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Confirmatory Factor Analysis of the Neuropsychological Assessment Battery of

the LADIS Study: A longitudinal analysis

Authors: Carla Moleiro PhD*, Sofia Madureira PsyD^a, Ana Verdelho MD^a, José M. Ferro, MD, PhD^a, Anna Poggesi, MD, PhD^b, Hugues Chabriat, MD, PhD^c, Timo Erkinjuntti, MD, PhD^d, Franz Fazekas, MD^e, Michael Hennerici, MD^f, John O'Brien, MD^g, Leonardo Pantoni, MD, PhD^b, Emilia Salvadori, MD^b, Philip Scheltens, MD, PhD^h, Marieke C. Visser, MD, PhD^h, Lars-Olof Wahlund, MD, PhDⁱ, Gunhild Waldemar, MD, DMSc^j, Anders Wallin, MD, PhD^k, Domenico Inzitari, MD^b, on behalf of the LADIS Study

Authors's affiliations:

^{*} Instituto Universitário de Lisboa (ISCTE-IUL), CIS-IUL, Lisbon, Portugal;

^aNeurology Department, Centro de Estudos Egas Moniz, Santa Maria Hospital, Lisbon, Portugal;

^b Department of Neurological and Psychiatric Sciences, University of Florence, Florence, Italy;

^c Department of Neurology, Hôpital Lariboisière, Paris, France;

^d Department of Neurology, Helsinki University Central Hospital and Department of Neurological Sciences, University of Helsinki, Finland;

^e Department of Neurology and MRI Institute, Karl Franzens University Graz, Graz, Austria;

^f Department of Neurology, University of Heidelberg, Klinikum Mannheim, Mannheim, Germany;

^g Institute for Ageing and Health, University of Newcastle, Newcastle-upon-Tyne, UK;

^h Department of Neurology, VU Medical Center, Amsterdam, The Netherlands;

¹Karolinska Institute, Department of Clinical Neuroscience and Family Medicine, Huddinge University Hospital, Huddinge, Sweden;

^j Memory Disorders Research Unit, Department of Neurology, Copenhagen University Hospital, Copenhagen, Denmark;

^k Institute of Clinical Neuroscience, Göteborg University, Göteborg, Sweden.

Correspondence regarding this paper should be addressed to:

Carla Moleiro

Instituto Universitário de Lisboa (ISCTE-IUL), CIS-IUL; Department of Psychology,

Avenida das Forças Armadas. 1649-026 Lisbon. Portugal.

Telephone: 351 21 7903216; Fax: 351 21 0464174; E-mail: carla.moleiro@iscte.pt

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ABSTRACT

Age-related white matter changes have been associated with cognitive functioning, even though their role is not fully understood. This work aimed to test a 3-factor model of the neuropsychological assessment battery and evaluate how the model fit the data longitudinally. Confirmatory factor analysis (CFA) was used to investigate the dimensions of a structured set of neuropsychological tests administered to a multicentre, international sample of independent older adults (LADIS study). Six hundred thirsty eight older adults completed baseline neuropsychological, clinical, functional and motor assessments, which were repeated each year for a three-year follow-up. CFA provided support for a three-factor model. These factors involve the dimensions of executive functions, memory functions, and speed and motor control abilities. Performance decreased in most neuropsychological measures. Results showed that executive, memory and speed of motor abilities are valid latent variables of neuropsychological performance among older adults, and that this structure is relatively consistent longitudinally, even though performance decreases with time.

