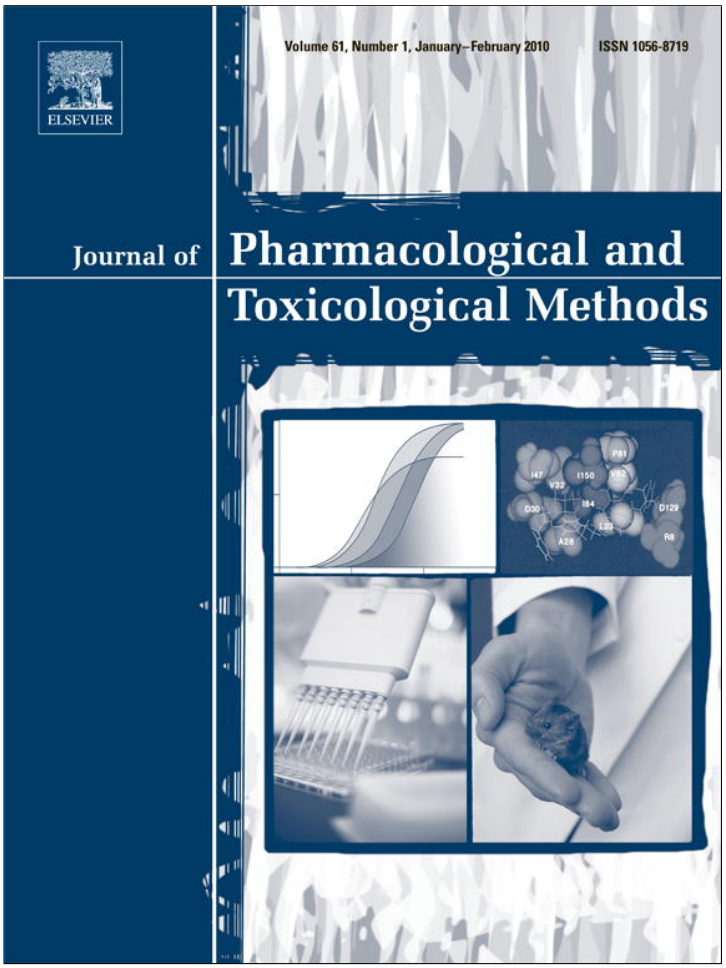

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Original article

A novel neuropsychological assessment to discriminate between ischemic and nonischemic dementia

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ABSTRACT

Introduction: In the present study we have elaborated a multivariate–multifactor diagnostic method for diagnosis of ischemic and nonischemic dementia, and validated it using different human populations. Our purpose was to improve dementia diagnosis by means of comprehensive neuropsychological assessment and the control of intervening variables.

Methods: Data were obtained from 114 healthy volunteers to 101 patients consecutively referred for suspected dementia. On the basis of neuromorphological criteria, the patient sample was subdivided into those with ischemic lesions (IL: $N = 12$) and without ischemic lesions (non-IL: $N = 89$). The patient groups and the healthy subjects (HS) were matched according to age, education, sex ratio and handedness. A comprehensive neuropsychological battery was administered to all the participants.

Results: The two patient groups differed in their Hachinski ischemic score, but not in terms of demographic variables, the Blessed rating scale, Mini Mental State, Geriatric Depression Scale, or other measures. Discriminant analysis selected fifteen neuropsychological variables from the comprehensive battery, and these were found to provide accuracy of classification in 98% of HS and 87% of the patients considered as a whole. Considering the three groups, those variables provided accuracy of classification in 98% of HS, 82% of IL patients and 82% of non-IL patients. Subtests were internally consistent (Cronbach's alpha: 0.87) and a positive association between ischemic lesions and cognitive impairment was observed when the 15 dependent variables were added.

Discussion: It is possible to select a combination of cognitive tests that discriminated HS from dementia patients and, within this category, patients with and without ischemic lesions. Analysis of the 15 variables provides an improved method for diagnosis of ischemic vs. nonischemic lesion dementia in humans.

1. Introduction

1.1. Background

Diagnosis of dementia type based on neuropsychological concepts is hampered by the extent of overlap in the present diagnostic criteria. The process of combining different overlapping diagnostic criteria to create an integrated assessment does not improve the accuracy of diagnosis (Bacchetta et al., 2007; Castiglioni et al., 2006; Erkinjuntti et al., 1997; Pohjasvaara et al., 1997; Viglieca, 2007; Wancata et al., 2007).

