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Spanish Multicenter Normative Studies (NEURONORMA Project): Methods and Sample Characteristics

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Abstract

This paper describes the methods and sample characteristics of a series of Spanish normative studies (The NEURONORMA project). The primary objective of our research was to collect normative and psychometric information on a sample of people aged over 49 years. The normative information was based on a series of selected, but commonly used, neuropsychological tests covering attention, language, visuo-perceptual abilities, constructional tasks, memory, and executive functions. A sample of 356 community dwelling individuals was studied. Demographics, socio-cultural, and medical data were collected. Cognitive normality and a cognitive screening test were validated via informants. Norms were calculated for midpoint age groups. Effects of age, education, and sex were determined. The use of these norms should improve neuropsychological diagnostic accuracy in older Spanish subjects. These data may also be of considerable use for comparisons with other normative studies. Limitations of these normative data are also commented on.

Keywords: Age factors; Demography; Educational status; Normative data; Neuropsychological tests/standards; Reference values

Introduction

In clinical neuropsychology, normative data are necessary to relate the performance of a subject to a reference group (Lezak et al., 2004; Strauss et al., 2006). Cognitive performance is largely influenced by multiple factors, such as the effect of

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sociodemographic variables or the psychometric properties of neuropsychological tests, which are crucial in any clinical approach (Mitrushina et al., 2005). Moreover, cross-cultural issues are also essential in neuropsychological assessment, and normative data must stem from a pertinent population (see Neil, 2000; Weeks et al., 2007; Wong et al., 2000).

The need of normative data for neuropsychological tests is well recognized, particularly for older people, as this group is at an elevated risk of suffering from cognitive impairment (Kryscio et al., 2006). Indeed, neuropsychological information in pathologies related to aging, such as dementia, is a major issue in diagnosis (Sano, 2006).

In Spain, there is a lack of normative neuropsychological data that are valid and appropriate for elderly people (García de la Rocha & Olazarán, 2003), as a consequence, normative studies are needed (Artiola et al., 2000). In fact, some tests only have Spanish Latin-American norms (e.g., Token Test, Ardila et al, 1994), some have norms that are not adequate for the elderly (e.g., Boston Naming Test, Quiñones-Ubeda et al., 2004), and finally, many tests do not have published norms (e.g., Tower of London Test, or Free and Cued Selective Reminding test).

This paper describes the normative sample and general methodology of the NEURONORMA project (Multicenter study of the normalization and validation of neurocognitive and functional tools with genetic and neuroimaging correlation for the detection, diagnosis, and follow-up of cognitive deterioration in aging and dementia (NEURONORMA)). The project was designed to collect normative and psychometric information from a sample of people aged over 49 years with a series of selected, but commonly used, neuropsychological tests. Findings for the entire battery are reported in this issue in independent papers. The NEURONORMA project also includes subjects with Mild Cognitive Impairment and Alzheimer's Disease with the future purpose of developing diagnostic norms (see Manly & Echemendia, 2007; Sliwinski et al., 2003; Smith & Ivnik, 2003) and the definition of the neuropsychological profiles of these clinical pictures. In this project we followed the principal methodological aspects developed at Mayo Clinic with the common goal of obtaining normative data for older people on a variety of neuropsychological tests: Mayo's Older Americans Normative Studies (MOANS) (Ivnik et al., 1992a, b, c, 1996) and Mayo's Older African Americans Normative Studies (MOAANS) (Ferman et al., 2005; Lucas et al., 2005a, b, c, d).

Materials and Methods

Research Participants

The study was performed in nine services of neurology and units of neuropsychology in different Spanish regions: Andalusia (Seville), The Basque Country (Bilbao), Catalonia (Barcelona and Terrassa), Galicia (Santiago de Compostela), Madrid (Madrid), and Murcia (Murcia). An observational cross-sectional study was used in order to increase generalizability, reduce expense, and address a broad range of questions. Ethical approval for the study was granted by the Research Ethics Committee of the Municipal Institute of Medical Care of Barcelona, Spain, and from the different participating centers. The study was conducted in accordance with the Declaration of Helsinki (World Medical Association, 1977) and its subsequent amendments, and the European Union regulations concerning medical research.

Participants were recruited from a variety of sources such as: (i) spouses of patients evaluated at the participating centers; (ii) different senior citizen activity centers; and (iii) by word of mouth. The ethnic background of all participants was Caucasian, and all were living in Spain, and educated in Spanish regardless of the first (native) language [Castilian (Spanish), Catalan, Galician, or Basque] in the case of bilinguals. Bilingual here refers to a Spanish citizen that is a Spanish-speaker and also speaks a local official language of Spain (Catalan, Galician, or Basque). Baseline enrollment occurred in 2004–2007 from urban sources. All participants were required to have an informant who knew them well and could answer questions about their cognition, function, and health. The relationships of the informants to the participants were spouse or significant other, adult child, other family member, or friend. Participants received no financial reimbursement or any other compensation for their time and effort.