INTRODUCTION

Age-related white matter changes (ARWMC) have been associated with cognitive deficits, mainly in speed of mental processing, executive functions and memory (Ylikoski, 1993; De Groot, 2000; Shmidt, 2003; Tulberg, 2004). These changes are frequently identified bilaterally on CT and MRI in the brains of elderly persons, in particular among those with vascular risk factors (The LADIS Group, 2011). However, despite the investigations done in the last 30 years, the role that ARWMC play in the progression toward disability in the elderly is still not completely understood. It has become clear, nonetheless, that depending on their severity, these changes are not innocuous (Debette & Markus, 2010; The LADIS Group, 2011). In fact, they have been found to relate to functional status (e.g. Inzitari et al., 2009), to cognition (e.g. Verdelho et al., 2010; Jokinen et al., 2009), to mood (e.g. Krishnam et al., 2006), to motor performance (e.g. Baezner et al., 2008), among others. In a recent systematic review and meta-analysis, Debette and Markus (2010) concluded that WMC were associated with an increased risk of stroke, dementia, and death, clearly indicating a higher possibility of occurrence of cerebrovascular events. In addition, the authors also pointed toward an association of white matter hyperintensities with a faster cognitive decline, including executive functions and processing speed.

The Leukoaraiosis and Disability in the Elderly Study (LADIS) is a longitudinal project that aims to determine the impact of ARWMC on the development of functional, neurological and cognitive deficits (Pantoni et al., 2004). Within these objectives, a neuropsychological battery was specifically designed for the assessment of the elderly population with ARWMC over a 3-year period (Madureira et al., 2006). According to the exploratory results found in the LADIS baseline data (Madureira et al., 2006), a three-factor underlying structure of neuropsychological performance was proposed.

This preliminary exploratory factor analysis accounted for a good amount of variance in the initial evaluation (49%) and was used to compute three compound variables - executive functions, memory and speed/motor functions. However, adjustments to extracted factors were made for theoretical and interpretability reasons, such as the exclusion of simple timed tests, and the addition of the Stroop test (which had loaded on an isolated factor) to the executive functions domain. This structure, therefore, warranted further support, as well as longitudinal analysis. The LADIS study concluded, after an analysis of the 3-year follow-up data, that comparing severe with mild WMC, the risk of transition to disability or death was more than 2-fold higher (The LADIS Group, 2011). Also, clinically, 90 patients had developed dementia and 147 had cognitive impairment/no dementia (Verdelho et al., 2010). In fact, there was a greater (3x) risk for the group of patients who had more severe WMC and lacunes of developing dementia, independent of age, sex and education (Jokinen et al., 2009).

Confirmatory Factor Analysis (CFA) has recently been used to test the underlying structure of the neuropsychological performance of both healthy and demented elderly populations (e.g. de Frias, Dixon & Strauss, 2006; Hull, Martin, Beier, Lane & Hamilton, 2008; Siedlecki, Honig & Stern, 2008). This approach has been utilized to determine the specificity of functioning within particular sub-samples of patients with different disorders (e.g. Fals-Stewart & Bates, 2003; MacDonald, Goghari & Hicks, 2005), and to evaluate a model or confirm a general structure underlying a particular process or ability (e.g. Goldstein, Allen & Minshew, 2008; Strauss, Thompson & Adams, 2000).

In the present research, we aim to evaluate the proposed model for the set of neuropsychological tests administered to the LADIS sample, across the 3-year period, using CFA. Hence, the main goals of the paper were (1) to examine whether

neuropsychological assessment was supported by three underlying factors, (2) to provide support for the previously reported compound measures of executive functions, memory, and speed and motor abilities; and (3) to evaluate how the model fits the data across the four time-points of this longitudinal study.

METHOD

The LADIS study rationale and methodology have been reported elsewhere (Madureira et al., 2006; Pantoni et al., 2004). Succinctly, it is a longitudinal multinational study involving 11 centres from 10 European countries (see Appendix), aiming to investigate the effect of white matter changes on the transition process to disability. Participant study inclusion criteria were defined as follows: a) age 65 to 84 years; b) white matter changes of any degree according to the modified Fazekas' visual rating scale (Fazekas et al., 1987); c) mild or no impairment on the instrumental activities of daily living (IADL) scale, as indicated by none or one item (Fazekas et al., 1987); and d) presence of a contactable informant and agreement to sign an informed consent. Exclusion criteria included: a) severe medical illness; b) severe unrelated neurological disease; c) leukoencephalopathy of non-vascular origin; d) severe psychiatric disorder; and e) inability or refusal to undergo brain MRI. Patients were recruited in each centre when presenting with minor neurological, cognitive or motor complaints, or with incidental findings on cranial imaging due to non-specific reasons (Pantoni et al., 2004).