The contribution of ischemic lesions to cognitive function is not clear. Jokinen et al. (2009) observed that subjects who suffered from subcortical ischemic vascular disease showed a progressive and global cognitive deterioration compared to control subjects. Kearney-Schwartz et al. (2009) observed that vascular abnormalities played a role in the setting of white matter lesions and memory complaints of elderly hypertensive patients. Tullberg et al. (2004) affirmed that white matter lesions (which were found in patients with ischemic vascular disease) were only associated to executive dysfunction. On the other hand, Swartz et al. (2008) observed that brain atrophy, subcortical vascular disease, and thalamus and cortical–strategic infarcts contributed independently to the pattern of cognitive disabilities in a sample of overlapped Alzheimer disease (AD) and vascular dementia (VaD) patients. In contrast, Modrego et al. (2008) found that the presence or absence of microinfarctions had no influence in the cognitive and behavioral scores of AD patients.

In summary, current evidence does not provide an accurate cognitive differentiation between ischemic and nonischemic dementias. As well, valid neuropsychological tests which discriminate between those dementias have not so far been developed.

1.2. General objectives

In the present study we have elaborated a multivariate–multifactor diagnostic method for diagnosis of ischemic (I) and nonischemic (NI) dementia, and validated it using different human populations.

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Our purpose was to improve dementia diagnosis by means of comprehensive neuropsychological assessment and the control of intervening variables.

1.3. Specific objectives

We wanted to see if the magnitude and quality of cognitive impairment varied according to the presence or absence of ischemic lesions. Except for that factor, patients showed unknown etiology for cognitive impairment. The two groups of patients were also compared with healthy subjects (HS), matched according to age, education, sex ratio and manual preference, so as to have a control parameter for the patients' cognitive impairment. Neuropsychological output in the three groups was assessed by the comprehensive battery of "Neuropsychological tests abbreviated and adapted for Spanish speakers" (Viglecca, 2004).

1.4. Hypothesis

As previous studies indicated that the said neuropsychological battery represented a valid instrument to detect neurological cognitive impairment (Viglecca et al., 2001; Viglecca, 2004; Viglecca et al., 2007) it was expected that it would also be a valid instrument to identify dementia patients. Regarding the neuromorphological criterion, we took into consideration the following deductive inference: if different anatomical expressions are related to different cognitive outputs, then we should be able to observe a difference between patients with ischemic lesions (IL) and patients without ischemic lesions (non-IL) in any test or group of tests of the neuropsychological battery. We could not anticipate the nature of this difference because of the lack of cognitive instruments to detect ischemic lesions.

2. Methods

2.1. Ethical statements

This study was performed pursuant to the ethical standards established in the 1964 Declaration of Helsinki (World Medical Organization, 1996). We had the participants' written informed consent (or the patients' caregivers), the approval of the Research and Ethics Committee for each contributor institution and the support of the CONICET. The neuropsychological evaluation did not pose any risk to the participants who, in all cases, were alert, and willing to perform the complete battery of tests, independently of their relative capacity or willingness to perform some of the subtests in particular. Participants did not receive any payment for their contribution.

2.2. Material

The Blessed dementia rating scale (BDRS) (Blessed et al., 1968), the Geriatric Depression Scale (GDS) (Yesavage et al., 1983), and the Mini Mental State (MMSE) (Folstein, Folstein & McHugh, 1975), were administered to the patients with the aim to neuropsychologically describe the IL and non-IL samples.

The battery of "neuropsychological tests abbreviated and adapted for Spanish speakers", a reliable instrument which has been validated by the cerebral location of the injury (Viglecca, 2004; Viglecca et al., 2001, 2007), was administered to all the participants in order to neuropsychologically evaluate the three samples in their inferential data. The battery consists of 36 cognitive subtests with 100 empirical indices and a careful interview of 37 items. Some items were specially added for this dementia study in order to better analyze the patients' medical and psychological backgrounds.

The items of the interview which analyzed if the patients had a history of focal physical neurological signs or symptoms, a clearly documented cerebrovascular disease, as well as the presence of emotional liability were included in this study as part of the Hachinski ischemic score (HIS) (Hachinski et al., 1975).

