure of stroke severity. Ischemic stroke subtypes were classified according to the TOAST classification [36].

Stroke
Rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting for more than 24h or leading to death, with no apparent cause other than that of vascular origin.

Transient Ischemic Attack
Sudden onset of clinical symptoms and/or signs related to focal cerebral or vision deficit attributable to vascular origin, with symptoms and/or signs lasting less than 24 h.

Arterial Hypertension
Hypertension was defined according to the World Health Organization Guidelines for the management of hypertension [37] as asystolic blood pressure of 140 mm Hg or greater and/or a diastolic blood pressure of 90 mm Hg or greater in subjects who are not taking antihypertensive medication. The diagnosis of hypertension had to be based on multiple blood pressure measurements, take non several separate occasions.

Lower Limb Arteriopathy/Peripheral Vascular Disease
Lower limb arteriopathy and peripheral vascular disease were defined according to the American College of Cardiology/American Heart Association Guidelines [38]. Symptomatic disease presenting as intermittent claudication and/or critical leg ischemia were considered according to the criteria reported below. Furthermore, a documented aortic aneurysm, if clinical records were available, was considered.

Definition of Lower Limb Arteriopathy

Depending on its severity, lower extremity arterial disease can present in different ways, including (1) asymptomatic arterial insufficiency, (2) symptomatic disease presenting as intermittent claudication with positive non invasive tests and (3) critical leg ischemia, which defines the subgroup of patients with symptomatic lower extremity arterial disease, in which the ischemic process endangers part or all of the lower extremity, and which includes patients undergoing surgical revascularization procedures or limb amputation.

Diabetes mellitus

Diabetes mellitus was defined and classified according to the American Diabetes Association Criteria [39].

Previous diagnosis and/or current treatment with insulin or oral hypoglycemic medications, or at least 8-hour fasting plasma glucose≥7.0 mmol/l (126 mg/dl) as in the reported criteria were considered.

Criteria for the Diagnosis of Diabetes mellitus

Symptoms of diabetes plus casual plasma glucose concentration≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss

or

fasting plasma glucose ≥126 mg/dl (7.0 mmol/l; fasting is defined as no caloric intake for at least 8 h)

or

2-hour plasma glucose ≥200 mg/dl during an oral glucose tolerance test. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Hyperlipidemias

Hyperlipidemia was defined according to the National Cholesterol Education Program Adult-Treatment Panel II [40]. Hypercholesterolemia included total cholesterol >200, low-density lipoprotein>130, high-density lipoprotein <35 mg/dl (each value found elevated in at least 2 measurements). Hypertriglyceridemia included serum triglyceride >200 mg/dl (in at least 2 measurements).

Migraine

Migraine was defined according to the Headache Classification Committee of the International Headache Society [41]. Criteria were the following.

Migraine without Aura

(A) At least 5 attacks fulfilling B–D.

(B) Headache attacks lasting 4–72 h (untreated or unsuccessfully treated).

(C) Headache has at least 2 of the following 4 characteristics:

(1) Unilateral location; (2) pulsating quality; (3) moderate or severe intensity (inhibits or prohibits daily activities); (4) aggravated by walking stairs or similar routine physical activity.

(D) During headache at least 1 of the following symptoms occur: (1) nausea and/or vomiting; (2) photophobia and phonophobia.

Migraine with Aura
(A) At least 2 attacks fulfilling B.
(B) Headache has at least 3 of the following 4 characteristics:(1) one or more fully reversible aura symptoms indicating focal cerebral cortical and/or brainstem dysfunction; (2) at least 1 aura symptom develops gradually over more than 4 min, or 2 or more symptoms occur in succession; (3) no aura symptoms last more than 60 min; if more than 1 aura symptom is present, accepted duration is proportionally increased; (4) headache follows aura with a free interval of <60 min (it may also begin before or simultaneously with the aura). (Pantoni *et al*. 60 Neuroepidemiology 2005; 24:51–62)

Losses of Consciousness
Seizures were defined according to the Commission on Classification and Terminology of the International League against Epilepsy [42–44] and syncopal episodes were registered on the basis of best clinical judgment.

Chronic Obstructive Pulmonary Disease
Chronic obstructive pulmonary disease was defined according to the British Thoracic Society guidelines for the management of chronic obstructive airways disease [45], as a chronic, slowly progressive disorder characterized by airways obstruction (FEV 1 <80% predicted and FEV 1 /VC ratio <70%) which does not change markedly over several months. The impairment of lung function is largely fixed but is partially reversible by bronchodilator (or other) therapy. Thus, a diagnosis in clinical practice requires: history of chronic progressive symptoms (cough and/or wheeze and/or breathlessness), objective evidence of airways obstruction, ideally by spirometric testing, that does not return to normal with treatment.

Depression
History of depression was based on the presence of previous depressive episodes requiring treatment or hospital admission, corroborated by specific tests assessing mood alterations (15-item Geriatric Depression Scale, Cornell Scale for Depression, DSM-IV criteria checklist) [46–48].

Osteoarthritis and Chronic Pain
Ostheoarthritis (OA) was defined according to the Workshop on Etiopathogenesis of Osteoarthritis [49]. OA of the knee, characterized by knee pain for most days of the prior month, OA of the hand, characterized by hand pain, aching or stiffness for most days of the prior month, and OA of the hip with hip pain for most days of the prior month were considered.
Chronic pain was defined according to the National Institute of Neurological Disorders and Stroke [50].

Appendix 3: Consent form

Instituto de Medicina Molecular, Unidade Neurológica de Investigação Clínica
Serviço de Neurologia, Hospital de Santa Maria

INFORMAÇÃO PARA OS FAMILIARES / CUIDADORES DOS PARTICIPANTES NO ESTUDO

ALTERAÇÕES DA SUBSTÂNCIA BRANCA, EVOLUÇÃO NEUROPSICOLÓGICA E IMPACTO NOS CUIDADORES: 10 ANOS DE SEGUIMENTO

Como é do seu conhecimento, estamos a dar continuidade ao estudo LADIS (Estudo do Impacto das Alterações da Substância Branca Relacionadas com a Idade), no qual o seu familiar participou entre 2000 e 2004 (ver folha em anexo). Com o objectivo de compreendermos melhor o impacto que estas alterações tiveram na vida dos doentes e na dos seus familiares / cuidadores, gostaríamos de o convidar a participar no estudo "Alterações da Substância Branca: perspectiva do cuidador".

O estudo consiste numa única entrevista, de cerca de 40 minutos, que será realizada no Piso 6 (por baixo do Serviço de Neurologia, local habitual das visitas do estudo LADIS) do Hospital de Santa Maria, aquando da consulta de reavaliação do doente, ou num dia a combinar conforme a sua disponibilidade.
A entrevista será feita pela Psicóloga (Dra. Sofia Madureira) e tudo o que disser será tratado com confidencialidade. O tratamento dos dados será feito sob anonimato e a confidencialidade dos mesmos assegurada mediante codificação dos dados, não sendo nunca guardados nomes com os dados recolhidos e não podendo ser identificados indivíduos a partir de informação em qualquer registo do estudo.

Para qualquer esclarecimento solicitamos que nos contacte (Dra. Sofia Madureira) para o telefone, nº 21 795 7474 (Ext.: 44197)

Agradecemos, desde já, a atenção que prestou ao nosso convite e esperamos contar com a sua colaboração.

Instituto de Medicina Molecular, Unidade Neurológica de Investigação Clínica
Serviço de Neurologia, Hospital de Santa Maria

ESTUDO : ALTERAÇÕES DA SUBSTÂNCIA BRANCA: PERSPECTIVA DO CUIDADOR

CONSENTIMENTO INFORMADO

Certifico que li a informação relativa à continuidade do **Estudo do Impacto das Alterações da Substância Branca Relacionadas com a Idade, perspectiva do cuidador** .

. Concordo em realizar esta entrevista no âmbito do estudo acima referido

Nome do Participante:_____

Assinatura: _____Data:_____

Nome da Psicóloga: Dra. Sofia Madureira

Assinatura:_____ Data: _____

Appendix 3: Consent form

Instituto de Medicina Molecular, Unidade Neurológica de Investigação Clínica
Serviço de Neurologia, Hospital de Santa Maria

INFORMAÇÃO PARA OS PARTICIPANTES NO ESTUDO
ALTERAÇÕES DA SUBSTÂNCIA BRANCA, EVOLUÇÃO NEUROPSICOLÓGICA E IMPACTO NOS CUIDADORES: 10 ANOS DE SEGUIMENTO

Como é do seu conhecimento, estamos a dar continuidade ao estudo LADIS (Estudo do Impacto das Alterações da Substância Branca Relacionadas com a Idade), no qual participou entre 2000 e 2004 (ver folha em anexo). Nesse sentido gostaríamos de o convidar a fazer uma nova consulta de avaliação geral da sua saúde bem como da sua capacidade cognitiva e desempenho motor, com o objectivo de comparar a evolução ao longo do tempo.

Consulta:
Tal como nas consultas anteriores, a avaliação clínica incluirá a compilação de dados demográficos, a identificação de factores de risco vasculares (hipertensão, diabetes, tabagismo etc), exame físico, e exame neurológico. A avaliação neuropsicológica engloba um conjunto de testes (tipo pergunta e resposta), dirigidos à avaliação das capacidades cognitivas. A capacidade motora será avaliada mediante provas simples de marcha e de equilíbrio. Ambas as consultas serão realizadas pelas Neurologista (Dra. Ana Verdelho) e Psicóloga (Dra. Sofia Madureira) que o / a acompanharam no estudo anterior.

Exames a realizar:
Tal como no estudo anterior, será realizada uma Ressonância Magnética para que se possa avaliar as alterações da substância branca. Este é um exame não invasivo (não traz incómodo ao doente em resultado da sua execução) do qual não se conhecem efeitos secundários. Apenas os doentes com algumas próteses metálicas cirúrgicas ou pace-maker artificial não poderão repetir o exame. A administração de contraste não será em princípio realizada. Nesta última eventualidade será solicitado o seu consentimento escrito, visto existirem numa pequena percentagem de doentes casos de reacções alérgicas.

Local:
A consulta será feita no Hospital de Santa Maria, através da Consulta Externa de Neurologia, com excepção feita à ressonância magnética que será efectuada no Hospital da Cruz Vermelha.

Confidencialidade: Tudo o que disser em consulta será tratado com confidencialidade. O tratamento dos dados será feito sob anonimato e a confidencialidade dos mesmos assegurada mediante codificação dos dados, não sendo nunca guardados nomes com os dados recolhidos e não podendo ser identificados indivíduos a partir de informação em qualquer registo do estudo. Se desejar ou concordar, poderemos informar o seu Médico de Família que realizou este exame e fornecer os dados que achar necessários (relatório da Ressonância Magnética, por exemplo)

É livre de recusar ou interromper a participação sem que isso afecte o seu tratamento ou o seu seguimento em Consulta Externa de Neurologia.

CONSENTIMENTO INFORMADO

ESTUDO: ALTERAÇÕES DA SUBSTÂNCIA BRANCA, EVOLUÇÃO NEUROPSICOLÓGICA E IMPACTO NOS CUIDADORES: 10 ANOS DE SEGUIMENTO

Certifico que li a informação relativa à continuidade do **Estudo do Impacto das Alterações da Substância Branca Relacionadas com a Idade, na Transição para a Dependência no Envelhecimento**

.Concordo em realizar esta avaliação no âmbito dos 10 anos de seguimento estudo acima referido

Nome do Participante:_____

Assinatura: _____Data:_____

Nome do Médico: Dra. Ana Verdelho

Assinatura: _____Data:_____

Nome da Psicóloga: Dra. Sofia Madureira

Assinatura:_____ Data: _____

Appendix 4

Methods in Neuroepidemiology

Neuroepidemiology

Neuroepidemiology 2006;27:101–116
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Development of a Neuropsychological Battery for the Leukoaraiosis and Disability in the Elderly Study (LADIS): Experience and Baseline Data

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Key Words

White matter changes · Aging · Cognitive performance · Neuropsychological tests

Abstract

The relationship between age-related white matter changes and cognitive performance in independent elderly people is still not clear. The Leukoaraiosis and Disability in the Elderly study (LADIS) involves 11 European centers. It aims to assess the role of the age-related white matter changes as an independent factor in the transition to disability, and in cognitive performance of an independent elderly population. A comprehensive neuropsychological battery was constructed in order to harmonize the cognitive assessment across countries. Patients were evaluated at baseline and during the 3-year follow-up with the Mini-Mental State Examination, a modified version of the VADAS-Cog (Alzheimer's Dementia Assessment Scale plus tests of Delayed recall, Symbol digit, Digit span, Maze, Digit cancellation and Verbal fluency), Trail making and Stroop test. Six hundred thirty-eight patients (mean age 74 ± 5 years; mean educational level 10 ± 4, F/M: 351/287) were included in this study. Neuropsychological data were analyzed test by test and also grouped in three compound measures (executive, memory and speed/motor control domains). Older subjects (>74 years) performed significantly worse than younger subjects on the ADAS-Mod and on the tests of memory ($t_{631} = 3.25$; $p = 0.001$), executive functions ($t_{581} = 4.68$; $p = 0.001$) and speed/motor control ($t_{587} = 4.01$; $p = 0.001$). Participants with higher educational level (>8 years of school) showed better performances on the compound measures for memory ($t_{631} = 3.25$; $p = 0.001$), executive functions ($t_{581} = 4.68$; $p = 0.001$) and speed/motor control ($t_{587} = 4.01$; $p = 0.001$). Using multiple regression analysis models to study the influence of demographic variables on cognitive performance, age and education remained im-

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portant variables influencing test performance. In the LADIS population baseline data, older age and lower educational levels negatively influence neuropsychological performance.

Introduction

The relationship between age-related white matter changes (ARWMC) and cognitive impairment has been described in several studies in different population samples [1, 2].

In community-dwelling and independent elderly subjects, some studies reported an association between the presence of ARWMC and deficits in global mental functioning, speed of mental processing and memory [3–9]. However, others failed to find a relationship between the presence of ARWMC and cognitive performance [10–12].

There are a number of factors that can explain the inconsistency of these results. They may be related to the design of the studies, the type of analysis performed on imaging and the neuropsychological evaluation. Further, regarding cognitive performance, the variability of results can be due to the use of different instruments and measures to assess cognition, the use of different criteria to define cognitively impaired performance, and the use of nonsensitive instruments, such as global measures of cognition, or tests sensitive to memory decline but not to executive functioning.

Despite the recent interest and effort to analyze the impact of ARWMC on cognition, there are still several issues that need to be explored. How is cognitive functioning influenced by ARWMC? Is there a threshold of ARWMC needed to affect cognition? Which cognitive domains are mainly affected by the presence of ARWMC and which domains are more sensitive to decline in parallel to the progression of ARWMC? Is there a neuropsychological profile related to the location of ARWMC?

The Leukoaraiosis and Disability in the Elderly study (LADIS) aims to assess the role of ARWMC as an independent predictor of disability in the elderly [13], contributing with answers to the above-mentioned issues. The LADIS study involves 11 centers of 10 European countries (appendix 1).

The assessment of cognitive functions is a difficult task, starting with the selection of the appropriate tests to evaluate specific domains. The difficulty increases in multinational studies since the performance in majority of the tests is dependent on educational, language, cultural and demographic variables.

The aims of the present work were to describe the development of the LADIS neuropsychological battery, to present LADIS neuropsychological baseline data, and to discuss the methodological problems and limitations of the cognitive assessment within the LADIS study.

Methods

LADIS organization and methodology have already been reported elsewhere [13].

Construction of the Neuropsychological Battery

The construction of the LADIS neuropsychological battery took into consideration that: (1) selected tests had to be available and familiar in the majority of the centers; (2) the tests had to be sensitive to cognitive decline; (3) the battery had to be innovative, comprehensive, easy to administer, but not too long; (4) all centers had to use the same version of each test; (5) the original English version of tests had to be translated into each local language.

In order to construct the neuropsychological battery for the LADIS study, we performed a review of the studies investigating elderly samples with ARWMC using comprehensive cognitive assessments published until 2001, and selected the most frequently used instruments. In this review, we also retrieved the criteria for the definition of abnormal performance on the neuropsychological tests used in each study. A list of tests was made according to the frequency they appeared in the studies. All participating centers received a questionnaire in which, for each test of the list, several questions were asked: (a) if the test was available at their center; (b) if it was routinely used for cognitive assessment; (c) if it had local/national validation norms; (d) if the original or other versions were used.

Of the eight tests initially selected, the Mini-Mental State Examination (MMSE) [14] and the Stroop test [15, 16] were the only tests available and in use for assessment in all centers. However, the versions used were slightly different from center to center and normative values existed in only 62% (MMSE) and 69% (Stroop) of the countries. Verbal fluency tests were also available in all centers, with normative values for 92% of the countries. Nevertheless, the variability of versions was wide: some centers used semantic fluency (animals, colors, fruits, cities, or supermarket goods), others used only controlled oral word association tests (using different letters such as FAS, PFL or LPS). The Wisconsin Card Sorting Test [17] was available in almost all the centers, but with different versions (original and modified). Further, in half of the centers it was not used on a regular basis.

The following tests were initially selected for inclusion in the LADIS neuropsychological battery: the MMSE to assess global mental status, the Stroop and Trail making tests [18] to assess executive functions. In the absence of any frequently used battery, we added the VADAS-Cog [19] which is a recently developed instrument used to assess the cognitive performance of patients with vascular dementia. It is composed by the well-known Alzheimer's Disease Assessment Scale (ADAS-Cog) [20], which assesses memory, orientation, language, ideational and construc-

Table 1. LADIS neuropsychological battery

	MMSE	ADAS-Mod	VADAS					Trail making		Stroop
			Symbol digit	Digit span	Maze	Digit cancellation	Verbal fluency	A	B	
Global mental functioning	+	+								
Orientation		+								
Memory		+		+						
Attention			+	+		+		+		
Language		+								
Constructional abilities		+								
Executive functions			+				+		+	+
Praxis		+								
Speed and motor control					+	+		+		

MMSE = Mini-Mental State Examination; ADAS-Mod = Alzheimer's Disease Assessment Scale, Modified; VADAS = ADAS-Mod plus timed tests.

tional praxis in addition to other specific tests that evaluate memory with interference, attention and executive functions (Delayed recall, Symbol digit, Digit span, Maze, Digit cancellation, Verbal fluency). The psychometric properties of these tests have been previously described with elderly populations [21, 22]. Table 1 tabulates the neuropsychological tests composing the initial LADIS battery and the cognitive domains they assess.