A total of 360 subjects were recruited and assessed, but four cases were excluded during the process of monitoring. The reasons for exclusion were the following: a case with a significant number of missing data, and three cases of violation of inclusion/exclusion criteria (a case with minor alcohol abuse, a case with depression, and a case with significant visual problems). Finally, a total sample of 356 subjects was studied.

Entry criteria included consecutive individuals according to the following inclusion and exclusion criteria:

Inclusion criteria: (a) signed informed consent; (b) subjects of both sexes aged over 49 years; (c) Spanish speakers with at least a minimal capacity in writing (correct writing regardless of orthographic errors due to low education); (d) community dwelling, and independent functioning measured with the Interview for Deterioration of Daily Living in Dementia (IDDD; Teunisse et al., 1991); (e) absence of cognitive impairment, measured by the MMSE (Folstein et al., 1975), adjusted for age and education. See *Diagnostic and Classification Tools* section subsequently.

Exclusion criteria: (a) personal history of central nervous disease possibly causing neuropsychological deficits (e.g., stroke, epilepsy, head injury, movement disorder, multiple sclerosis, brain tumor, severe head trauma); (b) a score of four or more on the Modified Ischemia Scale (Rosen, Terry, Fuld, Katzman, & Peck, 1980); (c) history of alcohol or other psychotropic substance abuse; (d) presence of active or uncontrolled systemic diseases associated with cognitive impairment (e.g., diabetes mellitus, hypothyroidism, B_{12} deficiency); (e) history of psychiatric diseases (e.g., major depression, bipolar mood disorder, psychosis); (f) presence of severe sensorial deficits (loss of vision and/or hearing) that might have impeded the administration of cognitive tests.

The following tools were used in the process of selection and classification of study participants:

- *Mini Mental State Examination* (MMSE) (Folstein et al., 1975). A validated Spanish version (Blesa et al., 2001) was administered. This version provides an adjustment of the scores according to age and education (adjusted range 0–32). The recommended adjusted cut-off in the validation study was 24 (Blesa et al., 2001).
- *Interview for Deterioration of Daily Living in Dementia* (IDDD) (Teunisse et al., 1991). A validated Spanish version (Böhm et al., 1998) was administered. This scale measures functional disability in self care (16 items) and complex activities (17 items). The range of the total score is 33–99 (self care range: 16–48, complex activities range: 17–51), and the recommended cut-off for dementia is 37.
- *Hamilton Depression Rating Scale* (HDRS) (Hamilton, 1960). This is a semi-structured interview to assess the severity of depression for clinical research. A 17-item Spanish version was used.
- *Modified ischemia score* (Rosen et al., 1980) was administered in order to assess cerebrovascular risk. A cut-off of 4 was considered appropriate.

As part of the general diagnostic and classification procedures, the following information was requested from all participants: (a) sociodemographic [e.g., age, education (years)]; (b) family antecedents (e.g., Alzheimer's Disease); (c) health habits (e.g., coffee consumption); (d) memory complaints; (e) anthropometric data (e.g., left/right handedness, weight); (f) ApoE $\varepsilon 4$ allele carriers (in a subsample); (g) medical antecedents (e.g., cardiovascular, metabolic/endocrine); (h) current drug treatments according to the American Hospital Formulary Service Pharmacologic-therapeutic classification.

Neuropsychological Measures

The neuropsychological protocol described subsequently was selected because the validity of these tests has been well established (see Ivnik et al., 1996; Lucas et al., 2005b; Mitrushina et al., 2005). All tests were administered and scored according to standardized procedures published in each test's manual. Tests included were the following: Verbal span (Digit Span forward and backward) Spanish version (Peña-Casanova, 2005); Visuospatial Span (Corsi's Test) from the WAIS-R-NI (Kaplan et al., 1991); Letter-Number Sequencing (WAIS-III) (Wechsler, 1997); Trail Making Test (Partington & Leiter, 1949; Reitan & Wolfson, 1993); Symbol Digit Modalities Test (Smith, 1973); Boston Naming Test (Kaplan et al., 2001; Quiñones-Ubeda et al., 2004); Token Test (De Renzi & Faglioni, 1978); Selected test of the Visual Object and Space Perception Battery (Herrera-Guzmán et al., 2004; Warrington & James, 1991); Judgment of Line Orientation (Benton et al., 1975, 1994); Rey-Osterrieth Complex Figure (Osterrieth, 1944; Rey, 1941); Free and Cued Selective Reminding Test (Buschke, 1973, 1984 [Copyright, 1996–2000. Albert Einstein College of Medicine of Yeshiva University. New York]); Verbal fluency (Ramier & Hécaen, 1970) including three semantic fluency tasks (animals, fruit and vegetables, and kitchen tools), three formal phonemic tasks (words beginning with p, m, and r), and three excluded letter fluency task (excluded a, e, and s) (Crawford, Wright, & Bate, 1995); Stroop Color-Word Interference Test (Golden, 1978; Stroop, 1935); Tower of London Drexel University version (Culbertson & Zillmer, 2001).