Other patient-descriptive data analyzed by means of this interview were: time since onset of condition (divided in months), the presence of additional risk for cognitive impairment (neonatal hypoxia, head trauma with loss of consciousness, malnutrition, genetic component of the illness, frequent contact with toxic agents, etc.), the presence of hypertension and the corresponding antihypertensive medication, as well as the following risk factors: heart disease, obesity, diabetes, smoking, and alcohol consumption. The following manifestations were also taken into account: degree of cooperation (from 1 to 3); emotional state (normal: 0; excited: 1: inhibited: −1); disability awareness from 0 to 3 (anosognosia); and the presence or absence of dysprosody, perceptual disorders (i.e., difficulty in recognizing known persons, places, moments or objects, independently of sensory acuity); sleeping disorders (i.e., insomnia, somnolence during the day, etc.); language disorders (i.e., paraphasias, anomies, echolalia, intrusions, reduced verbal comprehension or fluency, dysarthria, etc.); anxiety; irritability; lack of sphincter control; seizures; behavioral disorders (i.e., abnormal responses, difficulty in organizing action, changes of personality, etc.); as well as thought disturbances (i.e., hallucinations, delusions, sense of reality loss, etc.). The psychopharmacological medication administered to both groups of patients was controlled in its quantity and quality (presence or absence) for the categories of antipsychotic, anxiolytic, antidepressant, hypnotic, mood-stabilizing and anti-seizure medication. The administration of vitamins or dietary supplements as well as the administration of anti-dementia medication (either cholinesterase inhibitors or the N-methyl-D-aspartate (NMDA) receptor antagonist memantine) was also evaluated.

2.3. Subjects

HS were independent and adapted to daily life demands, without any known neurological or psychiatric disease, and were recruited from different areas of Cordoba province, such as cultural, recreational, and retirement centers. In order to include a subject in the healthy sample, we also took into consideration the information provided by the initial interview of the neuropsychological battery. This interview evaluated risk factors, background and their probable incidence on cognition and behavior. We excluded subjects who showed symptoms of neurological or psychiatric disease, any kind of medical illness which could affect neuropsychological performance, or sensorial or motor difficulties which could prevent them from carrying out the tests fluently.

Patients were consecutively referred by their neurologists for suspected dementia, counting on with clinical, neurological and neuroimaging studies to single out etiological factors. They were recruited from public and private health institutions of Cordoba province (Cordoba Hospital, Clinical Hospital, Italian Hospital and the Synapse neuroscience center from San Francisco).

Patients with other dementia causes (metabolic, infectious, etc.) or with other neurological diagnoses associated, according to either laboratory analyses or the physician's report were excluded. Likewise, lesions indicatory of hemorrhagic stroke, head trauma, arterio-venous malformation, aneurysm, tumor, abscess, hematoma, edema, hydrocephalus, multiple sclerosis, etc., according to either the radiologist' report or the physician's report (double blind) in the computed tomography scanning (CT) or magnetic resonance imaging (MRI), were excluded. For included patients, inconsistent neuroimaging reports between the radiologist and the physician were excluded. Patients who suffered from hemiparesis or hemihypoesthesia at the moment of evaluation, according to the physician's report, were also excluded from the present study.

All the consecutive patients included in this study ($N = 101$) had, in their pre morbid status, the characteristics described above for HS, i.e., they did not suffered from physical impairments, intellectual

Table 1
Demographic data.

Group	Age (Mean ± SD)	Education (Mean ± SD)	Women (%)	Right-handed subjects (%)	N
HS	68.46 ± 8.02	9.06 ± 4.57	61	92	114
Non-IL	68.98 ± 8.71	8.27 ± 5.23	48	97	89
IL	70.75 ± 8.35	7.66 ± 4.81	42	100	12
Total	68.80 ± 8.31	8.66 ± 4.87	55	94	215
	$F(2, 212) = 0.45$, $p < 0.64$	$F(2, 212) = 0.92$, $p < 0.39$	$\chi^2 = 4.35$; *df*: 2; $p < 0.11$	$\chi^2 = 2.69$; *df*: 2; $p < 0.26$	

χ^2: Chi square; HS: healthy subjects; non-IL: patients without ischemic lesions; IL: patients with ischemic lesions.

disability, psychosis or any kind of medical condition which could affect their independence or adaptation.

The group of HS ($N = 114$) was matched according to age, education, sex ratio and manual preference with the patient group.

2.4. Statistical analyses

Descriptive sample data were analyzed by ANOVA for continuous variables or by Chi square (χ^2) for categorical variables. In the patient sample, a content analysis of the CT and MRI reports was carried out in order to select the anatomical indices more frequently described by the specialists. A factor analysis was carried out with the selected indices by following the principal component method.

