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Cognitive performance following lacunar stroke in Spanish-speaking patients: Results from the SPS3 trial

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Abstract

Background—Cognitive impairment is frequent in lacunar stroke patients. The prevalence and pattern of among Spanish-speaking patients (SSP) are unknown and have not been compared across regions or to English-speaking patients (ESP).

Aims—To characterize cognitive impairment in SSP and compare to ESP.

Methods—The baseline neuropsychological test (NPT) performance and the prevalence of mild cognitive impairment (MCI), defined as a z score ≤ -1.5 on memory and/or non-memory tests, were evaluated in SSP in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial.

Results—Out of 3020 participants, 1,177 were SSP residing in Latin America (n=693), the US (n=121) and Spain (n=363). Low education (0-8 years) was frequent in SSP (49-57%). Latin American SSP had frequent post-stroke upper extremity motor impairment (83%). Compared to ESP, all SSP groups had smaller memory deficits and larger non-memory/motor deficits, with Latin American SSP showing the largest deficits (median z-score 0.6 to -1.3 for non-memory

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tests; −5.0 grooved pegboard; −0.4 to −0.7 memory tests). The prevalence of MCI was high and comparable to ESP in the US and Latin American SSP but not Spanish group: ESP=47%, Latin American SSP=51%, US SSP=40%, Spanish SSP=29%, with >50% characterized as non-amnesic in SSP groups. Older age (OR per 10-y =1.52, CI=1.35-1.71), lower education (OR 0-4-y=1.23, CI=0.90-1.67), being a Latin American resident (OR=1.31, CI=0.87-1.98), and post-stroke disability (OR Barthel Index<95=1.89, CI=1.43-2.50) were independently associated with MCI.

Conclusions—Mild cognitive impairment in SPS3 Spanish-speaking patients with recent lacunar stroke is highly prevalent but has a different pattern to that observed in English-speaking patients. A combination of socio-demographics, stroke biology, and stroke care may account for these differences.

Keywords

cognitive impairment; cognitive function; lacunar stroke; Spanish-speaking; Hispanic

Introduction

Lacunar strokes, are a common stroke subtype, accounting for more than 25% of all brain infarcts. Lacunar strokes are more prevalent in US minorities, particularly Hispanics, and have a higher stroke recurrence rate than non-Hispanic Whites¹⁻³. While the overall short-term outcome is better than for other stroke subtypes, lacunar strokes have an adverse impact on cognitive function and increase the long-term risk of cognitive decline and dementia⁴⁻⁶. In a cohort of English-speaking patients with lacunar stroke, we found that half met criteria for Mild Cognitive Impairment (MCI) with deficits largest on episodic memory and verbal fluency⁷. In addition a similar pattern of cognitive impairment was present in a systematic review of neuropsychological studies in lacunar stroke cohorts⁵.

Whether, the described lacunar-stroke-related cognitive impairment pattern generalize to non-North American non-English-speaking populations is unknown. To our knowledge, few data have been published to date on the cognitive outcomes associated with lacunar stroke in Spanish-speaking populations and none on Latin American and US populations specifically⁸.

The overall aim of this study was to describe the baseline cognitive function of the non-English-speaking participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial⁹. Our specific objective was to characterize the cognitive performance in Spanish-speaking participants residing in Latin America and the United States in relation to those of Spanish-speaking participants (SSP) residing in Spain and English-speaking participants (ESP) from North America⁷.

Methods

In this study we evaluated all SPS3 participants who reported a non-English language as their preferred language (spoken > 90%), or as the language spoken >50% of the time at home, with Spanish representing the vast majority. The SPS3 trial was a randomized, multicenter international trial conducted in 81 clinical sites in North America, Latin

America, and Spain to determine the optimal treatment to reduce stroke recurrence, cognitive decline, and major vascular events. The eligibility criteria for entry into the trial, published in detail elsewhere,⁹ were a symptomatic lacunar infarct confirmed by magnetic resonance imaging (the index stroke), and no evidence of cortical stroke, cardioembolic disease, or amenable carotid stenosis. Participants with dementia [age- and education-adjusted Mini Mental State Exam (MMSE) ¹⁰ 24] and those with severe disability due to stroke (modified Rankin scale = 4) ¹¹ were ineligible. Participants were randomized in a 2 x 2 factorial design to both an antiplatelet intervention and a level of blood pressure control. The SPS3 trial was approved by the institutional review boards of all participating centers, and all participants provided informed consent.