When needed, original tests in English were translated into Spanish within a sequence of forward and backward translations, as described in previous European multicenter studies (Erzigkeit et al., 2001; Verhey et al., 2003, 2004). First, three forward translations into Spanish were prepared by two researchers (J.P.C., Peter Böhm, or N.G.), and by a company of certified native translators (Celer-Pawlowsky SL, Traducciones, Madrid, Spain). The three forward translations were then reconciled into one forward version. In a next step, this forward version was translated backward into English by a translator native in English. Subsequently, the original English version was compared with the backward translation. Discrepancies were identified and considered in the preparation of an improved forward translation. This version was tested empirically for clarity and acceptability

of wording with four individuals who were native in Spanish. In the process called cognitive debriefing, all formulations found to be problematic were discussed and necessary changes worked in.

Procedures

In order to obtain harmonization across sites, careful steps were taken to standardize procedures, methods, and diagnostic criteria. All the onsite neuropsychologists were licensed as psychologists and highly experienced in neuropsychological test administration and diagnosis. The study neuropsychologists underwent training at the beginning of the project so that test administrations were completed in the same manner at each participating center. Two meetings were organized for discussion and harmonization of test procedures. A series of videotapes and cards with instructions were also created. Tests were administered and scored according to standard procedures described in test manuals.

Case Record Forms (CRF) were developed using an optical character recognition (OCR) software package (Teleform® Elite by Cardiff Software). Guidelines for CRF completion in accordance with the OCR software were provided to all study team members. The CRF also included general norms of the project and specific procedures for every test.

Subjects were studied in a two-step process. *The first step* (CRF-1, Day 1) consisted of the following parts: (a) informed consent, sociodemographic data, family antecedents, health habits, anthropometric data, medical antecedents (medical history), current drug treatments, and modified ischemia score; (b) clinical interview with the control/patient and an informant, physical and neurological examination; (c) neuropsychological, psychiatric, and functional assessment including the following tools: MMSE, IDDD, HDRS, and Ischemia Score; and finally, (d) diagnostic, and inclusion and exclusion criteria requirements were assessed.

The second step (CRF-2; Days 2 and 3) consisted of administration of the neuropsychological battery for the norming study. Two types of CRF were designed with different administration orders: A and B. All participants were tested individually in two interview sessions in consecutive days. The test battery took approximately 4 hr to complete.

No specific tests of visual and auditory acuity were performed, but results on the screening subtest (Shape Detection Screening) of the Visual Object and Space Battery (Warrington & James, 1991) were taken as a surrogate for sufficient visual acuity (Herrera-Guzmán et al., 2004).

Data Management and Statistical Analyses

Data management and statistics were carried out by the European Biometrics Institute (EBI) based in Barcelona, Spain. A series of procedures were established for collecting, entering, cleaning, and recoding data. All CRF and any queries that arose were monitored. All analyses were carried out by the EBI using SPSS 13.0, and SAS 8.2 for Windows.

Subjects were re-categorized into two groups (cut-off >65 years) in order to evaluate the effects of aging as well as memory complaints. This approach tries to reflect the theoretical differentiation of the Global Deterioration Scale (GDS; Reisberg et al., 1982): GDS-1 (normal adult) versus GDS-2 (normal-aged adult), regardless of reported subjective deficits.

Basic descriptive analyses included count, percentage of total, mean, standard deviation, confidence interval 95%, and range. Analyses that compared age groups were carried out by means of Student's *t*-test for continuous variables. For nominal and ordinal variables, comparisons between age groups $\chi 2$ test was applied, and Fisher's exact test when needed.

Considering that the ability to compare all co-normed test scores directly to each other facilitates clinical interpretation of neuropsychological test profiles, a uniform normative procedure was applied to all measures as in the MOANS studies (Ivnik et al., 1992a; Lucas et al., 2005d). The procedure was the following:

(a) *Maximization of the number of participants*. The overlapping interval strategy (Pauker, 1988) was adopted to maximize the number of participants contributing to the normative distribution at each mid-point age interval. Each mid-point age group provided norms for individuals of that age, plus or minus one year, except in cases below 57 years and participants of 80 years and over. The age range around each mid-point was 10 years, so that the mid-point of 58 had a range of all participants 53–63 years old, and so on. Age distribution of the sample made it possible to calculate norms for the following 10 mid-point age groups: 54–56, 57–59, 60–62, 63–65, 66–68, 69–71, 72–74, 75–77, 78–80, >80.

(b) *Definition of age, sex, and education effects*. Coefficients of correlation (r) and determination (r^2) of raw scores with age, sex, and years of education were determined for all tests (Lucas et al., 2005b, d).

(c) *Creation of age-adjusted normative tables*. To ensure a normal distribution, the frequency distribution of the raw scores was converted into age-adjusted scaled scores, NSS_A (Neuronorma Scaled Score-age adjusted), following the methodology described by Ivnik and colleagues (1992a). For each age range a cumulative frequency distribution

of the raw scores was generated. Raw scores were assigned percentile ranks in function of their place within the distribution. Subsequently, percentile ranks were converted to scaled scores (from 2 to 18) based on percentile ranges. This transformation of raw scores to NSS_A produced a normalized distribution ($M = 10$; $SD = 3$) on which linear regressions could be applied.