In the inferential section of this study, all the empirical indices of the battery were considered in principle equally important for the potential differentiation of HS, IL and non-IL patients. This was done this way because we did not know *a priori* if some particular part of the battery could contribute differentially in the exploratory model which we attempted to build. Then, only those indices which: a) showed a significant difference among groups in any direction and involved any pair of groups (according to one way MANOVAs), and b) had been performed by the maximum number of subjects (results not shown), were considered candidates to be included in a discriminant analysis. In order to see if the selected variables represented also a global index of cognitive performance, their internal consistency was analyzed by the standardized Cronbach's alpha coefficient. Sensitivity and specificity for that global index were calculated on the basis of the common median as cut-off point and the relationship between ischemic lesions and cognitive impairment was analyzed by $\chi^{2.}$ Some complementary neuropsychological information was analyzed by ANOVA and Pearson's correlation coefficient. Missing cases were excluded.

3. Results

3.1. Descriptive data and independent variables

The CT and MRI indices selected by content analysis were: 1) the report as normal or pathologic; the presence or absence of: 2) focal lesions; 3) ischemic lesions; 4) brain atrophy; 5) white matter lesions; and 6) ventricular enlargement. One factor was extracted by the principal component method (unrestricted factors) from those six anatomical indices explaining the 65% of the variance in this patient sample. As the presence or absence of ischemic lesions (loading: 0.76) was considered a representative index of the rest of the anatomical lesions analyzed, the other lesions were excluded (i.e., as IL and non-IL groups were also different in the other five indices analyzed, redundant information was discarded).

Five IL patients were reported to have unilateral brain lesions (2 right lesions and 3 left lesions) and only 2 non-IL patients were reported to have unilateral atrophy (both left).

IL ($N = 12$) and non-IL patients ($N = 89$) did not differ in their demographic data (Table 1). As well, these two groups of patients did not differ in the presence of hypertension and the corresponding antihypertensive medication, nor in the following risk factors: heart disease, smoking, obesity, diabetes, and alcohol consumption (all $\chi^2 \leq 0.96$; *df*: 1; $p \geq 0.326$). Both patient groups were also similar in the rest of the sample variables analyzed except for the HIS (Hachinski et al., 1975) thus indicating the presence of vascular etiology only for IL patients (Table 2).

As seen in Table 2, IL and non-IL patients scored >9 in the BDRS and between 10 and 19 in the Geriatric Depression Scale (GDS) thus demonstrating, respectively, the presence of dementia and mild depression for both groups (Blessed et al., 1968; Yesavage et al., 1983). In the Mini Mental State (MMSE), the two patient groups were similar in the total score (both means <24 indicating the presence dementia (Folstein et al., 1975)) but they differed significantly only in the attention item of the test, the IL patients showing a poorer performance than the non-IL patients ($\chi^2 = 4.01$; *df*: 1; $p < 0.045$).

IL patients showed a trend to have more behavioral disorders as well as more thought disturbances than non-IL patients but these differences were not statistically significant (Table 2).

Explicitly, both IL and non-IL patients showed, on average, empirical evidence of dementia (as indicated by MMSE and BDRS) but only IL patients showed physical evidence of vascular disease (as indicated by neuroimages and the HIS). Non-IL patients showed no evidence of any apparent disease that may have caused cognitive decline.

3.2. Inferential data and dependent variables

The following tests were selected by the exploratory stepwise discriminant analysis (see Appendix A): 1) Verbal auditory sustained attention, 2) Repetition of words and sentences, 3) Singing, 4) Praxia in response to complex (spoken) verbal commands, 5) Abstract ability for the interpretation of metaphoric verbal expressions, 6) Praxia in response to complex (written) verbal commands, 7) Oral verbal fluency in one minute, 8) Reading, 9) Postural imitation, 10) Visual memory, 11) Stereognosis, 12) Comprehension of non-verbal sounds, 13) Time required to perform the abbreviated tests of the battery, 14) Delayed story recall (free and cued), and 15) semantic verbal memory.

This model discriminated 98% of HS and 87% of the patient groups considered as a whole. The means of canonical variables for the preceding analysis were −1.39 for HS and 1.60 for the patient group. Considering the three groups, the means of canonical variables (Table 3) indicate that the first root mainly discriminated HS (towards negative values) from the two groups of patients considered as a whole (towards positive values) while the second root mainly discriminated IL (towards negative values) from HS and non-IL patients considered as a whole (near the zero point). Tables 4 and 5 show the precision of the model.[1] Discriminant analysis indicated an accurate classification of cases of 98% for HS, 82% for IL patients, and 82% for non-IL patients ($N = 213$, Table 4).[2]

[1] When the indices involving errors and time (subtests 1 and 13 of the model) were multiplied by −1, results were exactly the same. As a consequence, all the subsequent analyses involving those tests were carried out with their recoded scores.

