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-

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

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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 [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 log-arithmetic 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 Bonferroni 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)	
<i>Demographic factors</i>	
Age, mean $\pm$ SD, years	74.1 $\pm$ 5
Female/male	351 (55%)/287(45%)
Education, mean $\pm$ SD, years	9.6 $\pm$ 3.8
Living alone/with other	205 (32%)/434 (68%)
Working/retired	24 (4%)/610 (96%)
Married/not married	401 (63%)/237 (37%)
<i>WMC characteristics</i>	
Mild	284 (44.5%)
Moderate	196 (30.7%)
Severe	158 (24.8%)
<i>Reasons for referral</i>	
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 Tamahan'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.)

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 = visuocstructional; 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
<i>Model 1</i>												
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
<i>Model 2</i>												
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
<i>Model 3</i>												
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 = visuocstructional; 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-Totol
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-Totol
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 visuo-constructional 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

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