(d) *Education adjustments*. Years of education were modeled using the following equation:

$$NSS_A = k + (\beta * Educ) \quad (1)$$

The resulting equations were used to calculate age- and education-adjusted NEURONORMA scaled scores ($NSS_{A\&E}$) for each test. The regression coefficient (β) from this analysis was used as the basis for education adjustments. Following the MOANS projects, a standard linear regression (2) was employed to derive age- and education-adjusted scaled scores:

$$NSS_{A\&E} = NSS_A - (\beta * Educ) \quad (2)$$

Instead of formula (2) we decided to employ formula (3) outlined by Mungas and colleagues (1996).

$$NSS_{A\&E} = NSS_A - (\beta * [Educ - 12]) \quad (3)$$

The reason for this election was that formula (3) provided a better standard reference than formula (2), with a mean and a very similar standard deviation to the distribution of NSS_A. Following the method described by Mungas and colleagues (1996), the obtained NSS_A score was adjusted by the difference between the predicted scores based upon the subject's actual education and the predicted score given 12 years of education. The obtained value was truncated to the next lower integer (e.g., 10.75 would be truncated to 10). In the study of Mungas and colleagues (1996), the value of 12 years of education was arbitrary, but was selected because it provided a relatively standard reference point. In other studies (Guardia et al., 1997, 2005), 12 years of education were defined as a crucial cut-off for higher education.

Although the participants were told in advance of the length of the testing time, some were unable to complete the entire test battery. Few participants did not complete all measures.

Results

Table 1 summarizes the sample's demographic characteristics. Participants ranged in age from 50 to 90 years old. The sample included 40.4% men and 59.6% women; this represents a slight difference (5%) when compared with the estimated data of the National Statistics Institute (Madrid, Spain; www.ine.es/en/welcome_en.htm ([English pages] link: population by gender)) for participants aged over 49 years for 2006 (45.55% men, 54.44% women). The majority (82.3%) of study participants were married. Around 50% of participants reported having worked in blue collar jobs, and 35% in administrative or middle technical professions. Another 14% of participants reported as having worked in high technical professional specialties (e.g., lawyers, physicians).

First language (native language) was as it follows: Castilian (Spanish) 214 (60.1%), Catalan 114 (32.0%), Galician, 22 (6.17%), Basque 6 (1.68%). All participants were living in Spain and had been educated in Spanish.

In Tables 2–5, data are presented for the total sample and also re-categorized into two chronological age groups (younger [GDS-1] and older [GDS-2] participants, regardless of subjective complaints), otherwise it is impossible to describe the effect of supposed "normal" aging. Table 2 shows details on eligibility and classification criteria. Older participants had fewer years of formal education. The MMSE, although normal, was lower in older participants. Differences were not observed when the MMSE was adjusted for age and education. The IDDD showed all participants to be functionally normal. Depression and higher ischemia scores were exclusion criteria which were reflected by the mean scores of these variables.

Table 3 summarizes family antecedents, health habits, anthropometric, and Apo-E data. Differences were observed between younger and older participants for tobacco consumption (younger 20.8% vs. older 5.8%). Frequencies of $\varepsilon 4$ allele of ApoE were similar in younger and older participants. Memory complaints were around 50% in the whole sample, and significantly more frequent in older than in younger participants (55.2% vs. 41.4%, $p = .009$).

In Tables 4 and 5 medical antecedents and use of drugs are presented, respectively. Younger adults were healthier and took less medication than older adults. Age-related diseases are reflected in these tables. Hypertension (38.1%), hyperlipemia (30.8%), arrhythmia (7.3%), and diabetes (6.4%), plus smoking (13.48%) were the most frequent risk factors in the whole

Table 1. Socio-demographic characteristics

	Count	Percent of total
Sex		
Male	144	40.4
Female	212	59.6
Age (years)		
50–54	60	16.85
55–59	68	19.10
60–64	49	13.76
65–69	44	12.35
70–74	70	19.66
75–79	46	12.92
80+	19	5.33
Education (years)		
≤5	76	21.34
6–7	26	7.30
8–9	67	18.82
10–11	41	11.51
12–13	36	10.11
14–15	34	9.55
≥16	76	21.34
Professional/working class ($n = 341$)		
Unskilled blue collar	97	28.44
Skilled blue collar	75	21.99
Administrative	59	17.30
Middle technical professional	62	18.18
High technical professional	47	13.78
Marital status		
Single, never married	25	7.02
Married/de facto married	293	82.30
Divorced/separated	13	3.65
Widowed	25	7.02

sample. Older participants more frequently showed hypertension, cardiac insufficiency, ischemic cardiopathy, diabetes, hyperlipemia, cranial injury, glaucoma, cataracts, urinary incontinence, and arthrosis/arthritis. Personal antecedents of depression (21.6%) and anxiety (23%) were also reported (whole sample).