[2] Unfortunately, one patient of the IL group and one patient of the non-IL group refused to make the drawing required in the retrieval test of visual memory, thus producing two missing cases in the multivariate analysis. Those patients scored 0 and 1 points respectively in the recognition phase of this test, which evaluated the number of attempts required by the subject to recognize that item correctly among four possible options (range 0–3).

Table 2
Description of the known groups of patients.

Variable	Non-IL ($N=89$)				IL ($N=12$)				Statistical test
BDRS (from 4 to 28)	9.20 ± 3.56				9.46 ± 3.65				$F(1,99)=0.05$, $p<0.82$
GDS	14.82 ± 6.78				14.17 ± 6.16				$F(1,99)=0.10$, $p<0.75$
MMSE	21.15 ± 4.77				18.42 ± 4.76				$F(1,99)=3.47$, $p<0.06$
HIS*	6.43 ± 2.75				9.25 ± 3.65				$F(1, 99)=10.2$, $p<0.00$
Disease progression (months)	31.02 ± 48.99				16.50 ± 25.72				$F(1,99)=1.01$, $p<0.32$
Risk factors (0,1)	62		27		9		3		$\chi^2=0.14$; *df*: 1; $p<0.70$
Hypertension (0,1)	40		49		5		7		$\chi^2=0.05$; *df*: 1; $p<0.83$
Antihypertensive drugs (0,1)	44		45		6		6		$\chi^2=0.00$; *df*: 1; $p<0.97$
Degree of cooperation (1, 2, 3)	6	23	60	0	6	6			$\chi^2=3.45$; *df*: 2; $p<0.18$
Emotional state (−1, 0, 1)	14	70	5	1	10	1			$\chi^2=0.55$; *df*: 2; $p<0.76$
Disability awareness (0,1,2,3)	8	7	41	33	2	1	2	7	$\chi^2=3.98$; *df*: 3; $p<0.26$
Dysprosody (0,1)	76		13		11		1		$\chi^2=0.35$; *df*: 1; $p<0.55$
Perceptual disorders (0,1)	73		16		8		4		$\chi^2=1.57$; *df*: 1; $p<0.21$
Sleeping disorders (0,1)	38		51		4		8		$\chi^2=0.38$; *df*: 1; $p<0.54$
Language disorders (0,1)	45		44		6		6		$\chi^2=3.37$; *df*: 1; $p<0.06$
Anxiety (0,1)	54		35		6		6		$\chi^2=0.50$; *df*: 1; $p<0.48$
Irritability (0,1)	50		39		8		4		$\chi^2=0.47$; *df*: 1; $p<0.49$
Lack of sphincter control (0,1)	76		13		10		2		$\chi^2=0.35$; *df*: 1; $p<0.85$
Seizures (0,1)	87		2		11		1		$\chi^2=1.36$; *df*: 1; $p<0.24$
Behavioral disorders (0,1)	37		52		2		10		$\chi^2=2.77$; *df*: 1; $p<0.09$
Thought disturbances (0,1)	61		28		5		7		$\chi^2=3.37$; *df*: 1; $p<0.07$
Psychotropic drugs (number)	1.06 ± 0.89				0.66 ± 0.78				$F(1,99)=2.05$, $p<0.15$
Antipsychotics (0,1)	70		18		10		2		$\chi^2=0.09$; *df*: 1; $p<0.76$
Anxiolytics (0,1)	58		31		9		3		$\chi^2=0.46$; *df*: 1; $p<0.49$
Antidepressants (0,1)	72		17		10		2		$\chi^2=0.04$; *df*: 1; $p<0.84$
Hypnotics (0,1)	73		16		11		1		$\chi^2=0.70$; *df*: 1; $p<0.40$
Mood-stabilizing drugs (0,1)	86		3		12		0		$\chi^2=0.42$; *df*: 1; $p<0.52$
Anti-seizure drugs (0,1)	80		8		12		0		$\chi^2=1.19$; *df*: 1; $p<0.28$
Vitamins, nutriments (0,1)	64		25		9		3		$\chi^2=0.05$; *df*: 1; $p<0.82$
Anti-dementia drugs (0,1)	79		10		8		3		$\chi^2=2.22$; *df*: 1; $p<0.13$

χ^2: Chi square; *$p<0.002$ non-IL: patients without ischemic lesions; IL: patients with ischemic lesions; BDRS: Blessed dementia rating scale; GDS: Geriatric Depression Scale; MMSE: Mini Mental State.