At study entry, 2 weeks to 6 months following the index stroke, all eligible participants underwent assessments of their functional abilities (Barthel Activities of Daily Living Index) ¹² and their cognition utilizing tests validated for use in their respective languages. The neuropsychological test (NPT) battery, listed in Supplemental Table 1, included a cognitive global instrument (the Cognitive Assessment Screening Instrument – CASI), and tests probing the domains of episodic memory (the California Verbal Learning test, CVLT), visuo-construction (WAIS III Block Design [BD]), perceptual speed (WAIS III Symbol Search [SS]), verbal fluency (Controlled Oral Word Association [COWA]), attention (WAIS III Digit Span [DS]), executive functioning (Clock Drawing to Command [CLOX]) and motor dexterity (Grooved Pegboard [GP]). Test versions in Spanish and respective validation studies are also listed in Supplemental Table 1 ¹³⁻²². Only the Grooved Pegboard test is administered separately for each hand. For all other tests, the “best” hand was used if the test required use of upper extremity. Administration of any test requiring vision was not done for patients with uncorrected visual impairment. The battery was administered by native local Spanish and French speakers who were SPS3-certified examiners. The certification process and ongoing quality control process have been described in detail elsewhere ⁷.

As in the evaluation of the ESP cohort, a classification into Not Cognitively Impaired (NCI) or Mild Cognitive Impairment (MCI) was performed on the basis of individual test scores, grouped empirically into domains on the basis of Principal Component Analysis (PCA). Impairment on any test was defined as a z score ≤ -1.5 . An NCI classification was assigned if no impairment was present in any cognitive domain. An MCI classification was assigned if there was impairment in at least one domain. MCI was further distinguished into mutually exclusive subtypes: amnesic (impairment in the memory domain), non-amnesic (impairment in a non-memory domain(s)), or multi-domain (impairment in the memory domain plus impairment in a non-memory domain(s)) ⁷.

Statistical methods included the conversion of raw NPT into z scores with reference to the best available normative data, adjusted when possible for relevant factors including age, education, and geographic region (Latin America, US, Spain). We evaluated test score distributions with the Kolmogorov-Smirnov test, and NPT performance abnormalities by comparing the test medians to 0 with the Wilcoxon signed rank test. Demographic and clinical characteristics were compared across SSP groups using chi-square tests, ANOVA, and Kruskal-Wallis tests as appropriate. To undertake classification into NCI and MCI, we

first performed PCA with varimax rotation on the z scores of all NPT tests with the exception of the CASI and the GP. Because all SSP groups had lower education levels than ESP, PCA was done separately for those with 0-8 years of education and those with education ≥ 9 years. We then undertook classification into MCI and its subtypes. Multivariable associations with MCI were evaluated with consecutive logistic regression models, first assessing the contribution of sociodemographic factors, then that of pre-stroke and stroke-related factors, and finally the contribution of pre-stroke and stroke-related factors combined. Statistical significance was accepted at the 0.01 level, and all tests were 2-sided. Statistical analyses were done using SPSS 20.0 and MedCalc 12.1.0.

Results

Of the 3,020 patients randomized into the SPS3 trial, 43% were non-English speaking participants, the majority Spanish-speaking and residing in Spain ($n=366$), Latin America including Peru ($n=186$), Ecuador ($n=171$), Mexico ($n=165$), Chile ($n=127$), Argentina ($n=45$), or in the US ($n=124$). Nearly all had NPT completed at study entry (1177/1184). A small number spoke French (4%) or another language (2%), and resided in the US or Canada (Fig. 1). The French-speaking group resembled the previously described North-American ESP cohort⁷ in terms of age, education, and cognitive characteristics. (Table 1) Stroke-related characteristics including stroke localization, clinical syndrome and extent of residual disability ($>85\%$ had a Barthel Index $\geq 95\%$, $>60\%$ Rankin rating of 0 or 1) were also similar to those found in the ESP (Table 1). The small group speaking other languages did not have the entire NPT battery completed. The French-speaking and group speaking other languages were not considered further in this analysis.