Finally, Table 6 shows the 10 resulting midpoints groups based on 356 participants.

Discussion

This study forms part of a comprehensive research, the NEURONORMA project, and was designed following the model of the MOANS projects. Methods included a series of standards for normative research outlined by Ivnik (2005). In the subsequent paragraphs we highlight that these standards were fulfilled.

The primary objective of this research was to obtain normative data. As a consequence, the norms did not rely on convenience samples for other purposes (e.g., control data collected as part of research projects). Tests included in the project cover the principal cognitive domains (see for example Lucas et al., 2005b).

The definition of a cognitively normal subject was established before the project began. The study applied strict inclusion and exclusion criteria. Spanish speakers who also spoke a local official language of Spain (Catalan, Galician, or Basque) were included. This fact reflects the socio-demographic reality of the country. Moreover, the characteristics of the sample concerning anthropometrics, concomitant diseases, use of drugs, vascular risk factors, etc., were clearly described. It is noteworthy that memory complaints were around 50% in the whole sample and did not constitute a theoretical criterion of differentiation of GDS1 vs. GDS2 as is frequently stated in the literature (Reisberg et al., 1982).

Cognitive normality was validated via informants (ADL scale) and a cognitive screening test (MMSE). Volunteers need not be completely medically healthy to participate (see Pedraza et al., 2005). Subjects with active, chronic medical, psychiatric, or neurological conditions or with physical disabilities were included if the researcher judged that the condition was correctly controlled or resolved and did not cause cognitive impairment. The same criterion was applied in the case of use of psychoactive medications. This broader definition of normality provided a more accurate representation of the normative population of interest

Table 2. Eligibility and classification criteria: total sample and divided into two age groups

	Total sample ($n = 356$)	50–65 years ($n = 182$)	>65 years ($n = 174$)	p-value
Male, n (%); Female, n (%)	144 (40.4); 213 (59.6)	60 (32.9); 123 (67.5)	84 (48.3); 90 (51.7)	.0029
Age (years)				
M (SD)	64.9 (9.3)	57.0 (4.2)	73.2 (4.8)	<.0001
CI 95% of M	(63.9; 65.9)	(56.4; 57.6)	(72.5; 74.0)	
Range	50–90	50.0–65.0	66.0–90.0	
Education (years)				
M (SD)	10.4 (5.4)	11.6 (5.4)	9.2 (5.2)	<.0001
CI 95% of M	(9.9; 11.1)	(10.9; 12.5)	(8.5; 10.0)	
Range	0–20	0–20	0–20	
MMSE				
M (SD)	28.7 (1.5)	29.0 (1.3)	28.5 (1.6)	.0017
CI 95% of M	(28.6; 28.9)	(28.8; 29.2)	(28.3; 28.8)	
Range	22–30	23–30	22–30	
MMSE adjusted (age, education)[a]				
M (SD)	29.1 (1.4)	29.1 (1.3)	29.2 (1.5)	n.s.
CI 95% of M	(29.0; 29.3)	(28.9; 29.3)	(29.0; 29.5)	
Range	24–32	24–31	24–32	
IDDD				
Basic activities, M (SD)	16 (0.0)	16.0 (0.0)	16.0 (0.1)	n.s
CI 95% of M	(16; 16)	-	(16.0; 16.01)	
Complex activities, M (SD)	17.1 (0.5)	17.1 (0.4)	17.3 (0.7)	.0026
CI 95% of M	(17.1; 17.2)	(17.0; 17.2)	(17.2; 17.4)	
Total, M (SD)	33.1 (0.6)	33.1 (0.4)	33.3 (0.8)	.0028
CI 95% of M	(33.0; 33.2)	(33.0; 33.2)	(33.2; 33.4)	
Hamilton DRS, M (SD)	2.1 (2.5)	2.0 (2.3)	2.3 (2.7)	n.s
CI 95% of M	(1.9; 2.4)	(1.7; 2.3)	(1.9; 2.8)	
Ischemia score, M (SD)	0.1 (0.3)	0.1 (0.3)	0.2 (0.4)	.0323
CI 95% of M	(0.1; 0.2)	(0; 0.2)	(0.1; 0.4)	
Range	0–1	0–1	0–1	

Notes: [a]MMSE-Adjusted range: 0–32 (see Blesa et al., 2001).
CI = confidence interval; SD = standard deviation; M = mean.

(Pedraza et al., 2005). Obviously, MMSE alone was not the criterion for normal cognition, a clinician was in charge of the final decision. Furthermore, all CRF were carefully reviewed by two psychologists (N.G.F., Sonia Gonzalez Morote) and a neurologist (J.P.C.).

When necessary, tests were translated and cross-culturally adapted following accepted standards.