Just for informative purposes, when the number of cases was randomly matched in the three samples, discriminant analysis indicated a correct classification of 100% for HS, 100% for non-IL patients, and 91% for IL patients (results not shown but available upon request).

This group of tests useful to discriminate both patients with cognitive impairment and patients with ischemic lesions (T_ISC) turned out to be internally consistent (Cronbach's alpha = 0.87). Therefore, the dependent variables were added to see the group differences through a unique parameter. The distributions of frequencies according to the common median for the three samples in the T_ISC− total score are shown in Table 6. This table shows a significant positive association between ischemic lesions and cognitive impairment ($\chi^2=44.29$; *df*: 2; $p<0.001$). By taking the common median as cut-off point and by considering that HS served as control for any patient group, T_ISC showed a specificity of 69%. Likewise, a sensitivity of 100%, 72% and 75% to detect respectively IL, non-IL, and pooled patients (likelihood ratios: 3.26, 2.33, and 2.43) was observed with this cut-off point.[3]

3.3. Complementary information

Independently of the ischemic lesions, i.e., by considering the two groups of patients as a whole ($N=99$), there was a significant correlation between the T_ISC and the MMSE ($r=0.52$) and the T_ISC and the BDRS ($r=-0.40$) but not between the T_ISC and the GDS ($r=0.04$). Besides, by recoding the MMSE and BDRS into their corresponding cut-off points (MMSE <24 (Folstein et al., 1975) and BDRS >9 (Blessed et al., 1968)), the T_ISC was significantly different between patients with dementia or patients without dementia according to those tests (MMSE: patients with dementia ($N=60$): 75.22 ± 40.41, patients without dementia ($N=39$): 115.32 ± 45.13, ($F(1, 97)=21.21$, $p<0.001$)); BDRS: patients with dementia ($N=37$): 68.70 ± 41.17, patients without dementia ($N=62$): 104.34 ± 44.59 ($F(1, 97)=15.65$, $p<0.001$). A poor but still significant correlation was observed between the T_ISC and the HIS ($r=-0.26$) and, in recoding the HIS into two categories (cut-off point <4), T_ISC was significantly different between patients with degenerative dementia, and patients with vascular or mixed dementia according to the HIS (HIS: vascular/mixed ($N=86$): 86.35 ± 44.83, degenerative ($N=13$): 121.92 ± 47.09, ($F(1, 97)=7.02$, $p<0.009$)). When the ANOVA was carried out with the three original HIS categories of interpretation (Hachinski et al., 1975), not all the comparisons produced significant differences (results not shown).

4. Discussion

Present results demonstrated that the cognitive tests selected in this study significantly discriminated HS from dementia patients and, within this category, IL from non-IL patients. By following this approach, it is possible to select a combination of neuropsychological tests which improve the method for diagnosing ischemic vs. nonischemic dementias in humans.

T_ISC turned out to be internally consistent and its cognitive tasks involved the functions of attention, comprehension, abstract thinking,

Table 3
Discriminant analysis: means of canonical variables.

	Root 1	Root 2
HS	−1.39	−0.02
Non-IL	1.57	0.28
IL	1.89	−2.04

HS: Healthy subjects; non-IL: patients without ischemic lesions; IL: patients with ischemic lesions.

[3] The number of IL cases was enough to reject the null hypothesis in all the main results of this study with at most an alpha error of 5% (two-sided). Besides, those results were consistent throughout different statistical analyses. That more cases only will increase the significance of present differences is assumed.

Table 4
Discriminant analysis: classification matrix.

Group	Correct	$p=0.53$	$p=0.41$	$p=0.05$
Rows: observed classifications; columns: predicted classifications				
HS: $N=114$	98.25	112	2	0
Non-IL: $N=88$	81.82	12	72	4
IL: $N=11$	81.82	0	2	9
Total: $N=213$	90.61	124	76	13

HS: Healthy subjects; non-IL: patients without ischemic lesions; IL: patients with ischemic lesions.

Table 6
Distribution of frequencies according to the common median for HS, non-IL and IL in the total T_ISC score.