The SSP from Latin America and Spain were older (means 65 and 64 vs. 60 years; $p < 0.001$), and with more males (65% and 75% vs. 62%, $p < 0.001$) compared with the US SSP. Lower levels of education (0-8 years) were common ($\sim 50\%$) in all SSP groups (Table 1). Just 17% of SSP from Latin America were motor intact (defined as having no upper extremity weakness, sensory loss, or incoordination on neurological exam) following their qualifying stroke compared with 51% from Spain and 36% of US SSP ($p < 0.001$). They also showed more post-stroke disability by the mRankin ($p < 0.001$) and Barthel Index scales ($p < 0.001$) than other SSP. (Table 1)

There were NPT performance differences among SSP from different regions and between SSP and ESP (Table 2). In general, SSP showed smaller deficits on the CVLT measures, with median z scores ranging from -0.7 to -0.1 , and larger deficits on the GP (median z score range -5.7 to -2.6). Latin American SSP performed poorly on all non-memory tests, with large deficits ($z \leq -1$) on BD, SS, and Clox, even when only motor intact subjects were considered. US SSP showed similar deficits, with little or no advantage for motor intact subjects. Non-memory tests not requiring upper extremity function (i.e. COWA and DS) also showed large deficits (median z-score range -0.7 to -0.6) in Latin American SSP and US SSP. By contrast, SSP from Spain had deficits only on the COWA and Clox tests, again with little or no advantage for motor intact subjects. The pattern of lesser memory than non-memory impairment remained for all SSP, regardless of region, when only subjects with

education comparable to the ESP sample (9-12 years and any college) were considered (data not shown).

Because of the confound of education, with some but not all standardized scores adjusted for education, and ~50% of subjects with 0-8 years education among SSP from all regions, PCA was conducted separately for education groups (Supplementary Table 2). For those with ≥ 9 years education, the 3-factor solution was identical to that found for ESP, with an episodic memory, a perceptual/verbal processing, and an executive function factor. For those with 0-8 years of education, the analysis was conducted without the Clox score because of its strong association with sociodemographic and ethnic factors,^{23,24} and because the norms we used did not adjust adequately for these factors²⁴. For those with low education, we identified a 2-factor solution, with a memory and a non-memory factor. The PCA factor solutions were similar across SSP regions for both education groups (Supplemental Table 2).

Based on these results, for SSP with education ≥ 9 years we utilized the same MCI classification criteria as for the ESP: specifically we assigned amnesic MCI if $z \leq -1.5$ on at least two CVLT measures; non-amnesic MCI if $z \leq -1.5$ on 2 perceptual/verbal processing tests, and/or $z \leq -1.5$ on the executive function (Clox) test; and multi-domain MCI if criteria for both amnesic and non-amnesic were met. For SSP with education < 9 years, we excluded the Clox test from the criteria for non-amnesic MCI. With these criteria, 51% of Latin American, 40% of US SSP and 29% of SSP from Spain were classified as MCI (Table 3). Less than half of MCI among SSP had an amnesic impairment pattern compared with two-thirds in ESP. Irrespective of region, SSP with MCI showed a clear-cut impairment on the global cognitive tests (Table 3, CASI z -score, each region $p < 0.001$ and MMSE, each region $p < 0.05$). There were region-specific associations between MCI status, and demographic and stroke-related characteristics including age, sex, education, motor function, previous lacunar stroke, and Rankin score.

Among SSP, older age, lower education, and being a Latin American resident were independently associated with a higher likelihood of MCI (Table 4). None of the pre-stroke factors contributed additionally to a higher likelihood of MCI, and among stroke-related factors only Barthel Index < 95 did so independently. When pre-stroke and stroke-related factors were combined, only Barthel Index < 95 remained in the age-, education-, and region- adjusted model. Given the region-specific pattern of MCI correlates, we also looked at multivariable models of MCI for demographic, pre-stroke, and stroke-related factors for Latin America and Spain separately (the number of US SSP with MCI was too small compared to the number of variables). Among demographic factors, older age and lower education were associated with MCI in Latin American SSP but not Spanish SSP. No pre-stroke factor, including prior stroke, was associated with a higher likelihood of MCI in either region. Among stroke-related factors, Barthel Index < 95 was associated with a higher likelihood of MCI in Latin America, whereas Rankin > 0 was associated with MCI in Spain.