In order to reduce the time needed to administer the VADAS-Cog, only one trial was used on subtest 1 (Word recall) and subtest 8 (Word recognition), instead of the original three. On the VADAS-Cog, the translation of the words on subtests 1 and 8 was made according to the frequency of the words in each language [23]. On subtest 5 (Naming objects), we used drawings instead of real objects, as it was the best way to reduce the heterogeneity of administration. The subtest 'Delayed recall' of the words of subtest 1 was also included in the ADAS-Cog. This subtest is scored as the other items of the ADAS-Cog (higher score representing worse performance). Because of these modifications, we will use the designation ADAS-Mod instead of ADAS-Cog. Finally, part B of Trail making (original version) was locally adapted to the alphabet of each country.

The original English version of all tests was collected by the center responsible for the neuropsychological assessment work package and mailed to each center to be locally translated. A handbook with the instructions of all the tests was also distributed to the centers in order to guarantee that each instrument would be used in the same way.

For the 2nd year of follow-up, two additional tests were included: the 9-Word California Verbal Learning Test (CVLT) [24] and the Constructional praxis delayed recall, based on the CERAD battery [25], in order to improve the assessment of memory decline. Both these tests and the instrument used to assess participants who were unable to come to the visits – the Telephone Interview for Cognitive Status [26] – will be described and analyzed elsewhere, along with the results of the last follow-up.

Analysis of Neuropsychological Data

Neuropsychological data were analyzed as follows: (1) analysis of the test score distribution; (2) analysis of the differences on the neuropsychological performance related to the demographic variables and center; (3) analysis of the influence of demographic variables on cognitive performance; (4) analysis of the influence of other potential confounding variables such as visual deficit, previous stroke, or center of inclusion on the neuropsychological performance.

MMSE was used only as a global measure of cognitive functioning and analyzed either as a continuous variable or categorized using the cut-off of ≤ 23 (for dementia), or <25 (for cognitive deficit) [27]. The Stroop test was considered a measure of executive function, and the analyzed measure was time used to perform Stroop 3 minus the time to perform Stroop 2. The Trail making test was considered a measure of executive functions using the score 'time needed to perform part B minus the time to perform part A'. Trail making/A score was also used as a measure of speed and motor control. Higher scores on both the Stroop and Trail making tests represented worse performance. VADAS-Cog was analyzed in two ways: (a) as a global measure, consisting of the scores of ADAS-Mod items Word recall, Commands, Constructional praxis, Delayed recall, Naming, Ideational praxis, Orientation, Word recognition, Remembering instructions, Spoken language ability, Word finding difficulty, Comprehension, and Concentration/distractibility. Higher scores represented worse performance; (b) the 5 additional subtests Digit span backwards, Maze task, Digit cancellation, Symbol digit and Verbal fluency were evaluated independently. In all the tests except for Maze (where the score is the time to complete the task), higher scores represent better performance.

Depending on the aim of the study performed on the LADIS sample, cognitive variables will be analyzed as continuous or categorical using specific cut-offs (e.g. MMSE) or the quartiles of the distribution of the LADIS sample (table 2). For the present paper, all the test scores were analyzed as continuous variables.

Table 2. Quartiles of the distribution of the neuropsychological tests scores

		MMSE	Stroop 1	Stroop 2	Stroop 3	Stroop 3 – 2	Trail A	Trail B	Trail B – A	ADAS-TOTAL	Symbol digit	Digit span	Maze	Digit cancel	Verbal fluency
Valid		638	628	626	619	618	633	605	605	633	627	635	632	626	631
Missing		2	12	14	21	22	7	35	35	7	13	5	8	14	9
Mean		27.3	12.0	17.0	50.9	34.1	63.5	177.3	116.8	16.6	26.8	5.4	7.4	19.5	18.9
Median		28.0	11.0	15.0	43.0	27.0	52.0	143.0	91.0	16.0	27.0	5.0	6.0	20.0	19.0
Percentiles	25	26.0	9.0	13.0	32.0	18.0	41.0	106.0	59.0	12.0	19.0	4.0	4.0	14.0	14.0
	50	28.0	11.0	15.0	43.0	27.0	52.0	143.0	91.0	16.0	27.0	5.0	6.0	20.0	19.0
	75	29.0	14.0	19.0	60.0	42.0	72.5	233.5	154.0	20.0	35.0	6.0	8.7	24.0	23.0
Skewness		–1.36	2.44	3.49	3.25	3.66	2.78	2.19	2.93	1.10	0.32	0.31	3.90	0.14	0.22

The distribution of the test scores was analyzed for each variable. Non-normal distributions with marked skewness (>2) were transformed into normal or less skewed distributions using a logarithmic transformation of the scores. Data analysis was conducted using both the raw and the transformed scores. As the results of raw and transformed scores were similar, the results based on raw scores were presented.

To compare performances across tests and by cognitive domain, we used Z-standard scores, using the distribution of the LADIS sample. To analyze performances by domain, compound measures were calculated using standard scores. Three main domains were analyzed: (1) memory = z-scores of (Immediate word recall + Delayed recall + Word recognition + Digit span)/4; (2) executive functions = z-scores of [(Stroop 3 – 2) + (Trail making/B – Trail making/A) + Symbol digit + Verbal fluency]/4; (3) speed and motor control = z-scores of (Trail making/A + Mazes + Digit cancellation)/3. Z-scores of the tests that had higher scores representing worse performance were inverted (–Z) in order to calculate the compound measure score. A preliminary exploratory factor analysis was performed to evaluate the validity of the neuropsychological battery and the aforementioned compound measures using Principal Component Analysis as extraction method and Varimax Rotation. The obtained solution was compared with the theoretically derived dimensions.

The degree of ARWMC severity on MRI was rated into mild, moderate and severe using the visual scale of Fazekas et al. [28], taking only deep and subcortical white matter lesions into account.

The demographic variables considered for the present analysis were age, education, gender, living conditions (alone or with others), and employment status (retired, working). Age and education were analyzed as continuous variables, except when comparing demographic variables and neuropsychological performance where they were dichotomized using the median of the LADIS sample (74 years and 9 years, respectively).

There were several reasons for referral to the LADIS study, including minor cognitive or neurological complaints, stroke or other neurological disturbances [13]. Therefore, sources of referral were analyzed as variables that could influence the performance on neuropsychological testing. Other possible confounders for the analysis of cognitive performance, such as visual or hearing deficits, were also considered in data analysis.

Statistical Analysis

Descriptive statistics was performed to analyze the quality and distribution of the neuropsychological data. The distribution of demographic characteristics and test scores among centers was performed using box and whiskers plots. Differences among centers were calculated using one-way ANOVAs with Bonferroni or Tamhane's (equal variance not assumed) post-hoc analyses for multiple comparisons.

The neuropsychological performance in each test and domain was compared across demographic characteristics (age, sex, education, living conditions, employment status) using t tests. Performance across cognitive tests was also compared according to the sources of referral using one-way ANOVA with Bonferoni post-hoc analysis. In order to study the influence of demographic variables on cognitive performance, linear regression models (including all the significant variables in the previous comparisons, $p < 0.05$) were performed for each neuropsychological test and domain. Possible confounding variables that could influence the results of neuropsychological performance, such as presence of visual or hearing deficits, previous stroke or center of origin, were also included in an additional linear regression model.

Results

Baseline Neuropsychological Data

Six hundred and thirty-nine patients were enrolled in the LADIS study. Baseline demographic and WMC characteristics, as well as the reasons for referral of the patients are shown in table 3. Neuropsychological examination was performed on 638 (99.8%) patients.

Quality of Data and Distribution of the Test Scores

The highest number of missing values (33 patients, 5%) was observed on Trail making/part B (mental flexibility) and Stroop test/part 3 (3%). Five-hundred and seventy-eight patients (91%) had no missing values on the neuropsychological evaluation. Skewed distributions with a ceiling effect were observed in the subtests Command, Naming, Ideational praxis, Orientation, Mazes,

Table 3. Baseline demographic WMC characteristics and reasons for referral of the patients

Study population (n = 638)	
Demographic factors	
Age, mean ± SD, years	74.1 ± 5
Female/male	351 (55%)/287(45%)
Education, mean ± SD, years	9.6 ± 3.8
Living alone/with other	205 (32%)/434 (68%)
Working/retired	24 (4%)/610 (96%)
Married/not married	401 (63%)/237 (37%)
WMC characteristics	
Mild	284 (44.5%)
Moderate	196 (30.7%)
Severe	158 (24.8%)
Reasons for referral	
Minor cognitive complaints	168 (26.3%)
Minor stroke	122 (19.1%)
Motor complaints	28 (4.4%)
Psychic complaints	13 (2%)
Incidental CT/MRI findings[a]	107 (16.7%)
Other neurological disturbances	129 (20.2%)
Controls in other studies or volunteers	72 (11.3%)

[a] Subjects undergoing a neuroimaging study for nonspecific reasons such as tension headache, dizziness, minor trauma, hearing complaints.

Remembering instructions, Spoken language, Word finding difficulties, Comprehension and Concentration (fig. 1), which were transformed using the logarithmic of the scores. There were no differences in the results either using transformed or raw scores (data available on request).

Preliminary Exploratory Factor Analysis

Factor analysis of principal components with varimax rotation extracted three factors. The eigenvalues for the 3 factors were 5.90, 1.44 and 1.41, explaining 48.6% of the total variance. For factor 1, the most salient tests were Trail A, Trail B, Trail B – A, Symbol digit, Digit cancellation, Maze task and Verbal fluency. We denominated this factor as executive functions. Factor 2 was designated as Selective Attention because only Stroop 3 and Stroop 3 – 2 were loaded saliently. Factor 3 was designated as memory because the loadings of the tests of memory, i.e. Immediate word recall, Delayed word recall, Word recognition and Orientation, were the most salient. For the compound measure scores, we excluded the simplest timed tests, i.e. Trail A, Maze task and Digit cancellation from the executive functions, and added the Stroop test, for theoretical and interpretability reasons. The timed tests were grouped into a speed/motor control measure.

Distribution of the Test Scores by Center

Significant differences among centers were observed for all tests (one-way ANOVAs). Post-hoc analysis (Bonferroni's analysis was employed for all tests, except for Symbol digit and Verbal fluency which were analyzed with Tamanhe's test) showed that differences were randomly distributed, and no consistent pattern was found (there was no center always better or worse than the others). Figure 1 shows the distribution of the test scores by center.

The distribution of age and education by center was analyzed, as they are important variables for neuropsychological performance. No significant differences were found among centers with respect to age ($F_{10, 628} = 1.27$; $p = 0.24$). Education had a normal distribution with significant differences among centers ($F_{10,627} = 11.76$; $p < 0.001$). Using Bonferroni post-hoc test, we found that Lisbon and Florence centers differed systematically from the other centers as they had the lowest mean educational levels ($p < 0.01$ for both).

Mean Differences regarding Demographic Variables

Table 4 shows the differences in neuropsychological performance according to the demographic variables.

Age. Older subjects (>74 years) performed significantly worse than younger subjects on the ADAS-Mod Total based on the differences found on ADAS-Mod subtests Constructional praxis ($t_{513} = –3.09$; $p < 0.01$) and Delayed recall ($t_{607} = –3.12$; $p < 0.01$). Older subjects also showed worse performances on Stroop part 3 ($t_{617} = –2.63$; $p < 0.01$), Trail making A ($t_{537} = –3,16$; $p < 0.01$) and B ($t_{456} = –3.40$; $p < 0.01$), Symbol digit ($t_{625} = 3,72$; $p < 0.01$), Digit cancellation ($t_{631} = 4.94$; $p < 0.001$) and verbal fluency ($t_{629} = –2.83$; $p < 0.01$). Comparing the performance by cognitive domain, older subjects performed worse than younger subjects on executive functions ($t_{581} = 4.68$; $p < 0. 01$), memory ($t_{631} = 3.25$; $p < 0. 01$) and speed/motor control ($t_{587} = 4.01$; $p < 0.01$).

Gender. Women performed significantly worse on the ADAS-Mod subtest Constructional praxis ($t_{635} = 3.18$; $p < 0. 01$) and Maze ($t_{630} = 2.54$; $p < 0.01$). There were no gender differences considering the three cognitive domains: executive functions ($t_{581} = –0.99$; $p = 0.31$), memory ($t_{628} = –0.18$; $p = 0.85$) and speed/motor control ($t_{621} = –1.46$; $p = 0.14$).

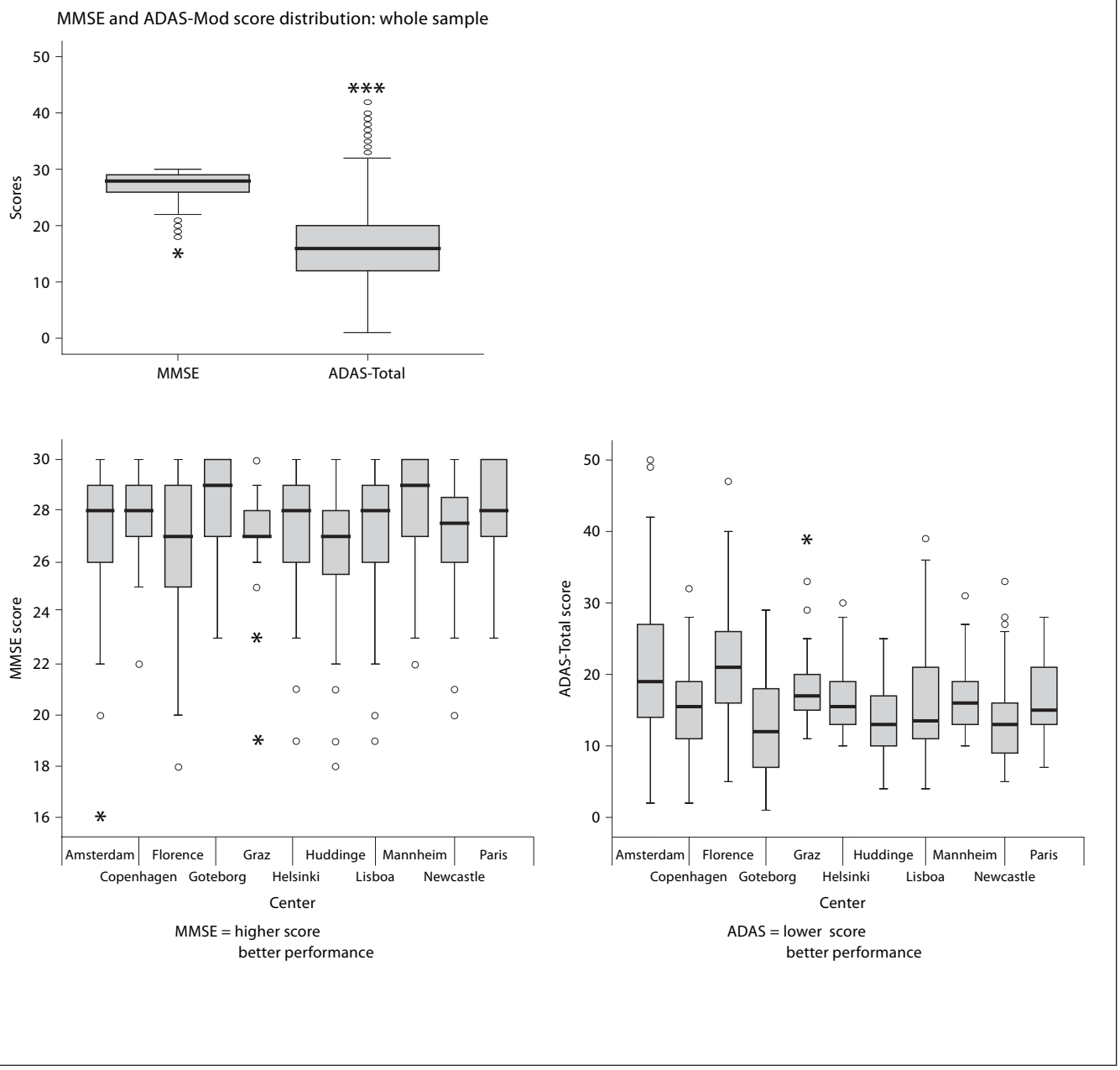
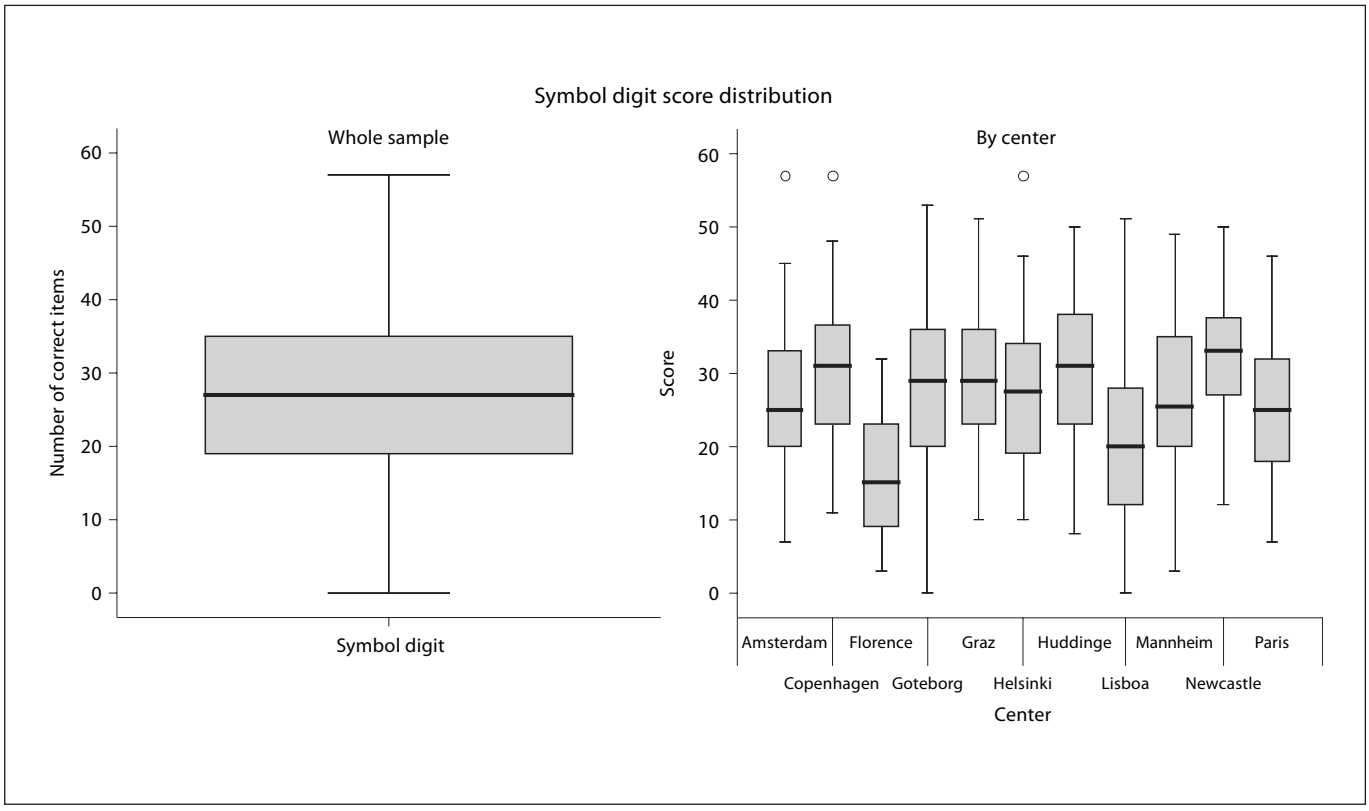
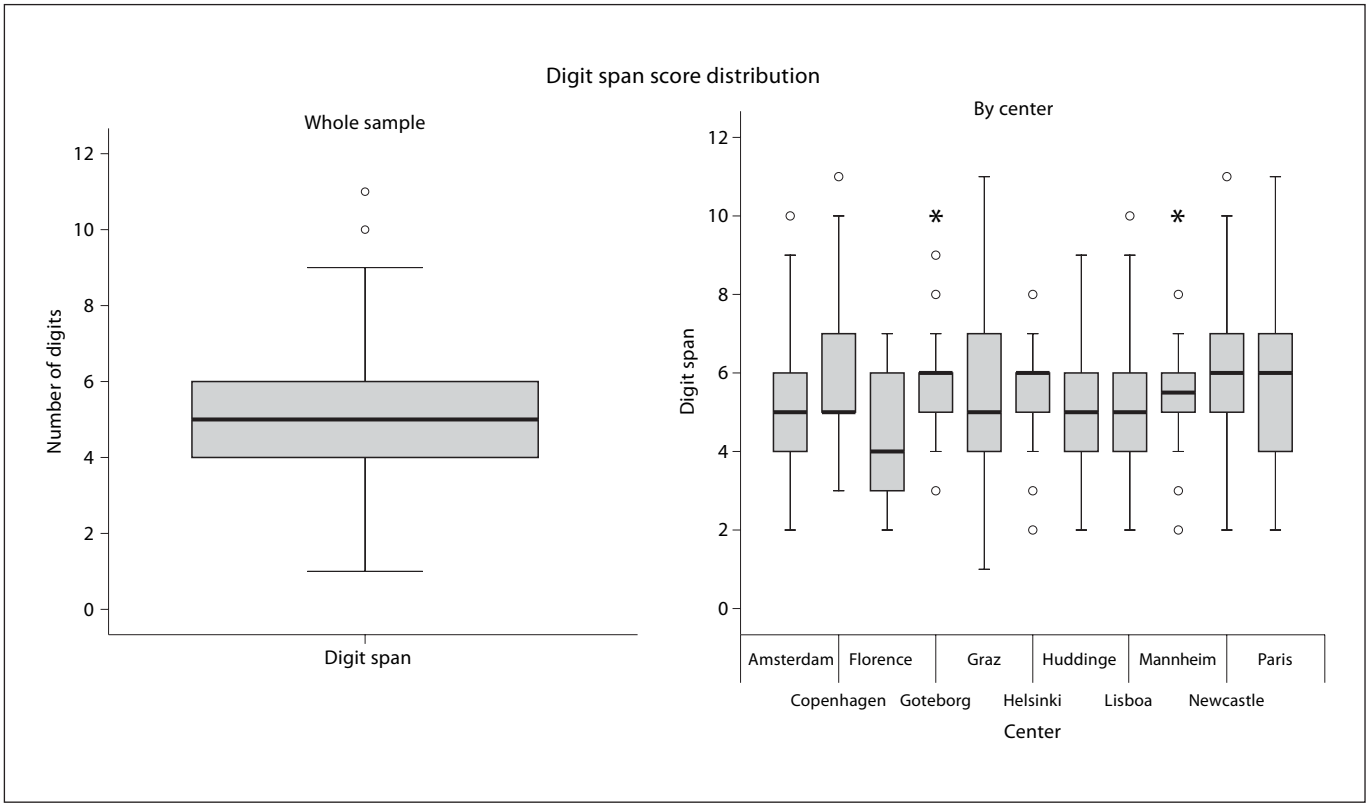