Participants underwent a comprehensive clinical, functional, motor and neuropsychological examination at baseline, which was repeated each year for a threeyear follow-up period. Specifically, the assessment included: 1) a standard cardiovascular exam; 2) a standard neurological exam; 3) functional status measured by

the IADL scale and the Disability Assessment for Dementia scale (Gelinàs et al., 1999); and 4) health-related quality of life measured by the Euro-QoL 5D (Euro-Qol, 1990).

MRI's were also performed at baseline and at the last follow-up visit, 3 years later. A standard protocol (Pantoni et al., 2004) was used, and white matter ratings and volumetric analyses were performed by a single centre (Amsterdam; van Straaten et al., 2006).

Participants

Six-hundred and thirty nine participants were included at baseline (from which one participant did not complete baseline assessment). Baseline demographic and clinical characteristics of the LADIS sample have been described elsewhere (Madureira et al., 2006). A summary table with demographic patient characteristics is presented here (Table 1).

Insert Table 1

Neuropsychological assessment

Participants underwent a standardized neuropsychological evaluation every year of the study. The construction of the neuropsychological battery was described in detail in a previously paper (Madureira et al., 2006). The following tests were included in the battery: 1) the Mini-Mental State Examination (MMSE; Folstein et al., 1975) as a measure of global cognitive status; 2) the Alzheimer's Disease Dementia Scale (ADAS-Cog) to assess memory, orientation, language, ideational and constructional praxis (Ferris, 2003); 3) the Vascular Dementia Assessment Scale-cognition (VADAS-cog) extension subtests (ADAS' 10-word list for delayed recall, and symbol digit, digit span backwards, maze, digit cancellation, and verbal fluency tasks); 4) the Trail-Making (Reitan, 1958) and Stroop tests (Stroop, 1935) to measure executive functioning (two indicators were used - time needed to perform Trail-making part B minus the time needed to perform trail-making part A, and time used to perform Stroop part 3 minus the time needed to perform Stroop part 2). Three main domains had been proposed in the neuropsychological battery based on exploratory analyses (Madureira et al., 2006): 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, Trailmaking/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.

Statistical analysis

Neuropsychological test scores were measured as continuous variables. The primary data analysis procedure utilized in this paper was Structural Equation Modeling (SEM), more specifically confirmatory factor analysis. SEM tests multiple, complex hypotheses at the construct level (i.e. latent variables) in a theory-driven approach, minimizing both Type I and measurement errors (Byrne, 2001). Measurement models can be tested through CFA.

The main hypothesized models were evaluated using AMOS 7.0 (Arbuckle, 2006). This program was chosen due to the method used to deal with missing values in covariance structure modelling, which are abundant in longitudinal data (Byrne, 2001). Instead of performing listwise or casewise deletion of cases with any missing data, which would decrease sample size and power, maximum likelihood estimation is used for incomplete data, namely the Full-Information Maximum Likelihood (FIML) method. The following indices were utilized to evaluate the overall model goodness of fit in this paper: Chi-Square (χ^2), the root mean square error of approximation (RMSEA; Browne & Cudeck, 1993), the comparative fit index (CFI; Bentler, 1990), the normed fit index (NFI) and the Tucker-Lewis coefficient (TLI; also known as the