Sample sizes were adequate and obtained from a multicenter project. The use of overlapping mid-point age intervals maximized data utility. The resulting groups varied in size from $n = 38$ for mid-point age 77+ to 136 for mid-point age 55. Group sizes determined by this method are sufficiently large to calculate percentile ranks and age-specific scaled scores (Lucas et al., 2005d).

Data transformations assured that raw scores were converted into scaled scores that were normally distributed. Linear transformation that adjusted for education was applied after raw scores were normalized into age groups.

Multiple cognitive and functional tests were normed at the same time (co-norming), enabling future research on the limits of normal, within-subject test score, variability (Ivnik, 2005). Co-norming has two main advantages: on the one hand, it gives the opportunity to establish norms for comparisons among different test scores, and, on the other hand, it permits the determination of the underlying factor structure of the series of tests administered together. A co-normed profile of tests could also be very helpful for valid differential diagnosis purposes. This approach allows the objective definition of identifiable and differentiable patterns of characteristic neuropsychological syndromes (see Zakzanis, Leach, & Kaplan, 1999).

This study has the intrinsic limitations of any normative study. Normative data are limited for use with patients whose demographic characteristics are similar to those of the normative sample and match the administration and scoring procedures of the test utilized (Mitrushina et al., 2005). Without empirical evidence, it is impossible to conclude that the norms can generalize to other Spanish-speaking populations. It is probable, however, that the data from this study could be used with caution to assess Spanish speakers from different countries. In a related study, a meta-analysis was performed using the means and standard deviations reported in published papers on semantic verbal fluency (SVF) in Spanish speakers (Ramirez et al., 2005; Ostrosky-Solís et al., 2007). The factors that influenced performance are educational level and age, more than the country of origin (Ramirez

Table 3. Family antecedents, health habits, anthropometric and ApoE data: Total sample and divided into two age groups

	Total sample ($n = 356$)	50–65 years ($n = 182$)	>65 years ($n = 174$)	p-value
Subjects with any family antecedent, n (%)[a]	141 (39.9)	88 (48.6)	53 (30.8)	.0006
Family antecedents				
Alzheimer's Disease, n (%)[b]	111 (31.3)	71 (39.2)	40 (23.0)	.0010
Parkinson's disease, n (%)[c]	25 (7.1)	19 (10.6)	6 (3.5)	.0091
Other dementing illnesses, n (%)[d]	17 (5.0)	8 (4.7)	9 (5.4)	n.s
Down Syndrome, n (%)[e]	2 (0.57)	1 (0.56)	1 (0.58)	n.s
Tobacco consumption, n (%)	48 (13.48)	38 (20.8)	10 (5.8)	.0001
Alcohol consumption, n (%)[f, g]	147 (41.3)	75 (41.0)	72 (41.6)	n.s
Less than a drink per day, n (%)	80 (54.4)	37 (49.3)	43 (59.7)	n.s
1–2 drinks day^{-1}, n (%)	60 (40.8)	35 (46.7)	25 (34.7)	n.s
More than 3 drinks day^{-1}, n (%)	5 (3.4)	2 (2.7)	3 (4.2)	n.s
Missing, n (%)	2 (1.4)	1 (1.3)	1 (1.4)	n.s
Memory complaints, n (%)[h]	170 (48.2)	75 (41.4)	95 (55.2)	.0095
Left handedness (from A-BT), n (%)	11.8 (6.8)	12.4 (7.8)	11.3 (6.1)	n.s
CI 95% of M	11.2; 12.4	11.3; 13.6	10.4; 12.3	
Cephalic perimeter, M (SD)	56.5 (3.5)	56.8 (4.4)	56.1 (2.2)	n.s
CI 95% of M	56.1; 56.9	56.2; 57.5	55.8; 56.5	
Weight (kg), M (SD)	72.2 (13.5)	73.4 (15.4)	71.0 (11.3)	n.s
CI 95% of M	70.8; 73.7	71.1; 75.7	69.3; 72.8	
Height (cm), M (SD)	162.9 (8.9)	163.5 (8.3)	162.4 (9.5)	n.s
CI 95% of M	162; 163.9	162.3; 164.7	160.9; 163.9	
BMI, M (SD)	27.0 (4.0)	27.2 (4.4)	26.9 (3.5)	n.s
CI 95% of M	26.6; 27.5	(26.6; 27.9)	(26.4; 27.4)	
Obesity (BMI > 30), n (%)[i]	66 (19.2)	38 (21.6)	28 (16.8)	n.s
ApoE ε4 sub-sample, n	147	70	77	
At least one ε4 allele of ApoE, n (%)	40 (27.21)	21 (30.0)	19 (24.7)	n.s