Fig. 1. Distribution of the test scores of the whole sample and by center. Box and whiskers represent the upper quartile (top of the box) and the lower quartile (bottom); bar represents the median; the largest value is on the superior whisker; the smallest value is on the inferior whisker. Open circles and asterisks signify outliers and extreme scores, respectively.

(For figure 1 see next pages.)


Symbol digit score distribution
Whole sample
Number of correct items
Symbol digit
By center
Score
Amsterdam
Florence
Graz
Huddinge
Mannheim
Paris
Copenhagen
Goteborg
Helsinki
Lisboa
Newcastle
Center


Digit span score distribution
Whole sample
Number of digits
Digit span
By center
Digit span
Amsterdam
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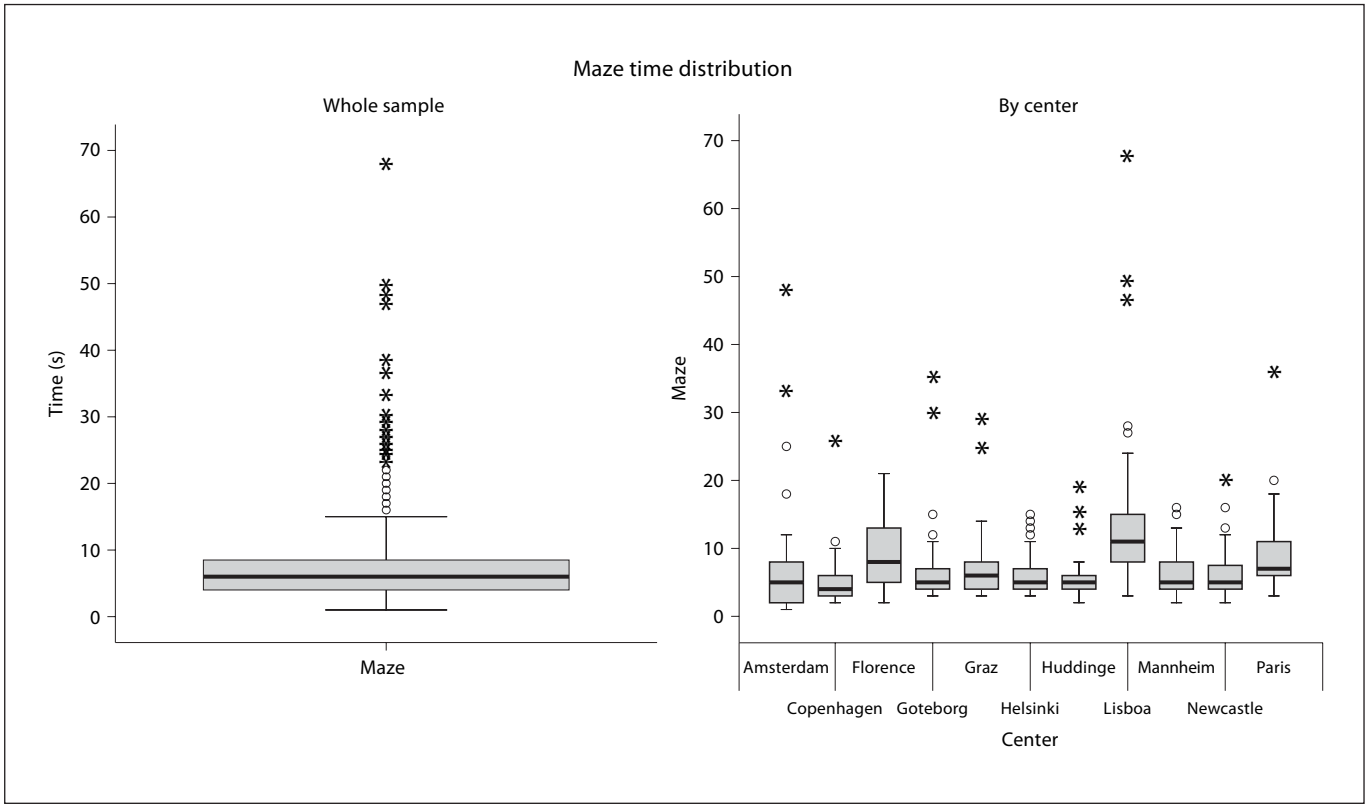
Maze time distribution
Whole sample
Time (s)
Maze
By center
Maze
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Florence
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Lisboa
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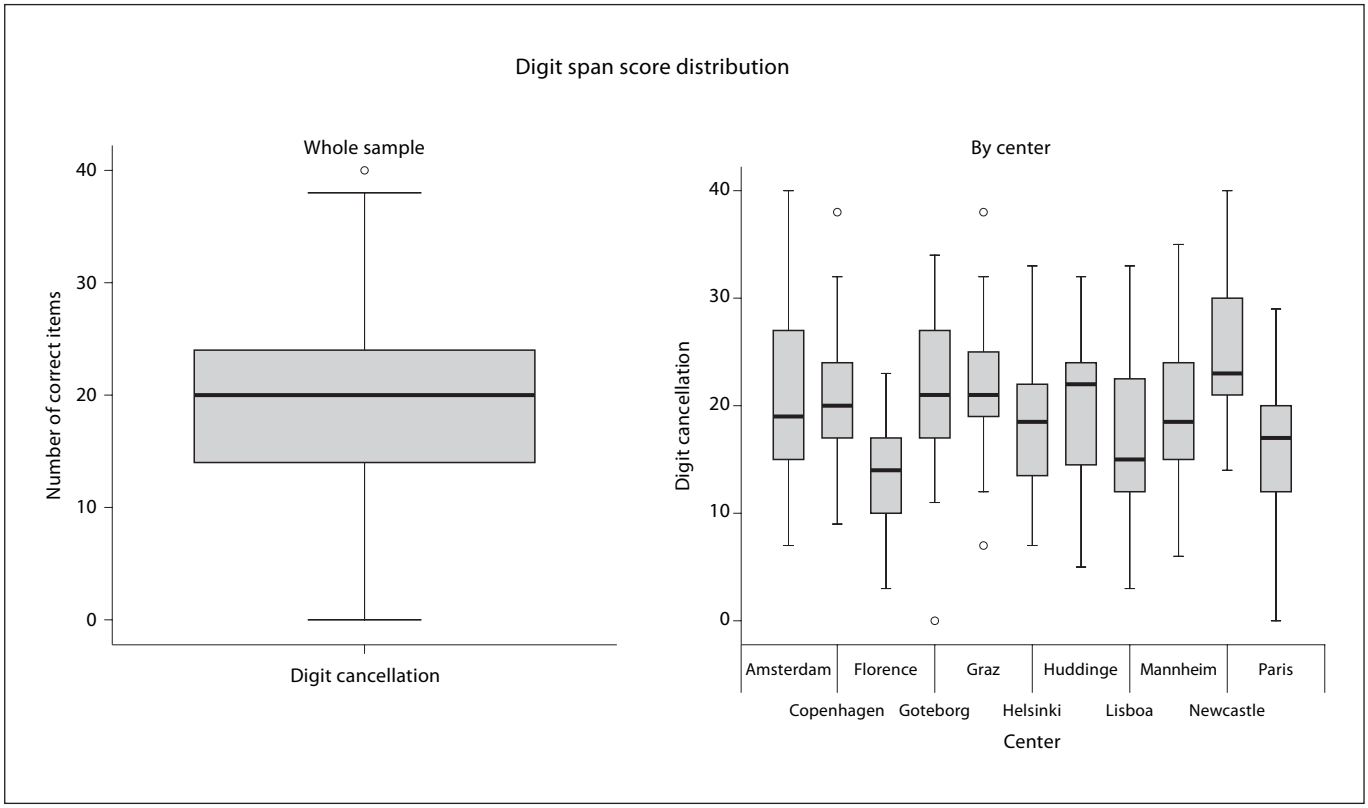
Digit span score distribution
Whole sample
Number of correct items
Digit cancellation
By center
Digit cancellation
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Florence
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Mannheim
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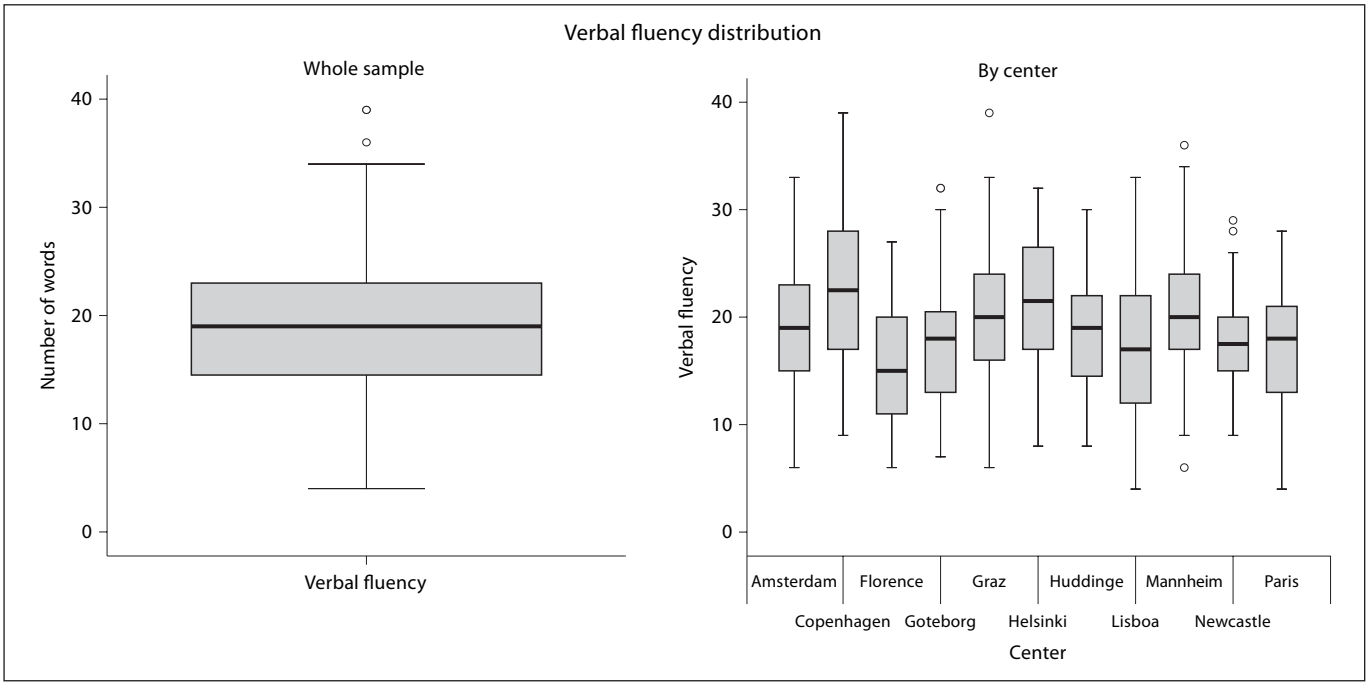
Verbal fluency distribution
Whole sample
Number of words
Verbal fluency
By center
Verbal fluency
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Florence
Graz
Huddinge
Mannheim
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Newcastle
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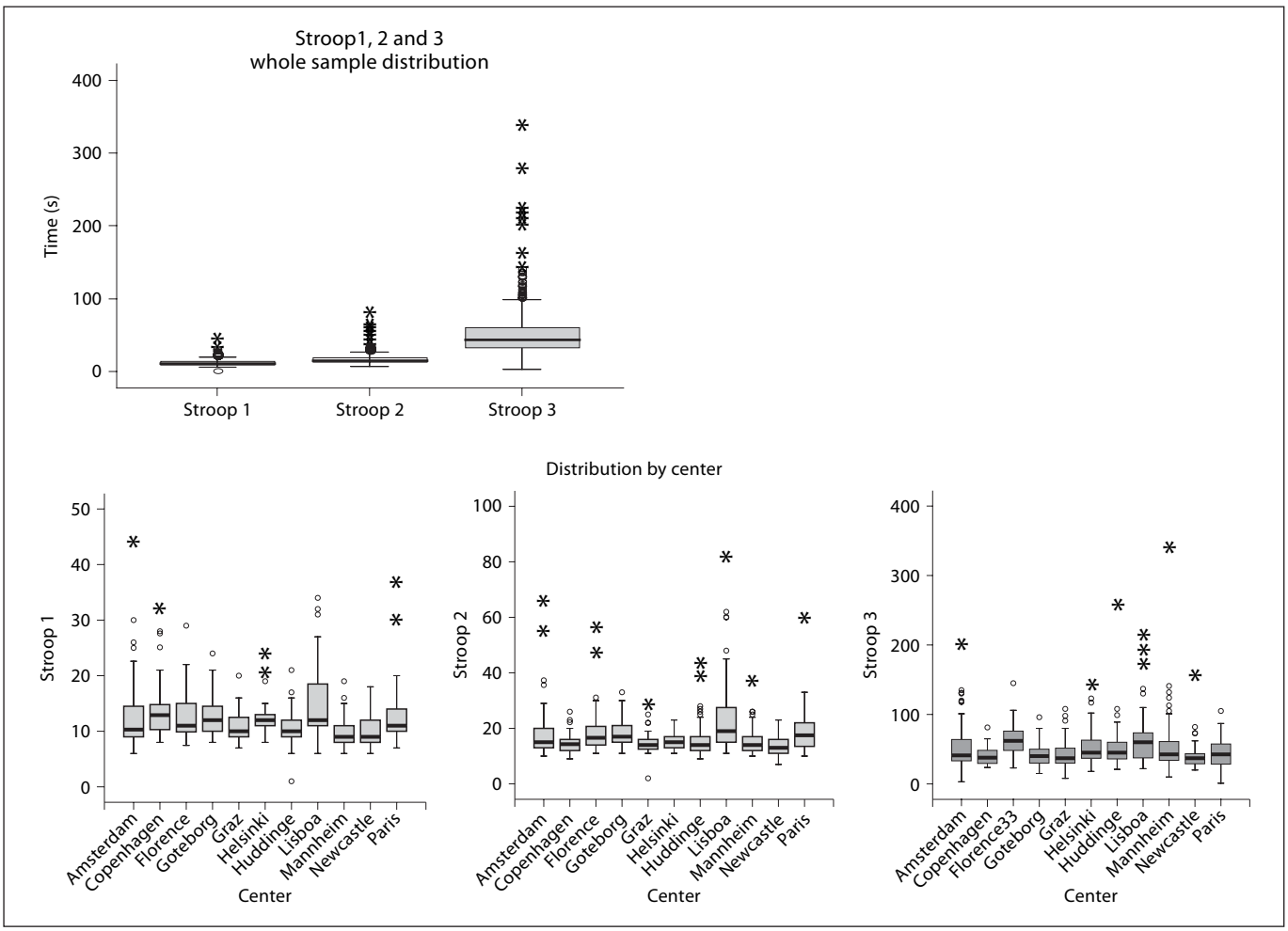
Stroop1, 2 and 3
whole sample distribution
Time (s)
Stroop 1
Stroop 2
Stroop 3
Distribution by center
Stroop 1
Stroop 2
Stroop 3
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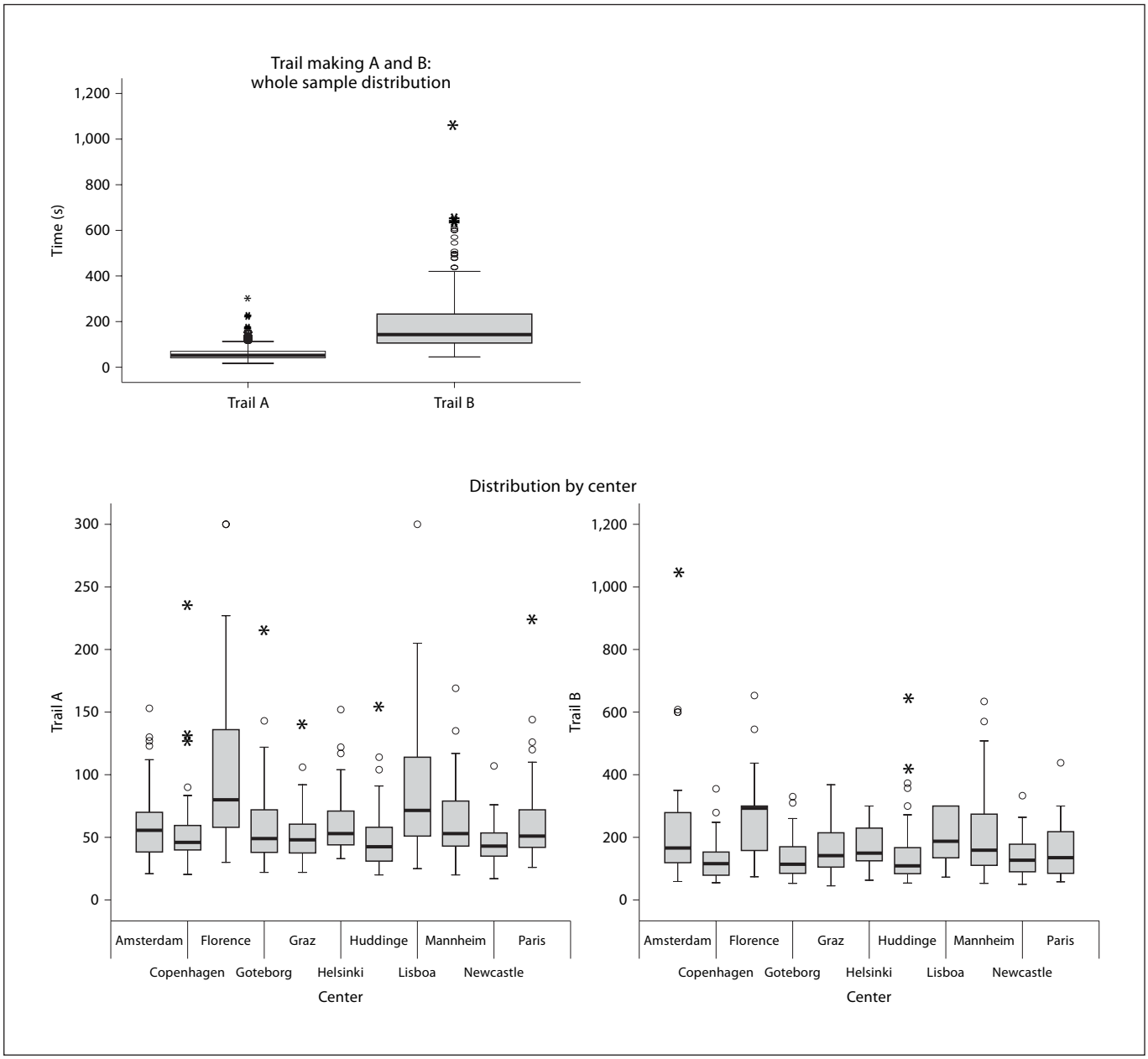
Helsinki
Huddinge
Lisboa
Mannheim
Newcastle
Paris
Center