Bentler-Bonett non-normed fit index, NNFI; ; Bentler, 1990). While the conventional χ^2 test is too stringent and tests for a perfect fit of the data to the model, the other three indices provide information on good or close fit to the data. In addition, fit can be indicated by the χ^2 to degrees of freedom ratio (CMIN/DF) in the range of two- to three-to one (less than five). The RMSEA index ranges from 0.00 to 1.00. A value of the RMSEA of about 0.05 or less indicates a close fit of the model in relation to the degrees of freedom, and that a value of 0.08 or less indicates reasonable fit. Conversely, an RMSEA greater than 0.10 can be interpreted as an unacceptable fit of the model. On the other hand, both the CFI and the NFI/NNFI also range from 0.00 to 1.00, but greater values translate better fit. Only values close to 1.00 (greater than 0.90) translate close or good fit (Browne & Cudeck, 1993; Hu & Bentler, 1999; MacCallum & Austin, 2000).

RESULTS

Descriptive Statistics

Rates of attrition and assessment completion for baseline and follow up years of the LADIS study were very acceptable, especially considering the population involved (75% came to the last follow-up visit). Descriptive statistics (means and standard deviations) for neuropsychological tests are presented in table 2 for all the years of the study.

Insert Table 2

Analyses of variance (ANOVA's) with repeated measures were able to show that neuropsychological performance decreased with time, as expected. An exception were the indicators Stroop 3_2 and Trail B_A [F (3,374) = 0.81, p=0.488; F (3,311) = 0.159, p=0.924, respectively]. In these two cases, even though the single trails demonstrated an increase in time needed for completion, the difference scores did not show statistically significant changes with time. The remaining two indicators of executive cognitive performance significantly decreased with time [symbol digit F (3,389) = 6.22, p = 0.000; and verbal fluency F (3,398) = 6.71, p = 0.000]. Motor control and speed performance also significantly decreased across the 4 time-points, as time for completion of tasks increased [Trial A F (3,350) = 4.07, p = 0.007; maze F (3,375) = 11.58, p = 0.000; digit cancel F (3,398) = 8.91, p = 0.000]. Finally, memory performance also displayed significant differences during the 4 years of the study [word recall F (3,399) = 12.45, p = 0.000; delayed recall F (3,392) = 42.41, p = 0.000; word recognition F (3,397) = 3.33, p = 0.019; digit span F (3,389) = 1.54, p = 0.203].

The measures utilized were also correlated with another measure of global cognitive functioning, namely the MMSE, for further convergent validity (MMSE change was also significant F(1,421) = 7.21, p = 0.000). Executive functioning indicators were significantly correlated with the MMSE for all time-points ($r_{trail B_A}$ ranged between -.42 and -.23, p < .01; $r_{stroop3_2}$ ranged between -.45 and -.35, p < .01; $r_{symbol digit}$ ranged between .47 and .54, p < .01; $r_{verbal fluency}$ ranged between .43 and .53, p < .01). Indicators of speed and motor control were also significantly associated with global cognition, with the exception for Maze at year 1 and year 2 (r_{trailA} ranged between .41 and -.55, p < .01; r_{maze} ranged between .03*ns* and -.55, p < .01; $r_{digit cancel}$ ranged between .36 and .50, p < .01). Finally, memory performance indicators were found to be significantly associated with the MMSE ($r_{word recall}$ ranged between -.34 and -.48, p < .01; $r_{delayed recall}$ ranged between -.35 and -.48, p < .01; $r_{word recognition}$ ranged between -.31 and -.54, p < .01; $r_{digit span}$ ranged between.37 and .40).

Main Analysis: Confirmatory Factor Analyses

<u>Baseline Neuropsychological Assessment</u>. Using neuropsychological scores at baseline, a three-factor model was tested, following the domains proposed in an earlier

paper (Madureira et al., 2006). This model involved three latent variables: executive functions, memory, and speed and motor control (see Figure 1). The model fit the data well, with fit indexes within a good range: $\chi^2 = 171.10$, df = 40, p < 0.001, with CMIN/DF = 4.28; NFI = .93; NNFI = .91; CFI = .95; RMSEA = 0.07 (see Table 3). The model presented factor loadings which were all found significant at a .01 level, as well as the correlations among the three latent variables. These correlations were in the expected direction. Single subtests accounted for a significant amount of variance, ranging from 14% (Word Recall) to 89% (Symbol Digit).