Notes: [a]Any family antecedent: total sample ($n = 353$); 50–65 years ($n = 181$); >65 years ($n = 172$).
[b]Alzheimer's disease: total sample ($n = 355$); 50–65 years ($n = 181$); >65 years ($n = 174$).
[c]Parkinson's disease: total sample ($n = 352$); 50–65 years ($n = 179$); >65 years ($n = 173$).
[d]Other dementing illnesses: total sample ($n = 339$); 50–65 years ($n = 172$); >65 years ($n = 167$).
[e]Down syndrome: total sample ($n = 351$); 50–65 years ($n = 178$); >65 years ($n = 173$).
[f]Alcohol consumption: total sample ($n = 356$); 50–65 years ($n = 183$); >65 years ($n = 173$).
[g]Drinks: total sample ($n = 147$); 50–65 years ($n = 75$); >65 years ($n = 72$).
[h]Memory complaints: total sample ($n = 353$); 50–65 years ($n = 181$); >65 years ($n = 172$).
[i]Obesity: $n = 343$.
BMI = body mass index; M = mean; CI = confidence interval; SD = standard deviation.

et al., 2005; Ostrosky-Solís et al., 2007). In other words: the SVF test yields similar data from one Spanish-speaking country to another, provided that the subjects' age and education are taken into account (Ramirez et al, 2005).

Despite the fact that the primary objective of the study was to obtain normative data, epidemiologic techniques of recruitment were not employed. A stratification table with nine cells corresponding to three age and educational groups was defined as a practical and economical alternative. Stratification started at age 50 which was a further limitation (Steinberg & Bieliauskas, 2005). Considering the Spanish demographical reality (younger adults are more educated than older adults), an asymmetrical sample was obtained due to the difficulty of recruiting young barely educated/illiterate subjects.

Normative studies are important, but self limited due to several reasons. With time every normative study eventually becomes outdated (Mitrushina et al., 2005). Factors such as cultural and social environment, educational opportunities, new technologies, genetics, diseases, etc., affect the skills tested, and new normative studies are needed (Ivnik, 2005; Manly, 2005). As a consequence, the data of the present study cannot be considered as an endpoint.

Conclusions and Future Development

The MOANS projects served as a benchmark to undertake this, in part similar, large-scale normative project. A previous Spanish project (Peña-Casanova et al., 1997) and other local studies provided normative and diagnostic information for an adequate selection and diagnosis of subjects for the present project. Despite limitations intrinsic to the use of a multicentric sample of community volunteers, this research represents the most comprehensive and largest normative study for a Spanish population on selected common neuropsychological tests covering major cognitive areas.

Table 4. Medical antecedents: total sample, and divided into two age groups

	Total sample ($n = 356$)	50–65 years ($n = 182$)	>65 years ($n = 174$)	p-value
Subjects with any disease, n (%)	320 (89.8)	153 (84.0)	167 (96.0)	.0001
Cardiovascular				
Hypertension	136 (38.1)	53 (29.0)	83 (47.7)	.0003
Cardiac insufficiency	8 (2.2)	0 (0.0)	8 (4.6)	.0029
Myocardial infarction	9 (2.5)	3 (1.6)	6 (3.4)	n.s
Ischemic cardiopathy	18 (5.0)	2 (1.1)	16 (9.2)	.0005
Arrhythmia	26 (7.3)	11 (6.0)	15 (8.6)	n.s
Peripheral vascular disease	23 (6.4)	9 (4.9)	14 (8.0)	n.s
Metabolic/endocrine				
Diabetes	23 (6.4)	6 (3.3)	17 (9.8)	.0125
Thyroid disease	10 (2.8)	7 (3.8)	3 (1.7)	n.s
Hyperlipemia	110 (30.8)	40 (21.9)	70 (40.2)	.0002
Gastrointestinal/hepatobiliary				
Gastric ulcer/gastritis	51 (14.3)	26 (14.2)	25 (14.4)	n.s
Cholelitiasis/cholecystectomy	18 (5.0)	6 (3.3)	12 (6.9)	n.s
Hepatic disease	17 (4.8)	6 (3.3)	11 (6.3)	n.s
Psychiatric/drug abuse				
Depression	77 (21.6)	44 (24.0)	33 (19.0)	n.s
Anxiety	82 (23.0)	51 (27.9)	31 (17.8)	n.s
Neurologic				
Transient ischemic attack[a]	8 (2.2)	4 (2.2)	4 (2.3)	n.s
Epilepsy	4 (1.1)	2 (1.1)	2 (2.3)	n.s
Cranial injury[b]	9 (2.5)	1 (0.5)	8 (4.6)	.0174
Headache	51 (14.3)	31 (16.9)	20 (11.5)	n.s
Ophtalmologic/otolaryngologic				
Glaucoma	10 (2.8)	0 (0.0)	10 (5.7)	.0006
Cataracts	52 (14.6)	0 (4.4)	44 (25.3)	<.0001
Renal/genitourinary				
Renal insufficiency	4 (1.1)	1 (0.5)	3 (1.7)	n.s
Urinary incontinence	18 (5.0)	2 (2.2)	14 (8.0)	.0114
Hematologic				
Anemia	19 (5.3)	10 (5.5)	9 (.2)	n.s
Respiratory				
Asthma	20 (5.6)	9 (4.9)	11 (6.3)	n.s
Chronic obstructive pulmonary disease	10 (2.8)	2 (1.1)	8 (4.6)	n.s
Musculoskeletal				
Arthrosis/arthritis	144 (40.3)	61 (33.3)	83 (47.7)	.0057
Neoplastic[c]				
Malignant	17 (4.8)	5 (2.7)	12 (6.9)	n.s
Benign (e.g., uterus leiomyoma, lipoma)	32 (9.0)	16 (8.7)	16 (9.2)	n.s

Notes: [a]Cases accepted by the center and by the monitoring committee of the study. No cognitive impairment, normal computed tomography or magnetic resonance imaging and ischemia score <4.
[b]With no/minor loss of consciousness and not affecting cognition.
[c]Brain tumors were excluded.