Education. Significant differences between subjects with higher (>8 years of school) and lower educational level (<9 years) were observed on all tests, except on ADAS-Mod Orientation ($t_{555} = 1.93$; $p = 0.05$, not shown in table 4), Immediate word recall ($t_{635} = 1.59$; $p = 0.11$), Word recognition ($t_{633} = 1.93$; $p = 0.05$), and Commands ($t_{577} = 1.94$; $p = 0.05$). Considering the compound measures of cognitive domains, subjects with lower educational level had worse performances on executive functions ($t_{581} = -10.74$; $p < 0.01$), memory ($t_{631} = -4.99$; $p < 0.01$), and speed/motor control ($t_{381} = -8.36$; $p < 0.01$).

Living Conditions. Participants who lived alone tended to perform better on Trail making A ($t_{568} = 2.19$; $p < 0.05$). However, there were no differences on the other tests, or on the cognitive domains executive functions ($t_{581} = 0.52$; $p = 0.60$), memory ($t_{631} = 0.46$; $p = 0.64$) and speed/motor control ($t_{530} = -1.20$; $p = 0.22$). As it was not a significant variable, it was not included in the regression models.

Employment Status. Participants who were still working performed worse on the ADAS-Mod Commands ($t_{29} = -3.28$; $p < 0.01$). No differences were found in other tests, or on cognitive domains executive functions ($t_{576} = 1.48$; $p = 0.14$), memory ($t_{626} = 1.05$; $p = 0.29$) and speed/motor control ($t_{616} = 1.02$; $p = 0.31$). As participants still working represented only 4% of the LADIS population, this variable was also not included in the regression models.

Neuropsychological performance was also compared by sources of referral. Using a one-way ANOVA, we found significant differences in all the cognitive tests, except for the MMSE ($F_{6, 631} = 0.72$; $p = 0.63$), ADAS-Mod subtests Word recall ($F_{6, 630} = 1.93$; $p = 0.07$), Commands ($F_{6, 630} = 1.33$; $p = 0.24$) and Constructional praxis ($F_{6, 630} = 1.67$; $p = 0.12$). Post-hoc analysis showed that healthy volunteers performed better in all the cognitive tests compared with patients with previous stroke or other complaints.

Multiple Regression Analysis

Multiple linear regression models were used to analyze the influence of the demographic variables on the neuropsychological performance. Table 5 shows the analyses performed with model 1, that included the variables age, education and gender; model 2, with added possible confounders, such as previous stroke, and any complaint or visual deficit, and model 3, in which center origin was added as a covariable. Age remained an important variable influencing the performance on ADAS-Mod Total ($R^2 = 0.10$; $F_{2, 630} = 35.41$; $\beta = 0.17$; $p < 0.001$) and cognitive domains executive functions ($R^2 = 0.22$; $F_{2, 580} = 79.99$; $\beta = -0.22$, $p < 0.001$), and speed/motor control ($R^2 = 0.16$; $F_{2, 619} = 59.68$; $\beta = -0.17$, $p < 0.001$).

There was no other significant influence of gender on neuropsychological performance except on ADAS-Mod Constructional praxis ($R^{2\text{change}} = 0.004$; $F_{6, 629} = 10.62$; $\beta = -0.10$, $p < 0.01$).

Education remained an important variable influencing the performance on all the tests and domains of executive functions, memory, and speed/motor control (table 5).

Variables that might work as confounders of cognitive performance, such as 'referral for any complaint' (vs. healthy volunteers), and previous stroke and visual problems, were included on the second linear regression model. To have any complaint remained an important variable influencing the performance on Trail making A ($R^{2\ \text{change}} = 0.02$; $F_{6, 625} = 19.48$; $\beta = 0.12$, $p < 0.01$), Trail making B – A ($R^{2\ \text{change}} = 0.10$; $F_{16, 587} = 11.81$; $\beta = 0.10$, $p < 0.01$), Symbol digit ($R^{2\ \text{change}} = 0.03$; $F_{6, 619} = 44.90$; $\beta = -0.13$, $p < 0.001$), Digit cancellation ($R^{2\ \text{change}} = 0.06$; $F_{6, 618} = 31.90$; $\beta = -0.21$, $p < 0.001$), Digit span ($R^{2\ \text{change}} = 0.01$; $F_{6, 627} = 18.62$; $\beta = -0.10$, $p < 0.01$) and compound measures speed/motor control ($R^{2\ \text{change}} = 0.03$; $F_{6, 615} = 24.03$; $\beta = -0.12$, $p < 0.001$) and executive functions ($R^{2\ \text{change}} = 0.02$; $F_{6, 576} = 30.32$; $\beta = -0.10$, $p < 0.01$). When visual impairment was included on the linear regression models, its influence was observed on the performance in Trail making B – A ($R^{2\ \text{change}} = 0.10$; $F_{16, 587} = 11.81$; $\beta = 0.10$, $p < 0.01$), Maze task ($R^{2\ \text{change}} = 0.03$; $F_{6, 624} = 14.57$; $\beta = 0.15$, $p < 0.001$) and Delayed recall ($R^{2\ \text{change}} = 0.03$; $F_{6, 628} = 10.34$; $\beta = -0.12$, $p < 0.01$).

On the third step of the models, center of origin was included as covariable. We found that centers influenced the performance of all the tests, but again the findings were randomly distributed and there was no center influencing systematically all the dependent variables in the same way (table 5).

In all the models, age and education remained important factors for neuropsychological performance.

Discussion

The LADIS Battery

The LADIS neuropsychological battery was constructed with the purpose to evaluate the cognitive performance of a cohort of independent subjects with ARWMC, during a period of 3 years of follow-up. It is a comprehensive but not too long instrument that can be administered on a single visit, making it less unpleasant and intrusive for older patients. This battery was chosen based on the familiarity of the tests and the validity of the instruments to assess the decline of cognitive functions of patients with vascular disease. The LADIS battery explores a whole range of cognitive functions. Along with widely known and validated instruments (MMSE, Stroop and Trail making tests), it included the recently developed VADAS-Cog, which provides detailed information on cognitive global and selective functioning. Although based on the Alzheimer's Disease Assessment Scale (ADAS), the inclusion of time-dependent tasks on VADAS (Symbol digit substitution, Maze tracing, Digit cancellation and Verbal fluency) complemented the evaluation of attention, speed of mental processing and motor control. These cognitive functions, along with executive functioning, are possibly more likely to be affected by white matter changes [29].

The inclusion of memory-specific measures, particularly the 9-word CVLT, during the 2nd and 3rd year of

Table 4. Influence of demographic variables on neuropsychological performance (t test results)

	MMSE	Executive functions						Attention		Speed and motor control		
		Stroop 3	Stroop 3 – 2	Verbal fluency	TM B – A	TM B	EXEC	DC	Sy Dig	TM A	Maze	speed
Age	NS	–2.63[a]	–2.55[a]	–2.83[a]	–2.86[b]	–3.40[a]	4.68[a]	4.94[a]	3.72[a]	–3.16[a]	–2.21[b]	4.01[a]
Gender	–2.31[b]	NS	NS	NS	NS	NS	NS	NS	NS	NS	2.54[b]	NS
Education	–6.66[a]	6.01[a]	5.14[a]	–7.37[a]	6.93[a]	8.33[a]	–10.74[a]	–9.80[a]	–13.48[a]	7.84[a]	5.87[a]	–8.36[a]
Living conditions	NS	NS	NS	NS	NS	NS	NS	NS	NS	2.19[b]	NS	NS
Employment status	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

[a] $p < 0.01$; [b] $p < 0.05$. TM = Trail making; EXEC = executive functions compound measure; DC = Digit cancellation; Sy Dig = Symbol digit; Dig Sp = Digit span; Im WR = Immediate word recall; Del WR= Delayed word recall; Word recog. = Word recognition; MEM = memory compound measure; Com = Commands; VC = visuoconstructional; Id = ideational.

Table 5. Influence of demographic variables on neuropsychological performance (linear regression analysis)

	MMSE	Executive functions					EXEC	Attention		Speed and motor control		
		Stroop 3	Stroop 3 – 2	Verbal fluency	TM B – A	TM B		DC	Sy Dig	TM A	Maze	speed
Model 1												
R^2	0.12[a]	0.07[a]	0.05[a]	0.12[a]	0.12[a]	0.18[a]	0.22[a]	0.18[a]	0.27[a]	0.14[a]	0.10[a]	0.16[a]
Age	NS	NS	NS	–0.14[a]	0.15[a]	0.18[a]	–0.23[a]	–0.23[a]	–0.18[a]	0.13[a]	NS	–0.17[a]
Education	00.33[a]	–0.24[a]	–0.20[a]	0.31[a]	–0.31[a]	–0.38[a]	0.40[a]	0.34[a]	0.49[a]	–0.34[a]	0.27[a]	0.36[a]
Gender	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Model 2												
$R^{2\ change}$	NS	0.02[b]	NS	NS	0.02[b]	0.03[a]	0.02[a]	0.06[a]	0.03[a]	0.02[b]	0.03[a]	0.03[a]
Age		NS			0.15[a]	0.17[a]	–0.22[a]	–0.22[a]	–0.17[a]	0.12[b]	NS	–0.15[a]
Education		–0.22[a]			–0.29[a]	–0.36[a]	0.38[a]	0.32[a]	0.46[a]	–0.33[a]	–0.26[a]	0.34[a]
Gender		NS			NS	NS	NS	NS	NS	NS	NS	NS
Any complaint		NS			NS	NS	–0.10[b]	–0.21[a]	–0.13[a]	0.12[b]	NS	–0.12[b]
Stroke		NS			NS	NS	NS	NS	NS	NS	NS	NS
Visual deficit		NS			NS	0.10[b]	NS	NS	NS	NS	0.15[a]	NS
Model 3												
$R^{2\ change}$	0.07[a]	0.05[a]	0.05[b]	0.09[a]	0.10[a]	0.13[a]	0.10[a]	0.07[a]	0.08[a]	0.10[a]	0.11[a]	0.10[a]
Age	NS	NS	NS	–0.16[a]	0.16[a]	0.18[a]	–0.22[a]	–0.22[a]	–0.18[a]	0.12[a]	0.12[b]	–0.17[a]
Education	0.37[a]	–0.20[a]	–0.17[a]	0.29[a]	–0.30[a]	–0.33[a]	0.37[a]	0.26[a]	0.43[a]	–0.25[a]	–0.21[a]	0.27[a]
Gender	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Any complaint	NS	NS	NS	NS	0.15[b]	0.14[b]	–0.12[b]	–0.12[b]	NS	NS	NS	NS
Stroke	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Visual deficit	NS	NS	NS	NS	0.10[b]	0.11[b]	NS	NS	NS	NS	NS	NS
Center	HU –0.18[a]	CO –0.20[b] GO –0.17[b]	CO –0.14[a] GO –0.15[b]	CO 0.20[a] HE 0.13[b]	CO –0.18[a] HU –0.13[b]	CO –0.22[b] FL 0.13[b] GO –0.16[b] HU –0.20[a]	AM –0.14[b] CO 0.14[b] FL –0.18[b]	CO 0.13[b] FL –0.12[b] GO 0.13[b] NC 0.21[a]	CO 0.19[a] HU 0.16[a] NC 0.15[b]	CO –0.21[a] GO –0.14[b] GR –0.14[b] HE –0.13[b] HU –0.22[a] MA –0.15[b] NC –0.21[a]	all centers	all except PA and FL

Values are standardized β. [a] $p < 0.001$; [b] $p < 0.01$; NS = $p > 0.05$. TM = Trail making; EXEC = executive functions compound measure; DC = Digit cancellation; Sy Dig = Symbol digit; Dig Sp = Digit span; Im WR = Immediate word recall; Del WR = Delayed word recall; Word recog. = Word recognition; MEM = memory compound measure; Com = Commands; VC = visuoconstructional; Id = ideational; AM = Amsterdam; CO = Copenhagen; FL = Florence; GO = Goteborg; GR = Graz; HE = Helsinki; HU = Huddinge; LS = Lisbon; MA = Mannheim; NC = Newcastle; PA = Paris.