Insert Figure 1 Insert Table 3

<u>Neuropsychological Assessment at the end of the 1st year</u>. An identical set of analyses was conducted with data of the same neuropsychological tests, performed at 1year follow up. The three-factor model was tested (see Figure 2). The model fit the data modestly, with the following fit indexes: $\chi^2 = 280.20$, df = 40, p < 0.001, with CMIN/DF = 7.00; NFI = .89; NNFI = .83; CFI = .90; RMSEA = 0.10 (see Table 3). In addition, factor loadings were all found to be significant at a .01 level, with the exception of maze, significant at .05. The expected direction of factor loadings, and weight and direction of correlations among the latent variables were also found significant. Single subtests accounted for a significant amount of variance, ranging from 14% (Word Recall) to 87% (Symbol Digit), with exception of Maze (only 3%).

Insert Figure 2

<u>Neuropsychological Assessment at the end of the 2nd year</u>. Following a similar procedure as before, the three-factor model was tested (see Figure 3). The model fit the data adequately, with fit indexes within an acceptable to good range: $\chi^2 = 186.90$, df = 40, p < 0.001, with CMIN/DF = 4.67; NFI = .91; NNFI = .89; CFI = .93; RMSEA = 0.08 (see Table 3). Furthermore, once again all factor loadings were found to be statistically significant (maze was the poorest, but still significant at .05 level). Correlations among factors were significant at .01 level, and followed the same directions as baseline and year one. Single subtests accounted for a significant amount of variance, ranging from 16% (Word Recall) to 80% (Symbol Digit), with exception of Maze (only 2%).

Insert Figure 3

<u>Neuropsychological Assessment at the end of the 3rd year</u>. The same battery of tests was administered to the participants at the last year of the study (year 3). The analysis using CFA followed the same procedure. The three-factor model was tested, achieving only acceptable but poorer fit indices: $\chi^2 = 300.40$, df = 40, p < 0.001, with CMIN/DF = 7.51; NFI = .87; NNFI = .81; CFI = .89; RMSEA = 0.10 (see Table 3). Moreover, just as in the three-factor models for the previous time-points, factor loadings revealed significant scores, as well as the correlations among the factors. Single tests accounted for a significant amount of variance, ranging from 17% (Word Recall) to 80% (Symbol Digit; see Figure 4).

Insert Figure 4

This set of analyses provided some support to configural invariance across timepoints. However, in order to further explore the question of longitudinal measurement invariance, three additional models were performed using MPlus (Muthén & Muthén, 1998-2007). Each of these models tested all time-points simultaneously and their focus was the comparison across groups (i.e. time). They included: Model 1 - Configural Invariance (same pattern of free loadings); Model 2 - Weak Measurement Invariance (fixed loadings across groups); and Model 3 - Strong Measurement Invariance (fixed loadings and intercepts across groups). The fit indices of these models are presented in Table 4.

Insert Table 4

The analysis of fit indices reveals that the models provide reasonable, but modest fit to the data. CFI and TLI indices ranged between 0.824 and 0.869, which were lower than 0.90 (relatively acceptable fit). However, the weak (84 free parameters) and strong (78 free parameters) measurement invariance models provided an acceptable (0.08-0.10) root mean square error of approximation, slightly better than the simple configural invariance (144 free parameters). Hence, overall, even though the fit was not good, we are able to accept measurement invariance across time-points.