The NEURONORMA test battery, in combination with previous normative studies, constitutes a co-normed series of tests in the same reference sample. This group of normative studies has a significant advantage of allowing objective and valid comparisons among test scores across all tests administered (Ivnik, 2005; Ivnik et al., 1996). These studies should improve clinical work, diagnostic accuracy, differential diagnosis, prognostic predictions, treatment planning, public health studies, and clinical research (Ivnik, 2005).

Five lines for further research are obviously of paramount importance: (a) to study subjects below age 50, and to complete a current sample; (b) to study different kinds of patients (e.g., Parkinson disease, Lewy body dementia) in order to define a series of cognitive profiles that may help in differential diagnosis; (c) to enlarge the list of validated tests, considering the present study as a core test battery; (d) to specifically study the effect of bilingualism on cognitive performance (see Ostrosky-Solís et al., 2007); and (e) as normative studies are intrinsically self limited, to plan future projects to improve current data.

Table 5. Use of drugs: total sample and divided into two age groups

	Total sample ($n = 356$)	50–65 years ($n = 182$)	>65 years ($n = 174$)	p-value
Subjects taking any drug, n (%)	285 (79.8)	128 (69.9)	157 (90.2)	<.0001
Drugs by subject, n (*SD*)	2.0 (1.7)	1.4 (1.4)	2.5 (1.9)	<.0001
Hypotensive agents	119 (33.3)	42 (23.0)	77 (44.3)	<.0001
Cardiotonic and antiarrhythmic agents	21 (5.9)	5 (2.7)	16 (9.2)	.0095
Antithrombotic agents including plat-AI	45 (12.6)	9 (4.9)	36 (20.7)	<.0001
Antidiabetic agents	18 (5.0)	4 (2.2)	14 (8.0)	.0114
Antilipemic agents	66 (18.5)	21 (11.5)	45 (25.9)	.0005
Bronchodilators	12 (3.4)	6 (3.3)	6 (3.4)	n.s
Analgesics–antipyretics[a]	42 (11.8)	18 (9.8)	24 (13.8)	n.s
Corticosteroids	5 (1.4)	4 (2.2)	1 (0.6)	n.s
Antiulcer agents and acid suppressants	40 (11.2)	8 (4.4)	32 (18.4)	<.0001
Anxiolytics/sedatives	45 (12.6)	27 (14.8)	18 (10.3)	n.s
Antipsychotics	2 (0.6)	2 (1.1)	0 (0.0)	n.s
Antidepressants	48 (13.4)	22 (12.0)	26 (14.9)	n.s
Hypnotics	28 (7.8)	10 (5.5)	18 (10.3)	n.s
Anticonvulsants	3 (0.8)	2 (1.1)	1 (0.6)	n.s
Anti-Parkinsonian agents	0 (0.0)	0 (0.0)	0 (0.0)	—
Anticholinergic agents	0 (0.0)	0 (0.0)	0 (0.0)	—
CNS agents, others[b]	4 (1.1)	1 (0.5)	3 (1.7)	<.0001
Calcium channel-blocking agents[c]	9 (2.5)	2 (1.1)	7 (4.0)	n.s
Anticholinesterasics	0 (0.0)	0 (0.0)	0 (0.0)	n.s
Thyroid agents	10 (2.8)	7 (3.8)	3 (1.7)	n.s
Hormone replacement therapy	18 (5.0)	16 (8.7)	2 (1.1)	.0005
Other	124 (34.7)	48 (26.2)	76 (43.7)	.0005

Notes: A subject may use several drugs. plat-AI = platelet-aggregation inhibitors.
[a]Includes non-steroidal anti-inflammatory agents (NSAIDs).
[b]Mainly "Nootropics" (pyracetam, and others).
[c]Not as hypotensive agents.

Table 6. NEURONORMA midpoint groups (sample = 356 subjects)

Groups	Midpoint age	Age range for midpoint	Age range for norms	Sample size
1	55	50–56	50–60	136
2	58	57–59	53–63	131
3	61	60–62	56–66	123
4	64	63–65	59–69	105
5	67	66–68	62–72	118
6	70	69–71	65–75	124
7	73	72–74	68–78	123
8	76	75–77	71–81	97
9	79	78–80	74–84	62
10	81+	81+	77+ (77–90)	38

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Conflict of Interest

None declared.

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