Memory					Language		Praxis		ADAS-Total
Dig Sp	Im WR	Del WR	Word recog.	MEM	Com	Naming	VC	Id	
NS	NS	–3.12[a]	–2.14[b]	3.25[a]	NS	NS	–3.09[a]	NS	–3.84[a]
NS	NS	NS	NS	NS	NS	NS	3.18[a]	NS	NS
–9.41[a]	NS	5.83[a]	NS	–4.99[a]	NS	6.7[a]	5.39[a]	2.97[a]	5.69[a]
NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
NS	NS	NS	NS	NS	–3.28[a]	NS	NS	NS	NS

Memory				MEM	Language		Praxis		ADAS-Total
Dig Sp	Im WR	Del WR	Word recog.		Com	Naming	VC	Id	
0.14[a]	0.02[a]	0.06[a]	0.04[a]	0.08[a]	NS	0.09[b]	0.10[a]	0.02[b]	0.10[a]
NS		0.15[a]	0.11[b]	–0.15[a]		NS	0.10[b]	NS	0.15[a]
0.38[a]	–0.12[b]	–0.18[a]	–0.15[a]	0.24[a]		–0.30[a]	–0.25[a]	–0.13[b]	–0.27[a]
NS	NS	NS		NS			–0.10[b]	NS	NS
NS	NS	0.03[a]	NS	NS	NS	NS	NS	NS	NS
		0.16[a]							
		–0.17[a]							
		NS							
		NS							
		NS							
		–0.12[b]							
0.06[a]	0.10[a]	0.29[a]	0.09[a]	0.14[b]	NS	0.12[a]	0.07[a]	0.06[a]	0.15[a]
NS	0.11[b]	0.17[a]	0.11[b]	–0.17[a]			NS	NS	0.16[a]
0.36[a]	–0.17[a]	–0.21[a]	–0.15[a]	0.27[a]			–0.26[a]	–0.11[b]	–0.29[a]
NS	NS	NS	NS	NS			–0.12[b]	NS	NS
NS	NS	NS	NS	NS			NS	NS	NS
NS	NS	NS	NS	NS			NS	NS	NS
NS	NS	NS	NS	NS				NS	NS
CO 0.13[b]	AM 0.13[b]	AM 0.14[b]	AM 0.17[b]	AM –0.20[a]		CO –0.20[a]	AM 0.19[a]	GO –0.14[b]	AM 0.30[a]
NC 0.19[b]	GO –0.15[b]	GO –0.19[a]	FL 0.15[b]	GR –0.25[a]		FL 0.15[b]	FL 0.23[a]	HU –0.14[b]	FL 0.21[a]
PA 0.12[b]	GR 0.27[a]	GR 0.29[a]	PA –0.15[b]			GO –0.16[b]	GO 0.17[b]	NC –0.17[b]	GR 0.19[a]
		HE 0.14[b]				HU –0.18[a]	HU 0.21[a]		
		HU –0.23[a]				MA –0.21[a]	MA 0.19[a]		
		NC –0.22[a]				NC –0.19[b]	NC 0.18[b]		
							PA 0.21[a]		

follow-up, was adopted as a way to improve the evaluation of memory decline minimizing the learning effect that might occur if the memory test or the VADAS word recall subtest were administered four times instead of two.

The use of the same version and guidelines for administration of the tests in all the centers reduced the heterogeneity of the cognitive evaluation and allowed the appropriate evaluation of the whole sample of the LADIS cohort.

Nevertheless, the neuropsychological battery adopted in the LADIS study has some limitations: (1) when trying to reduce the time to administer the cognitive battery by using one trial instead of three, as described in the original version of the VADAS subtest Word recall, we did not include any measure of learning memory on the baseline assessment and compromised the possibility of comparing the results of the LADIS sample with other studies that use the same instrument. However, this limitation was minimized by the inclusion of the 9-word CVLT during the second and third follow-up visits; (2) the test versions adopted were not validated in each center/country and there is no control group to compare the results of the LADIS sample. The absence of a control group is due to the fact that it would be necessary to perform MRI on normal volunteers and that would increase enormously the costs of the study; (3) using a handbook with all the administration norms for each test, we tried to reduce the differences concerning the training of the examiners that could lead to differences on the results.

Neuropsychological Data Analysis

Differences among centers were observed for almost all the tests except Naming and Ideational praxis. However, the differences were randomly distributed and no consistent pattern was found. Cultural and educational variables might explain some of the differences between centers. Despite that, when Florence and Lisbon (which had the lowest mean education level) were excluded from the analysis, differences among centers remained.

We found that, when compared with younger subjects, older subjects performed significantly worse on Trail making, Symbol digit, Digit cancellation tests and on executive functions and memory compound measures. Age remained an independent variable influencing the performance in memory and executive function domains even when controlling for ARWMC severity. The effect of age on neuropsychological performance of healthy subjects with ARWMC was also reported by Ylikoski et al. [6], who found that cognitive performance decreased on memory tests, constructional abilities, language, timed tests and speed of mental processing. Our results are similar to those found in that work.

Education was the most consistent factor influencing the performance in all the neuropsychological tests and domains. The association between education and cognitive performance remained significant in the presence of ARWMC. Memory performance seems to be independent of the effect of education. This could be explained by the fact that in the baseline assessment of our study, memory was mainly evaluated verbally (Word recall, Delayed recall, Word recognition, Digit span), reducing the influence of education on pencil/paper tests. Education seems to play a more important role on complex tasks such as executive functions. One study evaluating mainly speed and executive functions [30] reported the influence of education on the cognitive performance of a sample of elderly subjects with ARWMC. Dufouil et al. [30] found no relationship between WMC severity and cognitive performance in participants with a high level of education, reinforcing the hypothesis of the cognitive reserve [31]. Independent of the way it influences cognition, education should be considered as a covariate variable in analyzing the effect of ARWMC on neuropsychological performance.

In the LADIS sample, women performed worse on MMSE, Constructional praxis and Mazes. Female gender has been associated with difficulties performing visuoconstructional tasks and spatial orientation, which could explain the difficulties in performing both Constructional praxis and Maze task. Although some studies [9, 32] reported a prevalence of earlier and more severe ARWMC in women, in our sample the prevalence and severity of ARWMC was similar for both sexes. In our study, women tended to have less years of education, which might explain the difference on the MMSE. Ott et al. [33] in a large populational study, reported a stronger association between low education and dementia in women than in men. However, in a recent study, Ruitenberg et al. [34] found that this association was mainly significant among people over 90 years old and that the incidence of dementia was similar for both sexes before this high age.

In our study, the analysis of the baseline neuropsychological data showed a significant influence of demographic variables on cognitive performance. Neuropsychological performance in patients with ARWMC was influenced by age and education. Higher educational level was consistently associated with better performances on cognitive tasks, while older age was associated with

difficulties in memory and executive functions. The analysis performed on neuropsychological data in the LADIS study will, thus, have to use age and education as modifiers, and therefore as covariables.

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Appendix 1

List of Participating Centers and Personnel

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Appendix 5

Original Research Article

Dementia and Geriatric Cognitive Disorders

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Neuropsychological Predictors of Dementia in a Three-Year Follow-Up Period: Data from the LADIS Study

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Key Words

Neuropsychological predictors, dementia · LADIS · White matter changes

Abstract

Background: White matter changes (WMC) are related to cognitive deficits and dementia. Our aim was to determine the extent to which the performance in neuropsychological tests would be able to predict the clinical diagnosis of dementia. ***Methods:*** The LADIS (Leukoaraiosis and Disability) is a prospective study that evaluates the impact of WMC on the transition of independent elderly to disability. The subjects were evaluated at baseline and yearly during 3 years with a comprehensive clinical, functional and neuropsychological protocol. At each visit, dementia was classified according to clinical criteria. The performance in the neuropsychological batteries was compared according to the clinical diagnosis of dementia. ***Results:*** From the initially enrolled 639 subjects, 480 were evaluated at year 3. Dementia was diagnosed in 90 participants. The demented subjects had worse performance in almost all the baseline cognitive tests. Using receiver operating characteristic curves, we found that the Vascular Dementia Assessment Scale (VADAS) battery had higher sensitivity and specificity rates (area under the curve = 82%) to identify dementia compared with the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale. Worse performance on baseline MMSE ($\beta = 0.33$; $p < 0.001$) and VADAS ($\beta = -0.07$; $p = 0.02$) were predictors of dementia (regression analyses). ***Conclusion:*** Performance on the MMSE and the VADAS battery were important predictors of dementia at a 3-year period.

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Introduction

Age-related white matter changes (ARWMC) have been associated with cognitive impairment and dementia and represent a form of cerebrovascular disease. However, the relation between severity of ARWMC and progression to dementia or other forms of vascular cognitive impairment (VCI), which include vascular dementia and other cognitive impairment without dementia, is still not completely understood.

The Leukoaraiosis and Disability (LADIS) study is a large multinational 3-year longitudinal study [1] that aims to identify the importance of the presence of ARWMC on the transition to disability in a nondisabled elderly population. For this pan-European study, a specific neuropsychological battery was constructed in order to include instruments sensitive to changes related to the presence of ARWMC, mainly executive and speed of mental processing functions [2, 3].

The importance of the use of sensitive measures for the cognitive evaluation of this specific population was described by Ylikoski et al. [3]. Their results showed that the inclusion of tests reflecting mental speed and executive functions, the Vascular Dementia Assessment Scale – cognitive extension (VADAS-Cog) of the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) [4], was an important tool differentiating patients with mild to moderate and severe ARWMC. Although several instruments have been used in the assessment of cognitive dysfunction (including VADAS-Cog in clinical trials), it is important to validate sensitive tools for specific populations as it is the case of vascular patients, since different patterns of neuropsychological functioning are expected.

In addition, in a previously reported cross-sectional analysis of the neuropsychological baseline LADIS data, we identified the importance of other demographic (older age, lower educational level) and clinical (presence of diabetes, hypertension, previous stroke) factors on cognitive performance [2, 5] along with the presence of ARWMC.

Several studies performed with patients and healthy elderly have also associated specific cognitive deficits with ARWMC, such as speed of mental processing and executive functions [6–8]. However, there is less information regarding the way these deficits progress over time.

Recent studies [9, 10] tried to identify neuropsychological predictors of VCI, differentiating them from those frequently associated with Alzheimer's disease (AD). Ingles et al. [9] reported that low baseline scores on tests of free recall, similarities, comprehension, block design and verbal fluency were associated with incident VCI 5 years after the inclusion. Also a trend toward an association between low baseline scores on the similarities subtest and incident VCI was found, in comparison with incident AD.

The aim of this paper is to determine the extent to which in the LADIS population, the baseline performance in specific neuropsychological tests was able to predict the clinical diagnosis of dementia 3 years later.

Methods

Participants and Methods

The rationale and methodology of the LADIS study have been extensively reported elsewhere [1, 2]. Briefly, the LADIS is a longitudinal multinational study involving 11 centers from 10 European countries (see Appendix) which aims to evaluate the impact of white matter changes (WMC) on the transition to disability. Inclusion criteria were: (a) age 65–84 years, (b) WMC of any degree according to the modified Fazekas visual rating scale [11], (c) no or mild impairment (none or 1 item affected) on the instrumental activities of daily living scale [12], and (d) presence of a contactable informant and agreement to sign an informed consent. We excluded participants with: (a) severe illness likely leading to dropout, (b) severe unrelated neurological disease, (c) leukoencephalopathy of nonvascular origin, (d) severe psychiatric disorders, and (e) inability or refusal to undergo brain MRI. Patients were enrolled due to minor neurological, cognitive or motor complaints or incidental finding on cranial imaging due to nonspecific reasons (incidental finding in brain imaging) [1].

The participants were submitted to a comprehensive clinical, functional, motor and neuropsychological examination that was repeated yearly during a 3-year follow-up period. Clinical and functional assessment included: (1) standard cardiovascular and neurological examination; (2) functional status measured by means of the instrumental activities of daily living scale and the Disability Assessment for Dementia scale [13], and (3) health-related quality of life measured using the Euro-QoL 5D [14].

MRI was performed at baseline and at the 3-year follow-up visit using a standard protocol [1]. White matter rating and volumetric analysis was carried out by a single center (Amsterdam) [15].

A total of 639 participants were included at baseline and 638 performed the complete baseline assessment. In the 3rd year of the study, 475 (75%) came to the last follow-up visit.

Neuropsychological Evaluation

The participants were submitted to a standardized cognitive evaluation every year. The construction of the neuropsychological battery was described in detail in a previous paper [2]. The battery included: the Mini-Mental State Examination (MMSE) [16, 17] as a measure of global cognitive status; the ADAS-Cog to assess memory, orientation, language, ideational and constructional praxis [18, 19] used in the original version (except on the words list recall item, where we used 1 trial instead of 3); the

Table 1. Comparisons between participants with dementia and those with no dementia concerning demographic and clinical data

Demographic and clinical characteristics	Dementia		No dementia		t test	p value
	n	mean ± SD	n	mean ± SD		
Age, years	90	75.9 ± 4.7	498	73.7 ± 5.0	–3.71	<0.001
Education, years	90	8.8 ± 3.5	497	9.8 ± 3.9	2.57	<0.002
WMC						
Severe grade (χ^2)	90	47%	498	20%		<0.001
Volume	88	34.1 ± 2.9	480	18.7 ± 2.0	–4.73	<0.001

VADAS-Cog, which includes delayed recall of the ADAS's 10 word lists, a symbol digit test, a digit span backwards, a maze task, a digit cancellation task and a verbal fluency task (animal naming), and the Trail-Making [20] and Stroop tests [21] used to assess executive functions. The VADAS-Cog total score was calculated according to Ylikoski et al. [3]. The scores applied as measures of executive functions were 'time used to perform Stroop part 3 minus the time to perform Stroop part 2' and 'time needed to perform Trail-Making part B minus the time to perform Trail-Making part A'. As described in detail in a previous paper [2], compound measures were calculated in order to analyze performances by domain. Three main domains were considered: (1) memory, using the z-scores of immediate word recall, delayed recall, word recognition and digit span; (2) executive functions, using z-scores of Stroop 3 – 2, Trail-Making B-Trail-making A, symbol digit and verbal fluency; (3) speed and motor control, using z-scores of Trail-Making A, maze and digit cancellation.

Criteria of Dementia and Cognitive Impairment No Dementia

At each follow-up visit, a questionnaire for the clinical diagnosis of dementia and dementia subtypes included in the LADIS protocol was completed by the clinician.

The criteria used to define dementia, dementia subtypes and cognitive impairment no dementia (CIND) are described in detail in a previous paper [1]. For the current study, we used the clinical diagnosis of dementia defined according to the DSM-IV criteria [22] and CIND according to Wentzel et al. [23].

When analyzing the participants according to the clinical diagnosis, we used the last observation carried forward method to classify the participants who did not come to the 3-year follow-up visit. The diagnosis observed on the last visit of the participant was then considered as the final diagnosis and analyzed accordingly. The last observation carried forward method was used to reduce the number of missing values.

Statistical Analysis

Reasons of referral, as well as demographic (age, gender, years of education), clinical (WMC severity) and cognitive (scores on neuropsychological tests) baseline characteristics were compared between the participants who came to the 3-year follow-up visit with those who did not, using bivariate analysis (t test and χ^2). The same procedure was used to compare participants with and without the diagnosis of dementia at the last follow-up.

When comparing the baseline characteristics of the participants with dementia, CIND and no cognitive impairment, we used ANOVA with multiple-comparison analyses.

In order to ascertain the sensitivity and specificity of each neuropsychological test to predict diagnosis of dementia and CIND in the 3-year period, we used receiver operating characteristic (ROC) analyses.

Multinomial logistic regression models adjusted for the confound variables were then used to identify the neuropsychological baseline predictors of dementia at the last follow-up visit.

In order to reduce the chance of type I error, Bonferroni post hoc analyses were used for ANOVA comparisons. A more conservative p level of 0.01 was applied for single tests.

Results

Descriptive and Comparative Analysis

Baseline demographic and clinical characteristics of the LADIS population have been described elsewhere [2].

From the 639 participants enrolled in the LADIS study, 480 (75%) could be evaluated in the last follow-up visit 3 years later. The patients who came to the last evaluation were younger (t = 3.68; $p < 0.001$), had a higher level of education (t = –2.94; $p = 0.004$) and presented better performance in the baseline MMSE (t = –4.30; $p < 0.001$), ADAS-Cog (t = 4.24; $p < 0.001$) and VADAS-Cog (t = 5.80; $p < 0.001$), Stroop test (t = 4.53; $p < 0.001$) and Trail-Making (t = 6.17; $p < 0.001$) tests, when compared to those who were not able to come to the last follow-up. No differences were found considering WMC severity ($\chi^2 = 5.39$; $p = 0.07$) and reasons of referral ($\chi^2 = 7.44$; $p = 0.28$).

480 participants had the clinical diagnosis at the third-year visit of follow-up. Using the last observation carried forward method we had a total of 588 participants with clinical diagnosis. A total of 90 (14%) out of these 588 participants had a clinical diagnosis of dementia: 12 partici-

Table 2. Comparisons between participants with dementia and those with no dementia concerning neuropsychological baseline performance and compound measures

	Dementia		No dementia		t test	p value
	n	mean ± SD	n	mean ± SD		
Performance						
MMSE	90	25 ± 3	497	28 ± 2	–8.57	<0.001
ADAS-Cog total[1]	88	23 ± 8	496	15 ± 6	8.50	<0.001
Word recall	89	6 ± 1.8	497	5 ± 1.6	6.01	<0.001
Command	89	0.5 ± 0.7	498	0.3 ± 0.6	2.23	<0.03
Construction	89	0.8 ± 0.7	498	0.5 ± 0.7	3.49	<0.001
Naming	89	0.3 ± 0.6	498	0.1 ± 0.4	2.67	<0.001
Ideational praxis	89	0.4 ± 0.8	498	0.1 ± 0.5	2.98	<0.001
Orientation	89	1.1 ± 1.6	498	0.2 ± 0.8	5.43	<0.001
Word recognition	88	4.3 ± 2.8	498	2.5 ± 2.2	5.48	<0.001
Remembering instructions	89	0.5 ± 6.9	498	0.2 ± 0.6	3.24	<0.001
Spoken difficulties	89	0.3 ± 0.8	498	0.1 ± 0.4	2.28	<0.001
Word finding	89	0.5 ± 0.9	497	0.2 ± 0.5	3.28	<0.001
Comprehension	89	0.6 ± 0.9	498	0.2 ± 0.6	4.16	<0.001
Concentration	89	0.7 ± 1.1	498	0.3 ± 0.7	3.20	<0.001
VADAS-Cog total[1]	78	57 ± 11.6	483	41 ± 12.5	10.38	<0.001
Delayed recall	89	7.3 ± 2.1	497	5.5 ± 2.3	6.68	<0.001
Digit span	89	4.6 ± 1.6	497	7.3 ± 2.1	–5.15	<0.001
Verbal fluency	87	14.4 ± 5.6	495	20 ± 6.1	–8.25	<0.001
Symbol digit	84	18.2 ± 9.2	495	28.7 ± 10.5	–8.68	<0.001
Digit cancellation	84	15.2 ± 7	495	20.5 ± 6.5	–6.91	<0.001
Maze	84	11.9 ± 10.9	495	6.6 ± 4.6	4.36	<0.001
Stroop (3 – 2)[1]	84	51 ± 40	487	31 ± 23	4.47	<0.001
Trail-Making (B – A)[1]	85	144 ± 64	485	99 ± 59	5.93	<0.001
Compound measures						
Memory	88	–0.6 ± 0.6	496	0.1 ± 0.6	–9.52	<0.001
Executive functions	68	–0.6 ± 0.6	472	0.2 ± 0.7	–8.16	<0.001
Speed and motor control	80	–0.7 ± 1	490	0.2 ± 0.7	–7.10	<0.001

t test: non-parametric analysis was also conducted due to the skewness of the distribution of some tests. The results were similar. [1] Higher scores represent worse performance.

pants with diagnosis at the 1-year follow-up visit, 7 with diagnosis at the 2nd-year visit and 71 with the diagnosis at the 3rd-year visit.