DISCUSSION

The present study was guided by one primary goal: the confirmatory analysis of a structured set of neuropsychological tests in order to support, across time, the validity of the neuropsychological compound scores for three dimensions, namely, executive functions, processing speed, and memory. Through CFA, this study provided support for the construct and measurement validity of the compound measures across the four years of the study. As aforementioned, CFA allows for focused hypothesis testing and decreases the likelihood of chance findings. Cross-validation and missing values in longitudinal data are also suitably dealt with. This has led many researchers to use this methodology in the study of the organization of neuropsychological functions (de Frias, Dixon & Strauss, 2006; Hull et al., 2008).

Nonetheless, adjustment of the data to the three-factor structure seemed poorer at year 3 than at baseline and year 2 (where the model fit the data closely). This may be due, on the one hand, to lower statistical power (i.e. a number of patients missed the assessment in one or two of the study years). Attrition bias, including by death of participants, has been argued to produce underestimates of cognitive decline and to limit the interpretability of cognitive change (Ritchie & Tuokko, 2007). On the other hand, however, the poorer fit of the proposed structure to the data obtained in the last year may be due to other variables which may have influenced the participants' performance on neuropsychological tests, such as motor slowing (Baezner et al., 2008). Finally, the fit of the longitudinal invariance measurement models was only modest. Hence, while supporting the dimensions of executive functioning, memory, and processing speed, the results still warrant some caution regarding the assumption that these latent constructs reflect the same meaning over time.

ANOVA results revealed that, overall, performance decreased with time for all neuropsychological tests, and that test values correlated with general indices of functional status and global cognition. These findings provide further support for the construct validity of the measures and are in tune with extant literature on cognitive aging and ARWMC (Pantoni et al., 2004; Madureira et al., 2006). In fact, the clinical relevance of this decrease and its relation to changes in white matter hyperintensities have been documented in other studies (Debette & Markus, 2010; The LADIS Group, 2011).

The current study contributes to the literature in a number of ways. First, the present paper provides support for the construct validity of the neuropsychological

battery of the LADIS study, in a large, heterogeneous, multinational sample of independent elderly. It determined that the factor structure of the battery supports the proposed three domains. Second, and most importantly, the factor structure was tested longitudinally. The findings were, thus, cross-validated in four different datasets, which further supports its structure. We have shown that, even though neuropsychological performance of independent elderly decreases across time, the structural functioning is relatively consistent (i.e. groupings of functions continue to cluster together). We also found a decrease in model fit with time, which may suggest that the structure of functioning may be sensitive to some changes that occur in later life, such as ARWMC and the onset of cognitive impairment.

Although there are a number of strengths, some limitations can be identified in the present study. One limitation was that, because of small sub-group sizes, the model could not be tested separately on the group of patients who evolved to dementia and those who evolved to impairment/no dementia by the end of the study. Another limitation, as mentioned, was participant attrition over time.

Results suggest there are unique ways in which neuropsychological functions may group together over time, especially at the onset of mild cognitive impairment or dementia. Future research should continue to investigate the complex ways in which change in cognitive functioning may take place, such as by the addition of moderation analyses (e.g. dementia/non-dementia) or models of latent change (Willett & Sayer, 1994). In addition, the nature or meaning of these constructs, such as executive functioning, memory, and processing speed, may be further explored over time, as they may reflect slightly different processes.

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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 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, PsvD, 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 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, 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.

Table 1

Participant Demographic Information

	Total	Ν
Female	54.9%	639
Age – mean (sd)	74.1 (5.0)	639
Ethnicity		639
White	99.1%	
Minority	0.8%	
Marital Status		639
Single (never married)	4.9%	
Married	62.8%	
Widowed	27.5%	
Divorced or separated	4.7%	
Living Status		638
Alone	32.1%	
With other	67.9%	
Years of Education – mean (sd)	9.6 (3.8)	638
Employment		636
Employed	3.8%	
Retired	96.2%	