Sample	Median ≤	Median >	Total
HS	35	79	114
Non-IL	63	25	88
IL	11	0	11
Total	109	104	213

χ^2: Chi square = 44.29; *df*: 2; $p<0.001$. (Overall median: 122). HS: healthy subjects; non-IL: patients without ischemic lesions; IL: patients with ischemic lesions T_ISC: tests useful to discriminate patients with ischemic lesions.

expression (most of the tasks), processing speed, as well as perceptual discrimination and verbal and visual memory. The multiplicity of cognitive functions affected is consistent with the concept of dementia.

The difference between ischemic and nonischemic dementia patients in the T_ISC was obtained even for similar levels of cognitive impairment in the BDRS and MMSE except for the MMSE attention item in which IL patients scored lower than non-IL ones. Considering that frontal lobes are related to the ability to efficiently pay attention and respond, and that most of the T_ISC cognitive tasks involved an expressive component, this neuropsychological pattern could indicate that IL patients had their frontal functions more affected than non-IL ones (Tullberg et al., 2004; Reed et al., 2004). Nevertheless, that was not the only component of the present comprehensive profile (Kearney-Schwartz et al., 2009; Jokinen et al., 2009). In any case, the nature of the tasks involved in the T_ISC is clearly different from the one explored in the MMSE, which is recognized as a valid measure for detecting and grading AD (McKhann et al., 1984; Perneczky et al., 2006).

The positive association between ischemic lesions and cognitive impairment demonstrated that these lesions represented an additional risk factor for dementia. However, brain atrophy and ischemic lesions were related to one another in this sample. Swartz et al. (2008), unlike us, identified by means of factor analysis three brain measure-independent factors in a sample whose patients were diagnosed as overlapped AD and VaD. These factors were brain atrophy, subcortical vascular disease, and thalamus and cortical–strategic infarcts and the three lesions were associated to memory functions. This last finding would be coincident with our results considering that the present neuropsychological pattern also included verbal and visual memory functions.

The average prevalence of cases diagnosed as ischemic dementia in the present sample of patients was similar to the average prevalence of VaD cases in the postmortem study of Beach et al. (2007) when their non-AD cases were excluded (VaD/VaD + AD = 30/245 = 0.12). It is worth noting that, in the sample of Beach et al. (2007), subjects with a co-existing neuropathology of VaD and AD were considered as VaD. Considering the "vascular hypothesis" of AD (Beach et al., 2007), the possibility that in the present work some non-IL patients may have suffered from dementia associated to atherosclerotic risk without evident *in vivo* brain indices of cerebrovascular disease at the moment of evaluation cannot be discarded. Independently of the ischemic lesions, a significant correlation was observed among the T_ISC, BDRS, MMSE, and even, to some extent, HIS indicating some common underlying domain among these four instruments. T_ISC was also useful to differentiate between degenerative dementia and vascular/mixed dementia according to the HIS.

In this study, the commonly quoted association between depression and ischemic lesions (Baskys & Hou, 2007; Hachinski et al., 1975) was not confirmed, as indicated by either the correlation between GDS and T_ISC or the difference between IL and non-IL patients in the GDS. Yet, we did observe an averaged mild depression in these two groups of patients according to the GDS (Linden et al., 2002; Palmer et al., 2007).

Finally, it is necessary to emphasize that the most accurate approach for a correct diagnosis of dementia imply the use of multiple tools, including not only neuropsychological assessment but also, electrophysiology (electroencephalography, event-related potentials), imaging and biomarkers. The model described in this work only attempted to be an example of the cognitive results that can be obtained when an explicit and complex methodology is used. Multivariate approaches may indeed improve the diagnosis of dementia because they involve a more realistic and comprehensive analysis of the patient's situation than simpler cognitive assessments such as MMSE, BDRS or GDS. By following the present perspective, other neuropsychological models could be developed and other tests and instruments could be proved.

Table 5
Discriminant analysis: summary.