When comparing demographic and clinical characteristics of the participants diagnosed as having dementia and those without dementia on the last follow-up (table 1), we found that the patients with dementia were older (t = 3.71; $p < 0.001$), had a lower educational level (t = –2.38; $p < 0.02$), severer WMC (χ^2 = 39.07; $p < 0.001$) and a higher volume of WMC (t = 4.73; $p < 0.001$). Concerning baseline cognitive performance (table 2), the participants with dementia had had lower scores in all the neuropsychological tests, except for the ADAS-Cog following the command subtest (t = 2.56; $p < 0.02$). The participants with dementia had also had significantly lower scores in executive functioning (t = –8.21; $p < 0.001$), memory (t = –9.68; $p < 0.001$), speed and motor control (t = –9.55; $p < 0.001$) than the participants without dementia at the end of follow-up (table 2).

Demographic and Neuropsychological Predictors of Dementia

We performed ROC analyses to ascertain the sensitivity and specificity of each neuropsychological test and battery to identify participants with dementia following a 3-year period. On the single test analyses, we identified (table 3) symbol digit and verbal fluency as having the higher scores of sensitivity and specificity (AUC 78 and

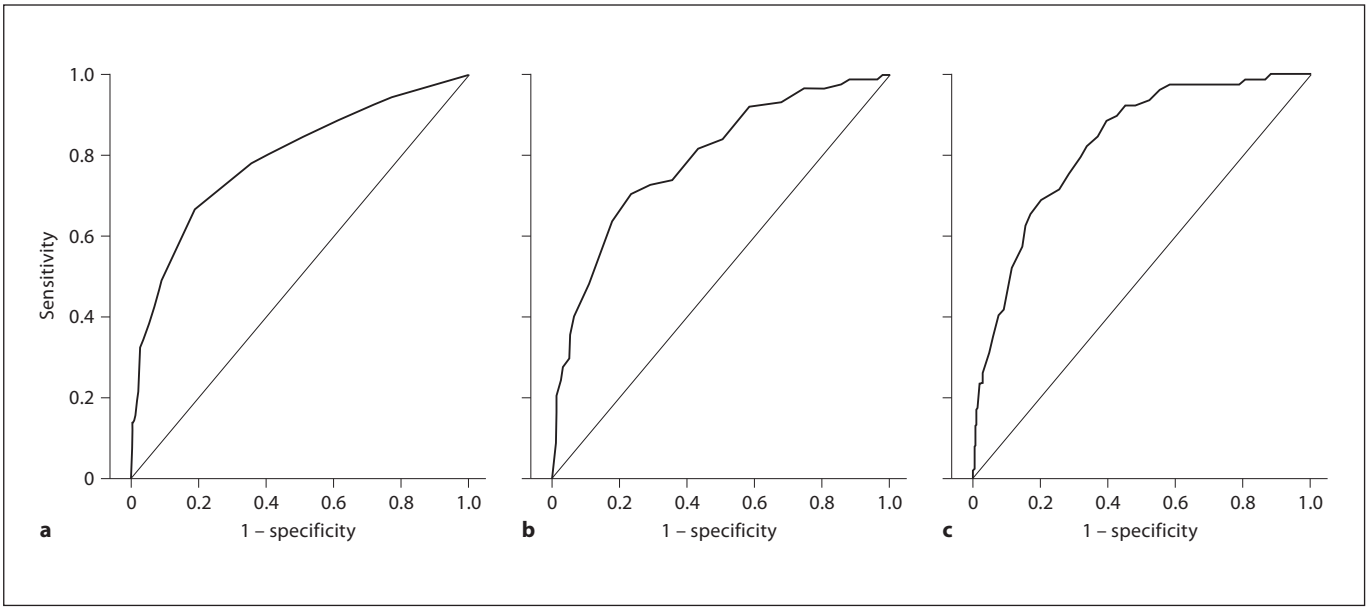

Fig. 1. ROC curves of the 3 batteries. **a** MMSE total (AUC = 79%). **b** ADAS-Cog total (AUC = 79%). **c** VADAS-Cog (AUC = 82%).

75%, respectively), although fair. Concerning the neuropsychological batteries, MMSE and ADAS-Cog obtained the same rate (79%) but VADAS-Cog had a good rate (82%) of sensitivity and specificity on identifying dementia at 3 years (fig. 1). VADAS extension alone obtained 79% of sensitivity and specificity for dementia at 3 years.

Using logistic regression analyses to identify neuropsychological predictors of dementia while controlling for age, education and WMC severity (as they are known predictors; see table 4), we found that worse performance on MMSE ($\beta = 0.33$; OR = 1.39, 95% CI = 1.19–1.62; $p < 0.001$) and VADAS-Cog ($\beta = -0.07$; OR = 0.93, 95% CI = 0.88–1.0; $p = 0.02$) were independent predictors of dementia. In order to know which component of the VADAS (ADAS or the VADAS extension) was the stronger predictor of dementia, we repeated the logistic regression model separating the ADAS score from the VADAS-extension total score (data not shown). In this model, VADAS extension was an independent predictor of dementia ($\beta = -0.08$; OR = 1.09, 95% CI = 1.02–1.15; $p < 0.01$).

Concerning the neuropsychological baseline compound scores, both memory ($\beta = 1.2$; OR = 3.33, 95% CI = 1.9–5.9; $p < 0.001$) and executive functions ($\beta = 0.69$; OR = 2.0, 95% = CI 1.15–3.46; $p < 0.01$) were independent predictors of dementia at the third year (table 5).

Table 3. ROC analyses, sensitivity and specificity of neuropsychological batteries and single tests

Batteries and tests	AUC %	Sensitivity, %	Specificity, %
Batteries			
MMSE	79	29	87
ADAS-Cog	79	20	84
VADAS	82	25	88
VADAS extension	79	8	82
Single tests			
Trail making (part B – A)	70	–	86
Stroop (part 3 – 2)	69	62	86
Word immediate recall	68	71	85
Delayed recall	71	20	85
Word recognition	69	54	85
Constructional praxis	62	–	85
Ideational praxis	59	40	85
Naming	56	–	84
Orientation	70	65	84
Symbol digit	78	68	87
Digit span	64	50	85
Digit cancellation	73	55	86
Maze	71	58	86
Verbal fluency	75	45	86

– = No positive cases were identified.

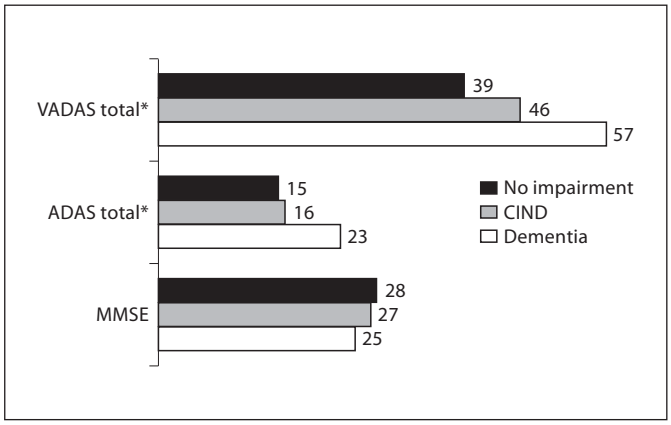

Fig. 2. Comparisons between participants with no impairment, CIND and dementia concerning baseline neuropsychological batteries (mean scores). All differences were significant (t test with $p < 0.001$). * Higher scores represent worse performance.

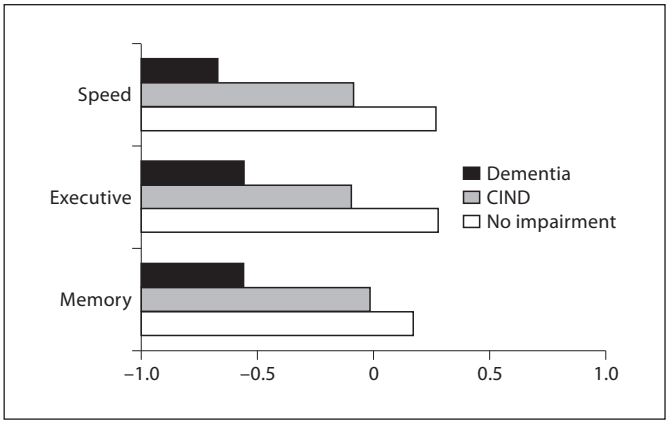

Fig. 3. Comparisons between participants with no impairment, CIND and dementia concerning baseline neuropsychological compound scores (mean z-scores). All differences were significant (t test with $p < 0.001$).

Table 4. Baseline neuropsychological predictors of dementia in a 3-year period (logistic regression analysis)

	β	p value	OR
Age	–0.069	0.03	0.93 (0.88–0.99)
Education	–0.116	0.01	0.89 (0.81–0.98)
WMH grade	–0.264	n.s.	0.77 (0.53–1.11)
MMSE total	0.328	<0.001	1.39 (1.19–1.62)
ADAS total	0.020	n.s.	1.02 (0.93–1.11)
VADAS total	–0.070	0.02	0.93 (0.88–0.99)
Trail B – A	–0.002	n.s.	1.00 (0.99–1.00)
Stroop 3 – 2	–0.002	n.s.	1.00 (0.99–1.01)

$R^2 = 0.34$. Figures in parentheses are 95% CI.

Table 5. Baseline compound measure predictors of dementia in a 3-year period (logistic regression analysis)

	β	p value	OR (95% CI)
Age	–0.07	0.02	0.93 (0.87–0.99)
Education	–0.09	0.03	0.91 (0.84–0.99)
WMH severity	0.87	0.03	2.36 (1.10–5.07)
Executive functions	0.69	0.01	2.00 (1.15–3.46)
Memory	1.20	0.001	3.33 (1.88–5.90)
Speed and motor control	0.47	0.04	1.61 (1.01–2.55)

Figures in parentheses are 95% CI.

Demographic and Neuropsychological Predictors of Cognitive Impairment (Dementia and Cognitive Impairment No Dementia)

We compared participants who were diagnosed as having dementia (DEM; n = 90) with those diagnosed as having CIND (n = 147) and those with no cognitive impairment (NCI) (n = 351) as clinically classified. Using ANOVAs with Bonferroni's multiple-comparison analyses (data not shown), we found that age was significantly different when comparing NCI participants with those with DEM (mean age NCI = 73.4 ± 5 years, DEM = 75.8 ± 5; $p < 0.001$) but not when comparing NCI with CIND patients (mean age NCI = 73.4 ± 5 years, CIND = 74.2 ± 5; $p = 0.41$) nor CIND with participants with DEM ($p = 0.05$). Differences in educational level were significant when comparing NCI with CIND (mean educational level NCI = 10.3 ± 4 years, CIND = 8.8 ± 4; $p < 0.001$) and DEM (mean = 8.8 ± 4, $p = 0.003$) but not when comparing CIND with DEM ($p > 0.05$). The volume of WMC was significantly different in the 3 groups (mean WMC volume NCI = 16.5, CIND = 23.9; DEM = 33.8; $p < 0.001$).

Concerning baseline scores of the neuropsychological tests, there were significant differences between the 3 groups in the global measures (fig. 2), compound scores (fig. 3) and in all the single tests, except for ADAS-Cog's subtest following command. Multiple-comparison analyses (data not shown) allowed us to conclude that for the ADAS-Cog subtests word recall, delayed recall, word recognition, orientation, construction, naming, idea-

Table 6. Baseline n tests predictors of no impairment, CIND and dementia (multinomial logistic regression)

	β	p value	OR
No impairment			
Age	−0.076	0.02	0.93 (0.87–0.99)
Education	−0.101	0.04	0.90 (0.82–0.99)
WMH grade	−0.36	0.06	0.70 (0.48–1.02)
MMSE total	0.311	<0.001	1.37 (1.16–1.60)
ADAS total	0.037	0.40	1.04 (0.95–1.13)
VADAS total	−0.090	0.01	0.91 (0.86–0.97)
Trail B – A	−0.001	0.66	1.00 (0.99–1.00)
Stroop 3 – 2	−0.003	0.68	1.00 (0.98–1.01)
CIND			
Age	−0.054	0.12	0.95 (0.88–1.01)
Education	−0.144	0.01	0.87 (0.78–0.96)
WMH grade	−0.121	0.55	0.89 (0.59–1.32)
MMSE total	0.36	<0.001	1.43 (1.20–1.70)
ADAS total	0.023	0.62	0.97 (0.89–1.07)
VADAS total	−0.023	0.48	0.97 (0.90–1.07)
Trail B – A	−0.004	0.25	0.99 (0.99–1.00)
Stroop 3 – 2	−0.002	0.73	1.00 (0.98–1.01)

The reference category is dementia. Accuracy rate: 63% (>57%).

tional praxis, remembering instructions, spoken, word finding, comprehension and concentration, the differences were significant only when the participants with DEM were compared with those with NCI. In these tests, in the MMSE and in the Stroop 'time to perform part 3 minus time to perform part 2', the participants with NCI did not differ significantly from the group with CIND. When comparing the group of CIND with DEM, we found significant differences in all the tests except in the ADAS-Cog subtests construction, naming and ideational praxis.

When using ROC analyses to assess sensitivity and specificity of the neuropsychological tests and batteries in identifying participants with CIND at the third year (excluding participants with DEM), we found that none of the tests, batteries or compound measures had good rates (data available when requested).

In the multinomial logistic analysis model ($R^2 = 0.28$), we included baseline global measures of MMSE, ADAS-Cog, VADAS-Cog, the Stroop and Trail-Making test, and used age, education and WMC (categorized) as covariates (table 6). MMSE [β = −0.311; OR = 1.36 (1.16–1.60); p = 0.001] and VADAS-Cog [β = −0.093; OR = 0.911 (0.858–0.968); p = 0.003] were independent predictors of dementia at a 3-year period of follow-up.

Discussion

The participants included in the LADIS study were followed during a 3-year period and assessed with a complete clinical and neuropsychological evaluation each year. At each visit, a clinical diagnosis of the mental status was made, which was defined as 'dementia', 'cognitive impairment no dementia' and 'no cognitive impairment'. When we analyzed the baseline results of these 3 groups, and despite the fact that the participants were all functionally independent at the time of inclusion, we found that those clinically diagnosed as having dementia at the end of the 3-year follow-up period had had lower scores in almost all the baseline neuropsychological tests, when compared with the participants without dementia. This is consistent with the understanding of dementia as a progressive disease that starts insidiously, usually without evident signs besides subtle differences in cognitive tests scores. In the LADIS study, the differences were observed in all the baseline tests and not only in those previously reported as sensitive enough to predict cognitive decline in normal individuals, such as episodic memory, executive functions or abstract reasoning and verbal fluency [9, 24]. Differences were also observed in the total scores of the MMSE, ADAS-Cog and VADAS-Cog batteries between the participants who developed dementia during a 3-year period and those who did not, showing that general cognitive capacities are also affected by ARWMC.

The participants with dementia were also older, had lower educational levels and severer ARWMC than the participants without the diagnosis of dementia. These results are in line with previous reported data on the LADIS study. Increasing age and low educational levels have been identified as risk factors for lower cognitive performance even in the presence of ARWMC [2].

Besides older age and lower educational levels, baseline scores in the MMSE were important predictors of the diagnosis of dementia at the end of follow-up. This had also been reported in previous studies that had tried to identify preclinical markers of vascular dementia and AD [9, 10]. Backman and Small [10] reviewed the data from a community-based, longitudinal study and reported the presence of preclinical deficits 3 years before the diagnosis of vascular dementia in the total score, delayed recall and orientation of the MMSE, used as an outcome measure. The MMSE is a common instrument assessing global functions and detecting cognitive impairment. However, its sensitivity and specificity decrease when used to assess mild cognitive impairment, at least when applying the original cutoff values. Nevertheless, in the LADIS

study, the median baseline score for MMSE of participants who developed dementia during the 3-year period (median = 26) was higher than the original MMSE proposed cutoff for dementia (<25). This is also consistent with the reports of the importance of using different cutoff scores for the MMSE according to age and level of education. In a recent paper [25], it is proposed that a higher cutoff score should be used for detecting dementia among patients with higher educational levels. This change might also increase the rates of sensitivity and specificity of the MMSE for mild cognitive impairment.

Concerning sensitivity and specificity rates, we found the MMSE to have lower scores compared with the VADAS-Cog battery. VADAS-Cog had previously been reported to be a more sensitive instrument to evaluate patients with WMC when compared with ADAS-Cog [3]. The authors identified that 5 (out of the 6) tests that compound the VADAS-Cog extension (namely, delayed recall, symbol-digit, maze, digit cancellation and verbal fluency) were able to differentiate among mild, moderate and severe WMC. Most of these 5 tests are used to assess speed of mental processing and executive functions, cognitive capacities shown to be impaired in patients with vascular disease or WMC [6]. However, in the LADIS population, none of the specific tests used to assess executive functions (Stroop and Trail-Making tests) were baseline predictors of dementia at the end of follow-up. Some studies have found no relationship between ARWMC and specific tests for the assessment of executive functions [26, 27]. Nevertheless, in our study, the compound score of executive functions that, besides the Stroop and Trail-Making tests, includes scores on symbol-digit and verbal fluency tests, was an independent predictor of dementia at the end of follow-up.

Memory baseline compound scores were also independent predictors of dementia. An association between WMC and memory impairment had been previously reported. Jokinen et al. [6] found that memory impairment was mediated by executive functions and mental speed. They suggest that executive dysfunction causes secondary deficits such as memory impairment. In the LADIS population, dementia at the end of follow-up might be related with other causes rather than a direct effect of ARWMC. The heterogeneity of the type of dementia (vascular dementia, AD with vascular component, others) might explain this multidomain pattern of cognitive impairment.

In this paper we also compared participants with no impairment (NI) with those with CIND and dementia at the end of follow-up. We found that performance on the baseline neuropsychological tests was distinctively different for the 3 groups clinically diagnosed at the end of the follow-up period, showing a consistent relation between clinical criteria and neuropsychological assessment.