Table 2

Means and Standard Deviations of Raw Scores of Neuropsychological Tests at

Neuropsychological	Ν	Baseline	Year 1	Year 2	Year 3	
Test			Follow-up	Follow-up	Follow-up	
MMSE	422	27.74 (2.29) ^{ab}	27.76 (2.49) ^{ab}	27.46 (3.04) ^b	26.93 (3.89) ^{bc}	
Stroop 2 (seconds)	389	16.60 (7.78) ^a	17.48 (11.09) ^a	17.04 (8.32)	18.08 (11.09) ^b	
Stroop 3 (seconds)	377	46.03 (22.47)	45.78 (30.27)	45.17 (25.80)	47.41 (30.58)	
Verbal Fluency	399	20.21 (6.30) ^a	19.81 (6.31) ^a	19.72 (6.69)	19.07 (7.00) ^b	
Symbol Digit	390	28.88 (10.32) ^a	28.80 (10.68) ^a	28.33 (11.37)	27.62 (11.26) ^b	
Trail A (seconds)	351	59.06 (34.52) ^a	60.13 (36.98)	59.95 (38.81)	64.26 (45.79) ^b	
Trail B (seconds)	313	151.17 (70.30)	150.82 (71.32)	149.93 (73.55)	154.96 (74.00)	
Maze 2 (seconds)	376	6.75 (5.22) ^a	12.99 (29.28) ^b	14.47 (33.92) ^b	8.65 (10.27) ^c	
Digit Cancel	390	20.33 (6.61) ^a	20.27 (6.62) ^a	20.04 (7.04) ^a	19.36 (6.77) ^b	
Word Recall	400	4.90 (1.61) ^a	4.80 (1.74) ^a	4.81 (1.74) ^a	5.26 (1.89) ^b	
Delayed Recall	393	5.47 (2.27) ^a	5.32 (2.44) ^a	5.82 (2.36) ^b	6.41 (2.44) ^c	
Word Recognition	398	2.75 (2.32)	2.42 (2.20) ^a	2.66 (2.31)	2.77 (2.46) ^b	
Digit Span	399	5.64 (1.72)	5.74 (1.87)	5.57 (1.96)	5.61 (2.02)	

different study time points

Note: Worse performance refers to higher scores on the following tests: Stroop 2 (time to complete task); Strop 3 (time to complete task); Trail A (time to complete task); Trail B (time to complete task); Maze 2 (time to complete task); Word Recall (number of words not recalled); Delayed Recall (number of words not recalled); Word Recognition (number of words incorrectly recognized). Worse performance refers to lower scores on the following tests: MMSE (number of correct items); Verbal Fluency (number of words); Symbol Digit (number of correct symbols); Digit Cancel (number of correct identifications); Digit Span (number of correct trails).

Pairwise comparisons performed with Bonferroni test and indicated in superscript.

Table 3

	χ^2	df	р	CMIN/DF	CFI	NFI/	RMSEA	90% CI
						NNFI		
Baseline	171.10	40	<.01	4.28	.95	.93/.91	.07	.0608
1 st year follow up	280.20	40	<.01	7.00	.90	.89/.83	.10	.0911
2 nd year follow up	186.90	40	<.01	4.67	.93	.91/.89	.10	.0911
3 rd year follow-up	300.40	40	<.01	7.51	.89	.87/.81	.10	.0911

Fit Indices for Confirmatory Factor Analyses Models

Note: CMIN/DF: ration between Chi-square and degrees of freedom; CFI: comparative fit index; TLI: Tucker-Lewis Index; RMSEA: root mean square error of approximation; 90% CI: 90% confidence interval for RMSEA.

Table 4

Fit Indices for Testing of Measurement Invariance

	χ^2	df	р	CFI	TLI	RMSEA
Configural Invariance	1109.42	164	<.01	0.87	0.82	0.10
Weak Measurement Invariance	1327.30	224	<.01	0.85	0.85	0.09
Strong Measurement Invariance	1343.56	230	<.01	0.85	0.85	0.09

Note: CFI: comparative fit index; TLI: Tucker-Lewis Index; RMSEA: root mean square error of approximation.