$N=213$	Wilks' lambda	Partial lambda	*F*-remove (2194)	*p*-Level	Toler.	1-Toler. (*R*-sqr.)
No. of variables in the model: 17; grouping factor: HS–non-IL–IL Wilks' lambda: 0.245 approx. $F(34,388)=11.65$ $p<0.0000$						
Auditory attention	0.27	0.92	8.27	0.00	0.86	0.14
Repetition	0.26	0.96	4.10	0.02	0.65	0.35
Singing	0.26	0.94	5.65	0.00	0.73	0.27
Praxia	0.26	0.94	5.70	0.00	0.66	0.34
Abstraction	0.26	0.94	6.06	0.00	0.76	0.24
Written comprehension/ praxia	0.26	0.95	4.80	0.01	0.78	0.22
Verbal fluency	0.26	0.96	4.47	0.01	0.71	0.29
Reading expression	0.27	0.92	8.27	0.00	0.61	0.39
Reading comprehension	0.27	0.92	8.73	0.00	0.68	0.32
Postural imitation	0.25	0.97	2.75	0.07	0.55	0.45
Visual memory	0.25	0.99	1.11	0.33	0.65	0.35
Right stereognosia	0.25	0.97	2.52	0.08	0.86	0.14
Auditory agnosia	0.25	0.97	3.52	0.03	0.87	0.13
Administration time	0.29	0.84	18.42	0.00	0.87	0.13
Free story recall	0.26	0.94	6.58	0.00	0.73	0.27
Cued story recall	0.25	0.97	3.27	0.04	0.80	0.20
Naming	0.25	0.96	3.92	0.02	0.61	0.39

HS: Healthy subjects; non-IL: patients without ischemic lesions; IL: patients with ischemic lesions.

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Appendix A

Description of the tests selected by discriminant analysis[4].

Verbal auditory sustained attention: phonemic discrimination of the letter "A" (by tapping the desk) among a series of 60 letters said by the interviewer. Index selected: errors of omission (range: 0–18). 2) Repetition of words and sentences: reproduction of ten items with a

[4] The battery of "Tests Neuropsicologicos Abreviados y Adaptados para Hispanoparlantes" was created for research purposes. T_ISC is freely distributed.

difficult combination of letters, syllables or words either in their length, grammar, pronunciation or semantics; each item scored from 0 to 3 according to the number of attempts (out of 3) necessary to repeat the item correctly (3 = one attempt (range: 0–30)). 3) Singing: song retrieval in response to a verbal command ("sing *happy birthday*") and song— discrimination and reproduction in response to a simple and very well known song sung by the interviewer; each item scored from 0 to 3 (range 0–6) according to accuracy of reproduction. 4) Praxia in response to complex (spoken) verbal commands: execution of eight items scored from 0 to 3 according to the number of attempts required by the subject to perform the item correctly (range: 0–24). 5) Abstract ability for the interpretation of metaphoric verbal expressions (two items scored from 0 to 3 according to the quality of comprehension (range 0–6)). 6) Verbal written comprehension: Praxia in response to three complex (written) verbal commands each one scored from 0 to 3 according to the number of attempts required by the subject to perform the item correctly (range: 0–9). 7) Oral verbal fluency in one minute: phonemic word association, i.e., maximum number of words, which started with "F" (range 0–29). 8) Reading (a story): indices: oral expression (scored from 0 to 3 according to the ability to read) and comprehension/abstraction (scored from 0 to 3 according to the ability to understand the story meaning). 9) Postural imitation: (kinesthesia, allocentric left/right notion and motor coordination): six items: a) sequence: fist–chin–hand–chin–hand–head, one hand at a time; b) touching the fingers with the thumb, one hand at a time; c) "butterfly": interlaced thumbs with the palms toward the chest; d) fist-palm alternation using both hands; e) rhythmic sequence (3 beats with the right hand, 2 beats with the left hand successively repeated); and f) copy of graph sequences; each item scored from 0 to 3 (range: 0–18) according to reproduction accuracy. 10) Visual memory: indices: recognition of only one face among six possible options: scored from 0 to 3 according to the number of attempts necessary to recognize the previously seen target face. Retrieval (written response) of a complex figure (scored from 0 to 8 according to reproduction accuracy (number of elements and organization)). 11) Stereognosis: Index selected: right hand stereognosis: ability to recognize one common object by tactile-kinesthetic exploration, each hand scored from 0 to 3 according to the number of attempts required by the subject to recognize the item correctly.12) Comprehension of non-verbal sounds (pure auditory agnosia): ability to recognize two common noises (paper crunching, keys) each one scored from 0 to 3 according to the number of attempts required by the subject to recognize the item correctly (range: 0–6). 13) Time (in minutes) required to perform the abbreviated tests of the battery (range 35–102).14) Delayed story recall: indices: free or spontaneous recall of 25 passages, each one scored from 0 to 4 according to recall accuracy (range: 0–100), and cued or induced recall (interviewer's questions for only those passages which were not spontaneously remembered by the subject, each one scored from 0 to 1 (range: 0–25). 15) semantic verbal memory, i.e., naming by picture confrontation (number of correct names out of 60).

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