We found that the patients with CIND were older than the patients with NI and younger than those with dementia. This group of patients also had a lower educational level when compared with the participants with NI but did not differ from those with dementia. Concerning cognitive performance at baseline, the patients with CIND differed from the patients with dementia in almost all the tests and global measures. When compared with those with NI, the patients with CIND had no significant differences on the baseline performance of MMSE, Stroop and ADAS-Cog. These findings show the heterogeneity of this particular group, which seems to be in the continuous line between 'no impairment' and 'dementia'. In the CIND group, we found participants with similar performances to those with no impairment but also to those with dementia, along with more risk factors for dementia such as older age. These results illustrate the difficulty of identifying predictors in the CIND group, since it is very heterogeneous.

A possible limitation of this study is related to the use of dichotomized or categorized variables such as dementia/no dementia or NCI/CIND, including patients with different types of dementia in the same group. However, splitting these groups would reduce the statistical power and compromise the results. Also the absence of sensitive measures of memory, such as verbal learning and cued recall, limits our interpretation of the baseline results. However, the introduction of these tests during the follow-up of the LADIS study will permit us to analyze the evolution of memory performance over time in further studies.

The present study contributes to the identification of sensitive measures to assess participants with ARWMC and to evaluate the risk of progression for dementia in a population with no functional or major cognitive impairment in initial evaluations. It also enhances the importance of the neuropsychological assessment to the study of subtle changes on progression to dementia.

Appendix

List of Participating Centers and Personnel

Helsinki, Finland (Memory Research Unit, Department of Clinical Neurosciences, Helsinki University): Timo Erkinjuntti, MD, PhD, Tarja Pohjasvaara, MD, PhD, Pia Pihanen, MD, Raija Ylikoski, PhD, Hanna Jokinen, PhD, Meija-Marjut Somerkoski, MPsych, Riitta Mäntylä, MD, PhD, Oili Salonen, MD, PhD. *Graz, Austria* (Department of Neurology and Department of Radiology, Division of Neuroradiology, Medical University Graz): Franz Fazekas, MD, Reinhold Schmidt, MD, Stefan Ropele, PhD, Brigitte Rous, MD, Katja Petrovic, MagPsychol, Ulrike Garmehi, Alexandra Seewann, MD. *Lisboa, Portugal* (Serviço de Neurologia, Centro de Estudos Egas Moniz, Hospital de Santa Maria): José M. Ferro, MD, PhD, Ana Verdelho, MD, Sofia Madureira, PsyD, Carla Moleiro, PhD. *Amsterdam, The Netherlands* (Department of Radiology and Neurology, VU Medical Center): Philip Scheltens, MD, PhD, Ilse van Straaten, MD, Frederik Barkhof, MD, PhD, Alida Gouw, MD, Wiesje van der Flier, PhD. *Goteborg, Sweden* (Institute of Clinical Neuroscience, Goteborg University): Anders Wallin, MD, PhD, Michael Jonsson, MD, Karin Lind, MD, Arto Nordlund, PsyD, Sindre Rolstad, PsyD, Ingela Isblad, RN. *Huddinge, Sweden* (Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Karolinska University Hospital Huddinge): Lars-Olof Wahlund, MD, PhD, Milita Crisby, MD, PhD, Anna Pettersson, RPT, PhD, Kaarina Amberla, PsyD. *Paris, France* (Department of Neurology, Hôpital Lariboisière): Hugues Chabriat, MD, PhD, Karen Hernandez, psychologist, Annie Kurtz, psychologist, Dominique Hervé, MD, Sarah Benisty, MD, Jean Pierre Guichard, MD. *Mannheim, Germany* (Department of Neurology, University of Heidelberg, Klinikum Mannheim): Michael Hennerici, MD, Christian Blahak, MD, Hansjorg Baezner, MD, Martin Wiarda, PsyD, Susanne Seip, RN. *Copenhagen, Denmark* (Memory Disorders Research Group, Department of Neurology, Rigshospitalet, and the Danish Research Center for Magnetic Resonance, Hvidovre Hospital, Copenhagen University Hospitals): Gunhild Waldemar, MD, DMSc, Egill Rostrup, MD, MSc. Charlotte Ryberg, MSc, Tim Dyrby MSc, Olaf B. Paulson, MD, DMSc, Ellen Garde, MD, PhD. *Newcastle upon Tyne, UK* (Institute for Ageing and Health, Newcastle University): John O'Brien, DM, Sanjeet Pakrasi, MRCPsych, Mani Krishnan MRCPsych, Andrew Teodorczuk, MRCPsych, Michael Firbank, PhD, Philip English, DCR, Thais Minett, MD, PhD.

The Coordinating center is in *Florence, Italy* (Department of Neurological and Psychiatric Sciences, University of Florence): Domenico Inzitari, MD (study coordinator), Luciano Bartolini, PhD, Anna Maria Basile, MD, PhD, Eliana Magnani, MD, Monica Martini, MD, Mario Mascalchi, MD, PhD, Marco Moretti, MD, Leonardo Pantoni, MD, PhD, Anna Poggesi, MD, Giovanni Pracucci, MD, Emilia Salvadori, PhD, Michela Simoni, MD.

The *LADIS Steering Committee* is formed by Domenico Inzitari, MD (study coordinator), Timo Erkinjuntti, MD, PhD, Philip Scheltens, MD, PhD, Marieke Visser, MD, PhD, and Peter Langhorne, MD, BSC, PhD, FRCP, who replaced Kjell Asplund, MD, PhD, in this role at the beginning of 2005.

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Appendix 6

Dementia and Geriatric Cognitive Disorders

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Original Research Article

White Matter Changes and Cognitive Decline in a Ten-Year Follow-Up Period: A Pilot Study on a Single-Center Cohort from the Leukoaraiosis and Disability Study

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Key Words
Cognition · Neuropsychological predictors · White matter lesions · Dementia

Abstract
Aims: To describe the contribution of white matter lesions to the long-term neuropsychological profiles of different groups of clinical diagnoses, and to identify neuropsychological predictors of cognitive impairment in a 10-year follow-up. ***Methods:*** The Lisbon subcohort of the Leukoaraiosis and Disability (LADIS) study was re-evaluated performing a clinical, functional and cognitive evaluation [including Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog) and ADAS-Cog with the extension for vascular impairment (VADAS-Cog), the 9-word version of the California Verbal Learning Test (CVLT-9), the Trail-Making test and the Stroop test] as well as an MRI scan. Using clinical diagnostic criteria, participants were identified as having no cognitive impairment (NI), cognitive impairment but no dementia (CIND) or dementia (DEM), and the effect of time on clinical diagnosis and neuropsychological profiles was analyzed. ***Results:*** From the initial group of 66 participants, 37 out of 41 survivors (90%) were re-evaluated (mean age 81.40 years, 57% women). Fifteen patients (41%) had DEM, 12 (32%) CIND and 10 (27%) NI. Over time, the three groups presented distinct profiles in the MMSE [$F_{2, 62} = 15.85$, $p = 0.000$], ADAS [$F_{2, 62} = 15.85$, $p = 0.000$] and VADAS [$F_{2, 48} = 5.87$, $p = 0.008$]. Logistic regression analysis identified higher scores on MMSE ($\beta = 1.14$, $p = 0.03$, OR = 3.13, 95% CI 1.09–8.97) as predictors of NI after 10 years of follow-up. ***Conclusion:*** Higher scores on baseline MMSE were the only neuropsychological predictors of NI after 10 years.

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Introduction

Longitudinal studies in the general population of cognitively intact participants have demonstrated that increasing volume and increased progression of white matter lesions (WMLs) are related to lower global cognitive performance and conversion to mild cognitive impairment and dementia [1, 2]. In the 3-year follow-up of the Leukoaraiosis and Disability (LADIS) study, WMLs and lacunae were found to progress over time, appearing mostly in the subcortical white matter. Progression was related to more severe WMLs and a higher number of lacunae at baseline as well as to several vascular risk factors [3]. The impact of diabetes and severity of WMLs on the decline of cognitive performance was also reported by Verdelho et al. in the LADIS study [4]. In the same sample, neuropsychological predictors of dementia (DEM) and cognitive impairment but no dementia (CIND) were both identified, above and beyond clinical and demographic factors [5]. Patients who developed CIND or DEM 3 years after the inclusion already presented lower scores on cognitive baseline performance in global measures such as the Mini-Mental State Examination (MMSE) and the Vascular Dementia Assessment Scale (VADAS) compared with those who had no cognitive impairment (NI) or CIND at the 3-year follow-up, despite the fact that they were all functionally independent at baseline. Very long-term follow-up studies on the impact of WMLs on the transition to dementia are still rare [6–8], and none of them followed a group of initially nondependent participants with WMLs. Furthermore, prediction of no impairment is particularly less common in the literature and, hence, it is one of our foci using both global batteries and subtests scores.

In the present study we aimed to evaluate a subcohort of the LADIS study after 10 years of follow-up who had been functionally independent at baseline in order to (1) locate the cognitive evolution of different groups of cognitive clinical diagnoses and (2) identify neuropsychological predictors of NI, CIND and DEM.

Methods

Participants and Methods

For the purpose of this study, we included all the 66 participants of the Lisbon center who had previously been enrolled in the longitudinal European multinational LADIS study. The rationale and methodology of the LADIS project has been extensively reported in other papers [9, 10]. Briefly, the LADIS study started in 2001 and aimed to evaluate the impact of WMLs on the transition to disability during a follow-up of 3 years. Each of the eleven European centers involved had to include participants with (a) age 65–84 years, (b) WMLs of any degree according to the modified Fazekas visual rating scale [11], (c) no or mild impairment (none or one item affected) on the instrumental activities of daily living scale [12], and (d) presence of a contactable informant and agreement to give written informed consent. Patients were enrolled due to minor neurological, cognitive or motor complaints or incidental findings on brain imaging due to nonspecific grounds (controls in other studies and volunteers) [9]. The participants were submitted to a comprehensive clinical, functional, motor and neuropsychological examination that was repeated yearly, and MRI was performed at baseline and at the end of the 3-year period.

For the current study, all the surviving Lisbon participants were contacted by a neuropsychologist (S.M.) and invited to come to an extra evaluation in the 10th year of follow-up. This visit consisted of the following: (1) A clinical and functional evaluation performed by a neurologist (A.V.), according to the LADIS protocol [9]. (2) A neuropsychological assessment which included the LADIS battery consisting of: the MMSE [13], a measure of global cognitive status; the Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog) to assess memory, orientation, language, and ideational and constructional praxis [14, 15], with the extension for vascular impairment (VADAS-Cog) [16], which adds the delayed recall of the ADAS's 10-word lists, a symbol digit test, a digit span backwards, a maze task, a digit cancellation task and an animal naming verbal task; the Trail-Making [17] and Stroop tests [18] to assess executive functions; and the 9-word version of the California Verbal Learning Test (CVLT-9) [19] to assess memory and learning (for a

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more detailed description of the battery, see Madureira et al. [10]). (3) An MRI scan was performed according to the LADIS protocol [9], at the same center and with the same equipment which had previously been used in the LADIS study. The severity of WMLs was rated visually by a neurologist (A.V.), who was blind to neuropsychological data, using the Fazekas scale [11]. CD copies of the MRI scans were sent by mail to the same researcher who had rated the follow-up MRI evaluation in the LADIS study (A.G.) and who was blind to clinical details and neuropsychological data. Progression of the WMLs and presence of new lacunae were visually rated in a side-by-side fashion; the entire procedure is described elsewhere [3]. Briefly, WML progression was rated on FLAIR images according to the modified Rotterdam Progression Scale (range 0–9) [20], in which 'no progression' or 'progression' (0 and 1, respectively) was rated in three periventricular regions (frontal caps, occipital caps, bands), four subcortical white matter regions (frontal, parietal, occipital, temporal), the basal ganglia and the infratentorial region. Progression was also classified as 'no progression', 'mild' (progression in one to three regions) or 'severe' (progression in more than three regions) [3]. New lacunae were also visually assessed according to the number and location in five brain regions (frontal, parieto-occipital, temporal, basal ganglia, and infratentorial). New cortical/lobar infarcts were also identified according to number and location [3].

For participants who were unable to come to the hospital for assessment, home visits were conducted for clinical and neuropsychological evaluation. Information concerning nonsurviving participants was collected in a face-to-face or telephone interview with the caregivers/informants. This interview included a dropout/death questionnaire used in the LADIS study which collects clinical and functional data.

The study was submitted to and approved by the Ethics Committee of Santa Maria University Hospital, Lisbon.

Neuropsychological Data and Cognitive Status

For the purpose of this study, neuropsychological battery scores were analyzed as previously described in detail [10]. Briefly, we used both subtest scores and total raw scores of ADAS and VADAS-Cog, the latter calculated according to Ylikoski et al. [21]. We considered 'time used to perform Stroop part 3 minus time to perform Stroop part 2' and 'time needed to perform Trail-Making part B minus time to perform Trail-Making part A (raw scores)' as measures of executive functions. CVLT-9 scores used for the purpose of this study were the total raw score of the five learning trials and the raw score of both short and long delayed free recall tasks, as measures of verbal learning and retrieval.

The participants' cognitive status was evaluated clinically and classified into three groups accordingly to previously established sets of criteria [22] by a neurologist (A.V.) who had access to MRI results but was blind to neuropsychological data: (1) NI, (2) CIND and (3) DEM. Briefly, for CIND two types were considered: (1) amnestic mild cognitive impairment [23] and (2) vascular cognitive impairment without dementia [24]. For dementia the following subtypes were considered: probable Alzheimer's disease (AD) [25], probable vascular dementia (VD) [26], frontotemporal dementia [27] and dementia with Lewy bodies (DLB) [28].

Statistical Analyses

To test associations of clinical diagnosis or progression of WMLs with different variables as well as differences between participant groups, bivariate analyses were used: (a) comparing survivors and nonsurvivors and (b) those who came to the follow-up evaluation at 10 years with those who did not, to assess potential selection bias, using nonparametric tests (Mann-Whitney test, χ^2 test); (c) comparing groups of diagnosis (NI, CIND, DEM) concerning neuropsychological performance using nonparametric statistics such as the Mann-Whitney test and Kruskal-Wallis test for multiple groups. Repeated measures ANOVA was performed in order to study how test scores changed across the three time points (baseline, 3rd and 10th years of follow-up), exploring the effect of time, clinical diagnosis group and the interaction between them. In these series, time and clinical diagnosis at 10 years (NI vs. CIND vs. DEM) were used as independent variables. We also performed regression analyses (linear and logistic) to identify predictors of clinical decline using the most significant demographic, clinical and neuropsychological data as independent variables. For each analysis, age and education were included in step 1 as independent variables, since they are known to influence cognitive performance. Baseline WML severity (mild, moderate or severe) was added in step 2 and cognitive baseline performance was included in step 3. No more than four variables were included in each model to avoid type I errors. Specifically we tested the effects of known clinical predictors (diabetes and stroke) and global neuropsychological measures. A 0.05 level of significance was used except when comparing multiple tests with multiple variables, where a more conservative level of 0.01 or 0.001 (Bonferroni's correction) was adopted. Data analyses were performed using the SPSS 21.0 software.

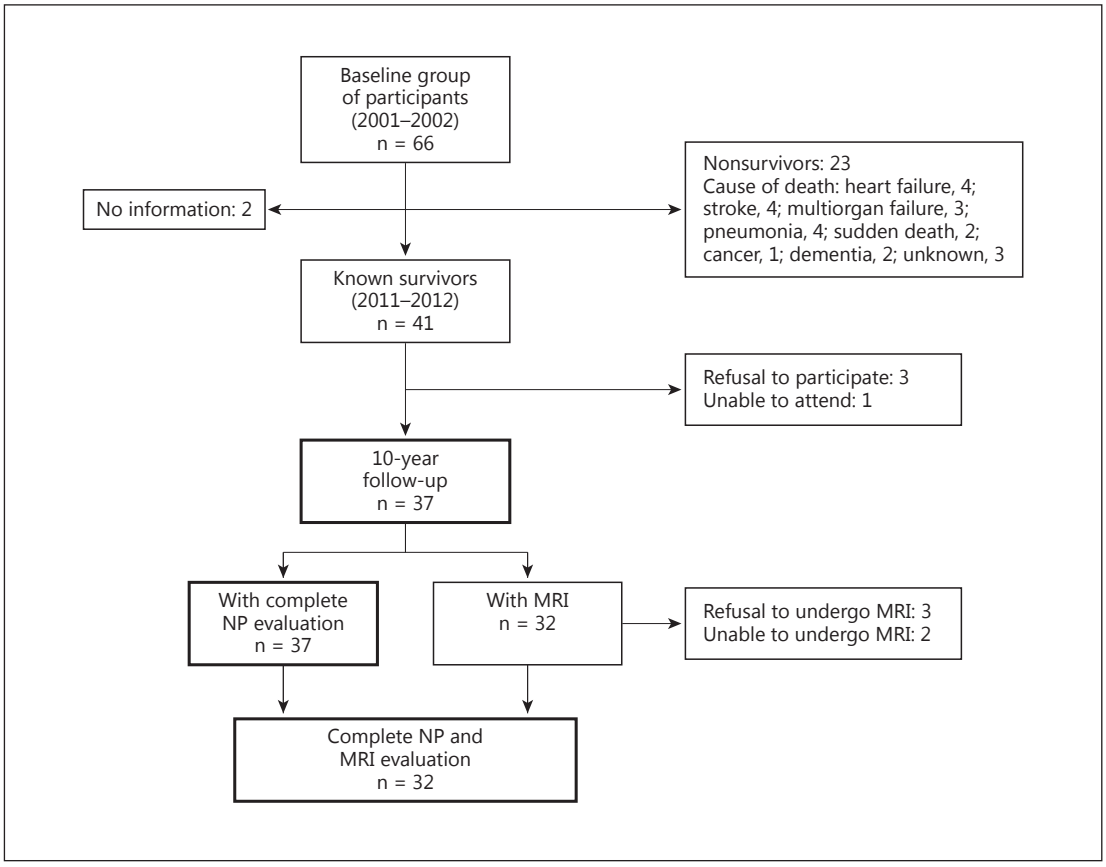

Fig. 1. Schematic representation of participants assessed at year 10. NP = Neuropsychological.

Results

From the initial group of 66 Portuguese elderly participants who had been enrolled in the LADIS study in 2001–2002, 41 (62%) were still alive at the 10-year follow-up visit (fig. 1). Twenty-three participants had died during the 10-year period (1 during the first year of the study, 1 in 2004 and 21 between 2005 and 2012). The most frequent cause of death was stroke (4 patients) and heart failure (4 patients). Two participants were lost to follow-up and we were unable to obtain any further information. One of them was lost during the first year of the study.

There were no significant differences between survivors (n = 41) and nonsurvivors (n = 23) concerning sex ($\chi^2_{(1)} = 0.03$, p = 0.88), educational level (U = 368, p = 0.11) and WML severity ($\chi^2_{(2)} = 2.56$, p = 0.28) or WML volume (U = 590, p = 0.10) at baseline. Nonsurvivors (mean age at baseline 74.7 ± 4.8 years) tended to be older than survivors (mean age at baseline 72.1 ± 5.1 years; U = 691, p = 0.04). Concerning the cognitive clinical diagnosis at the third year of evaluation, survivors and nonsurvivors showed no significant differences ($\chi^2_{(2)} = 4.66$, p = 0.10).

Of the 41 participants who were alive 10 years after enrollment in the LADIS study, 3 refused to participate, and 1 was living in a nursing home far from Lisbon and it was not possible to evaluate him in the new residence. Thus 37 (90%) could be evaluated at the 10-year follow-up. Participants who came to this evaluation (n = 37), when compared with all those who did not come (n = 29), had a higher level of education (U = 377, p = 0.02), but

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Table 1. Comparison between participants who attended the 10-year follow-up and those who did not

	Participants who attended (n = 37)	Participants who did not attend (n = 29)	p value
Mean age at baseline, years[a]	72.35	74.28	n.s.
Mean age at 10-year follow-up, years	81.30	–	–
Mean education, years[a]	8.2	5.6	0.02
Sex[b]			
Female	21	17	n.s.
Male	16	12	n.s.
Baseline WMLs[b]			
Mild	20	14	n.s.
Moderate	9	6	n.s.
Severe	8	9	n.s.
Mean baseline WML volume, ml[a]	19.11	18.65	n.s.
Third-year clinical diagnosis[b]			
NI	16	10	n.s.
CIND	17	11	n.s.
DEM	4	7	n.s.
Mean MMSE score[a]			
Baseline	27.57	26.69	n.s.
Three-year follow-up	27.28	25.81	n.s.

n.s. = Nonsignificant. [a] Mann-Whitney test. [b] χ^2 test.

were not different concerning sex, age, baseline WML severity or clinical diagnosis at the 3rd year. There were also no differences concerning MMSE scores at baseline (U = 434, p = 0.18) and at the 3-year follow-up (U = 275, p = 0.08), as illustrated in table 1. Of the 37 participants who came to the 10-year follow-up, 5 refused (n = 3) or had contraindications (n = 2) to repeating the MRI scan. Thus, a final group of 32 (78%) participants underwent the complete neuropsychological assessment and also had MRI evaluation at the 10-year follow-up.

In the sample at the 10-year follow-up there were 37 participants (21 women, 57%), with a mean age of 81 years (range 74–92 years) and a mean educational level of 8.2 years (range 4–26 years). Of those who underwent MRI, severe WMLs at follow-up were observed in 16 (43%), moderate WMLs in 7 (19%) and mild WMLs in 9 (24%).

Fifteen patients (41%) were clinically diagnosed with DEM (VD = 10, AD = 4, DLB = 1), 12 (32%) with CIND, and 10 (27%) with NI.

Compared to the clinical diagnosis in the 3rd year of follow-up, 14 participants had cognitively declined: 6 participants (16%) had changed from NI to CIND (mild cognitive impairment = 2, vascular cognitive impairment without dementia = 1) and DEM (VD = 1, AD = 1, DLB = 1), and 8 participants (22%) had changed from CIND to DEM (VD = 6, AD = 2).

Cognitive performance for the total sample as well as for the groups of participants with NI and participants with any impairment (CIND or DEM) at the 10-year follow-up is presented in table 2. Overall the data showed that, as expected, neuropsychological performance after 10 years was statistically better for NI participants than for those who had CIND or DEM.

Changes in Cognitive Performance across the 10-Year Period

Regarding general scores of neuropsychological measures, we used repeated measures ANOVA to evaluate the main effect of time and group in each battery or test. For MMSE scores, the main effect of time was significant [$F_{2, 66} = 21.52$, p = 0.000], with performance decreasing

Table 2. Neuropsychological performance at the 10-year follow-up (raw test scores)

Neuropsychological performance	No impairment		Any impairment		Total		Mann-Whitney U value
	n	mean ± SD	n	mean ± SD	n	mean ± SD	
MMSE	10	28.20±1.62	27	21.19±7.98	37	23.08±7.52	214**
ADAS-Cog							
Total[a]	10	17.00±5.67	25	28.92±12.78	35	28.77±17.47	51**
Word recall[a]	10	5.00±1.41	26	6.69±2.21	36	6.22±2.14	n.s.
Command[a]	10	0.20±0.63	26	0.69±1.26	36	0.56±1.13	n.s.
Construction[a]	10	0.70±0.95	25	0.96±1.21	35	0.89±1.13	n.s.
Naming[a]	10	0.30±0.48	25	1.52±1.61	35	1.17±1.48	52.5**
Ideational praxis[a]	10	0.80±1.03	26	1.96±1.48	36	1.64±1.46	n.s.
Orientation[a]	10	0.10±0.32	26	2.31±2.43	36	1.69±2.29	47.0**
Word recognition[a]	10	3.00±2.26	25	6.24±3.92	35	5.31±3.79	n.s.
Remembering instructions[a]	10	0.00±0.00	27	1.37±1.90	37	1.00±1.72	75.0*
Speaking difficulties[a]	10	0.00±0.00	27	1.07±1.71	37	0.78±1.53	n.s.
Word finding[a]	10	0.00±0.00	27	1.04±1.63	37	0.76±1.46	n.s.
Comprehension[a]	10	0.10±0.32	27	0.81±1.50	37	0.62±1.32	n.s.
Concentration[a]	10	0.10±0.32	27	0.63±1.15	37	0.49±1.02	n.s.
VADAS-Cog							
Total[a]	10	49.30±11.10	22	66.72±16.44	32	61.28±16.92	40.5**
Delayed recall	10	6.90±2.28	26	8.23±1.90	36	7.86±2.07	n.s.
Digit span	10	4.00±2.11	25	3.24±1.86	35	3.46±1.93	n.s.
Verbal fluency	10	19.60±4.14	26	11.23±6.31	36	13.56±6.88	224.5**
Symbol digit	10	18.40±9.83	23	10.57±9.71	33	12.95±10.27	n.s.
Digit cancellation	10	16.60±7.30	24	10.00±6.74	34	11.94±7.46	n.s.
Maze[a]	10	12.20±6.34	23	16.00±11.05	33	14.85±9.92	n.s.
Stroop							
Stroop 3-2[a]	10	34.00±31.78	19	47.79±29.14	29	43.03±30.25	n.s.
Stroop 1[a]	10	10.70±4.30	21	27.76±16.63	31	22.26±15.99	20.5**
Stroop 2[a]	10	18.20±4.24	21	37.05±30.02	31	30.97±26.20	41.0**
Stroop 3[a]	10	52.20±32.93	20	77.50±34.69	30	69.07±35.67	n.s.
Trail-Making							
Trail-Making B-A[a]	10	124.7±55.16	19	143.50±73.63	29	137.00±67.42	n.s.
Trail-Making A[a]	10	67.90±35.46	23	150.43±90.89	33	125.42±86.70	44.5**
Trail-Making B[a]	10	192.60±77.25	19	273.63±47.32	29	245.69±69.96	24.0**
CVLT-9							
Total	10	36.20±6.70	27	21.63±10.73	37	25.57±11.7	236.5**
Short delay	10	7.30±1.8690	27	2.70±2.63	37	3.95±3.18	241.0**
Long delay	10	6.80±2.15	27	3.11±2.47	37	4.11±2.88	232.0**
Recognition	10	7.80±2.82	27	6.93±2.95	37	7.16±2.90	n.s.

[a] Tests in which higher scores indicate worse performance. * $p < 0.01$; ** $p < 0.001$.

after the 3rd year; the main effect of participant group (NI, CIND, DEM) was also significant [$F_{2, 66} = 17.65$, $p = 0.001$], with the DEM group demonstrating the lowest results; the interaction effect of time × group was significant [$F_{4, 66} = 14.24$, $p = 0.000$]. A steeper decline was found among DEM participants even though all three groups showed decreased performance over time (fig. 2).

A similar analysis was performed for ADAS-Cog, in which we also found a significant main effect of time [$F_{2, 62} = 37.88$, $p = 0.000$], of group [$F_{2, 62} = 15.85$, $p = 0.000$], and of time × group interaction [$F_{4, 62} = 8.97$, $p = 0.000$]. Cognitive performance also decreased with time, especially after year 3, and the group whose results had worsened most was the DEM group (fig. 2).

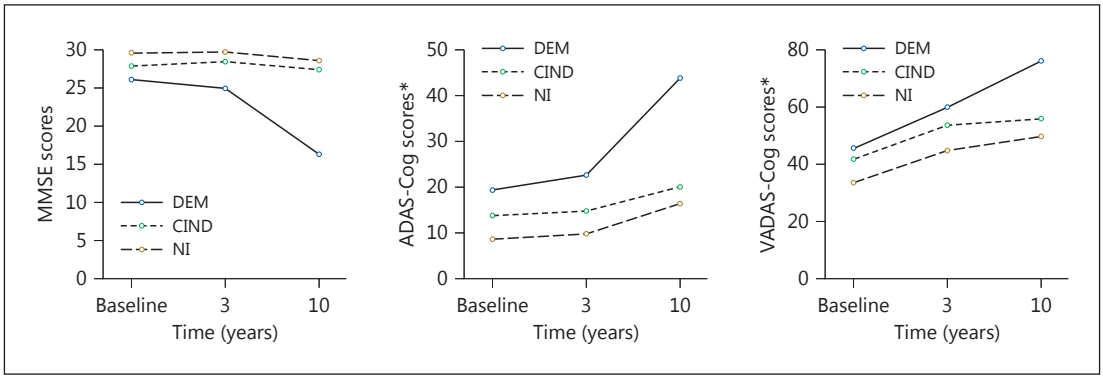

Fig. 2. MMSE, ADAS-Cog and VADAS-Cog scores over 10 years for participants with NI, CIND and DEM. * Higher scores represent worse performance.

The VADAS-Cog was also explored in terms of the change across the 10-year period. The main effect of time [$F_{2, 48}$ = 41.35, p = 0.000], the main effect of group [$F_{2, 48}$ = 5.87, p = 0.008], and the interaction effect [$F_{4, 48}$ = 3.430, p = 0.018] were significant as well (fig. 2).

When changes across time were explored for the executive measures of both the Trail-Making and Stroop tests, only a significant effect of time [$F_{2, 46}$ = 6.95, p = 0.002] and group [$F_{2, 46}$ = 5.98, p = 0.008] was found for Trail-Making B-A, but the time × group interaction was not significant.

WML Progression, Cognitive Performance and Clinical Diagnosis

Four (13%) out of the 32 participants who underwent MRI showed no WML progression from the baseline assessment. Mild WML progression was observed in 11 (34%) participants, and 17 (53%) had severe WML progression (fig. 3 illustrates an example of WML progression from baseline to the 10-year follow-up). Presence of at least one new lacuna was identified in 9 (28%) participants. Participants with severe WML progression had a tendency to have lower education compared with those who did not progress or had mild progression (U = 178.5, p = 0.05). No other differences were found concerning age (U = 170, p = 0.11) or WML volume at baseline (U = 142, p = 0.58). There were no significant differences between participants with NI and those with any impairment concerning WML progression (U = 102.5, p = 0.96) or presence of new lacunae (U = 90, p = 0.47). Concerning WML severity at the 10-year follow-up, participants with NI had less severe WMLs than participants with any impairment ($\chi^2_{(2)}$ = 9.21, p = 0.01).

Predictors of Clinical Diagnosis at the 10-Year Follow-Up

Participants with NI at 10 years also had no significant differences concerning the volume of WMLs at baseline when compared with participants with CIND or DEM (U = 72, p = 0.031), the presence of medial temporal lobe atrophy (U = 86, p = 0.08) or WML progression rated at year 3 (U = 104, p = 0.60). Regarding the presence of new stroke (n = 4) or lacunae (n = 9) during the long-term follow-up, the effect also failed to reach statistical significance comparing participants with NI or any cognitive impairment.

A logistic regression was performed in order to determine the ability to predict NI after 10 years based on the cognitive measures that appeared to distinguish participants with NI from those with any cognitive impairment. For each analysis, step 1 included the demographic variables of age and education, given their known association with cognitive performance, in order to control for their effect. Step 2 entered the baseline WMLs, and in

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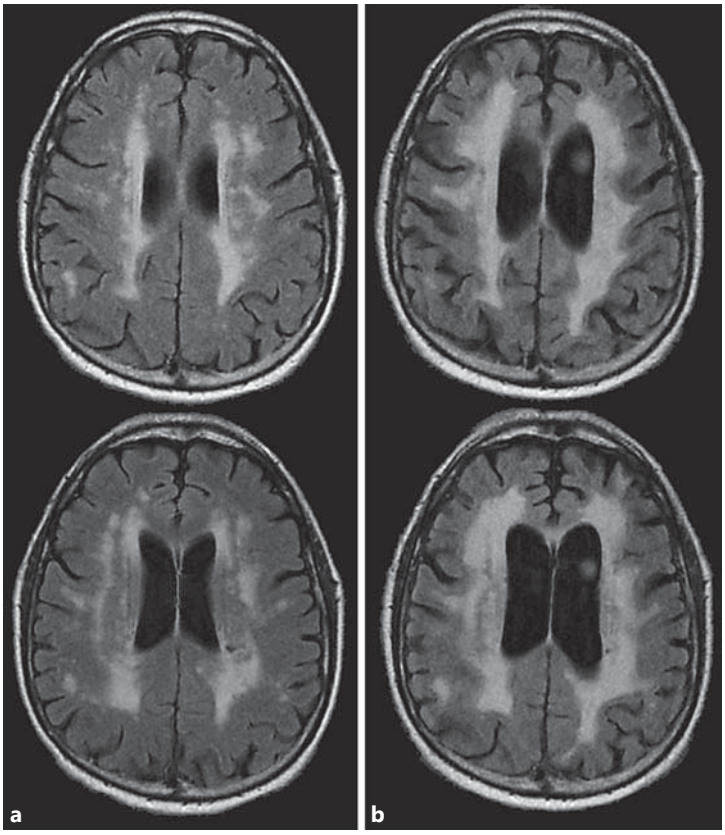

Fig. 3. MRI axial FLAIR images of one patient at baseline (**a**) and 10 years after (**b**) show clear progression of WMLs in the frontal caps and bands of the periventricular region.

step 3 cognitive scores were included as dependent variables. Only MMSE (β = 1.14, p = 0.03, OR = 3.13, 95% CI 1.09–8.97) and ADAS (β = 0.61, p = 0.02, OR = 0.54, 95% CI 0.32–0.91) scores at baseline were found to be significant predictors of NI after 10 years of follow-up, with both models (MMSE $\chi^2 = 14.66$, $R^2 = 0.48$; ADAS $\chi^2 = 21.20$, $R^2 = 0.63$) able to make correct predictions for 87% of the participants. No effects were found for age and education.

Discussion

In this study, the Lisbon group of functionally independent elderly people with age-related WMLs who had been included in the multinational European LADIS study was followed during a period of 10 years. The long-term follow-up allowed the identification of different profiles of evolution of the three groups of clinical diagnoses. As expected, the group of participants with DEM showed more prominent decline over time, while the group with a clinical diagnosis of CIND revealed a profile closer to that of NI participants, even after such a long period of time. Differences between groups of diagnoses were observed in the main batteries MMSE, ADAS-Cog and VADAS-Cog, but not in executive measures when composed scores (Stroop 3-2 and Trail-Making B-A) were used: in both the Stroop and Trail-Making tests, only the effect of time was significant. The absence of differences in composed executive measures could be explained (1) by the fact that age-related decline in processing speed might contribute to an increase in time needed to perform the task in less complex parts (reading words, naming colors and connecting ordered numbers), reducing the

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magnitude of the difference between both tasks [29], and (b) by the increasing number of persons who performed the first part of the tests but were not able to perform the more complex parts. Considering these findings, the best discriminative measures in long-term follow-up evaluations seemed to be the individual scores of each task and not the differences between them.

When baseline clinical and neuropsychological variables were analyzed, we found that the only predictor of NI at the end of the 10 years was the baseline MMSE score. MMSE baseline scores had already been identified as predictors of dementia in a sample of independent elderly participants with WMLs after a 3-year follow-up period [5]. Moreover, MMSE mean scores were relatively high and suggestive of the importance of establishing high cut-off scores for early identification of CIND. Another study has also reported the importance of using higher cut-off scores on MMSE to detect people at risk of dementia in a group of highly educated elderly subjects [30].

More than half of the participants showed progression of WMLs in more than three regions, which was consistent with what had been previously described in a similar group of patients [3]. However, in our cohort, we did not find an association between severe progression of WMLs and demographic factors, vascular risk factors or baseline severity of WMLs. It has already been described that some factors related to progression of WMLs in a medium follow-up period might disappear in the longer run [31], which might explain the absence of these associations in our study. On the other hand, in the visual rating of some MRI scans obtained at the 10-year follow-up, white matter atrophy with prominent ventricular enlargement could be seen in the absence of an expressive WML increase. This could lead us to the hypothesis that the disease might have a different expression of progression after such a long-term process.

The interpretation of these results might be limited by some aspects of the present research. Such long-term periods of follow-up in elderly populations are associated with high rates of attrition, either due to death or the presence of other diseases that might interfere with the natural progression of WMLs. Moreover, the small number of patients did not allow more specific analysis, for instance regarding what type of dementia could be better predicted. Nevertheless, we were able to evaluate a group of older adults with severe vascular risks and/or vascular disease for a period of 10 years. The small sample, an intrinsic risk in long-term follow-up studies performed in elderly populations, contributes to a loss of statistical power in some analyses. The use of a conservative level of significance in order to reduce type I error can also explain the absence of associations regarding some variables that are consistently reported as related to cognitive decline in this population (e.g. age or educational level). Still, this procedure allowed us to identify some significant findings, such as the identification of a global battery like the MMSE as a potential predictor of nonimpairment in this very long follow-up period. However these findings, as well as the absence of a clear association between WML progression and cognitive performance, reflect the importance of the present data and of replication of the study with a larger population.

In this study we presented different longitudinal profiles of cognitive performance in a cohort of independent elderly participants with WMLs, and identified higher scores on baseline MMSE cognitive performance as the strongest predictor of long-term clinical diagnosis of no cognitive impairment. Higher cut-off points on global batteries such as the MMSE should be used to identify participants at risk of cognitive decline over long-term periods.

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