Discussion

In this well characterized cohort of MRI-defined patients with recent lacunar stroke, we evaluated the pattern, prevalence and determinants of cognitive impairment on

neuropsychological tests in the non-English speaking participants in the SPS3 trial, with a particular focus on the Spanish-speaking cohorts residing in Latin America, the US, and Spain. The SSP cohort differed from the North American ESP cohort on demographic characteristics (older age, lower education, preponderance of male sex). Within the SSP cohort, patients residing in Latin America had a greater proportion of stroke motor syndromes and a higher degree of post-stroke disability. All SSP cohorts, regardless of region of residence, had less impairment on memory measures and more impairment on perceptual and visuo-constructional measures. SSP cohorts differed on severity and prevalence of cognitive impairment, with about half of SSP from Latin America and the US but only 29% of SSP from Spain meeting criteria for MCI. For all SSP, as observed previously in the ESP cohort,⁷ post-stroke functional impairment was the only factor associated with MCI after adjustment for demographic factors.

The finding of proportionately lesser impairment of memory than non-memory functions in the SSP cohorts (in the case of the SSP from Spain, no impairment) contrasts with our own findings of prominent episodic memory impairments in the ESP cohort⁷ and with our systematic review of neuropsychological data on lacunar stroke in European and North American countries⁵. This difference may be related to sociodemographic and/or lacunar stroke differences, and cannot be conclusively evaluated in the absence of NPT data on normal and non-lacunar stroke SSP and ESP controls. From a sociodemographic standpoint, the SSP groups had markedly lower levels of formal schooling compared to the ESP group. Spanish, but not English, norms for the CVLT take into account education,²⁵ whereas this is not done in norms for either language for the WAIS-III (the source of the majority of non-memory tests). This might have placed the less educated SSP at a relative advantage on memory tests and a relative disadvantage on non-memory tests. However, the mean CVLT raw scores for the SSP were similar to those for the ESP, and the education-adjustment in the CVLT norms is modest: 7 vs. 9 words for a delayed-recall z-score=0 for a 60-y old SSP with education=0-4 years vs. 9-12 years. It is more likely that the cognitive impairment pattern in the SSP groups is related to the greater prevalence of post-stroke motor impairment. Only a small proportion of Latin American subjects were deemed motor intact, and fewer US SSP were motor intact relative to the ESP cohort. As well, these motor intact SSP had a poorer performance on the Grooved Pegboard compared to the ESP cohort. Performance of tests of visuo-construction and perceptual speed could have disproportionately suffered because of these motor limitations in the SSP. That the cohort of SSP from Spain had the highest proportion of motor intact individuals may at least partially explain the relatively low prevalence of MCI observed in that cohort.

The significant motor impairment observed in the Latin American and US SSP cohorts may be related to stroke education and care. Stroke studies from Latin American countries²⁶⁻²⁸ report that medical attention is received only by a small percentage of patients within three hours of symptoms onset and most not treated by neurologists²⁷. Disparities in stroke care among Hispanics in US have been also reported^{2,29,30}. These factors may have contributed to greater residual stroke disability in our Latin American SSP, and in turn shaped the balance of amnesic and non-amnesic impairments.

Our estimates of MCI prevalence in the Latin American (51%) and US SSP (40%) are consistent with the prevalence for our ESP cohort (47%), and even comparable to other published estimates on all-cause stroke populations, with different MCI criteria. The only Latin American study (Santiago, Chile) on cognitive impairment following stroke estimated its prevalence at 66% after 3 months³¹ and at ~40% when individuals with prior cognitive impairment were excluded. These numbers are very similar to those reported in Finland and Australia (62 and 53-58%)³²⁻³⁴ and suggest that the frequency of post-stroke cognitive impairment is similar across racial-ethnic and geographic groups. As for determinants of MCI, our findings for the SSP cohorts align well with those for our ESP cohort and findings from the Chilean study³¹. Post-stroke functional disability but none of the pre-stroke factors were associated with a higher likelihood of MCI. We failed to find an association between prior stroke and MCI, observed in the ESP cohort, though the SSP cohort was smaller⁷.

This analysis of the SPS3 trial is the first to investigate the impact of MRI-confirmed lacunar stroke on cognitive function in a large sample of SSP from different ethnic groups, including residents from 5 different Latin American countries, and to allow comparisons with a large sample of North American ESP, predominantly non-Hispanic Whites^{9,35}. Our estimates must be interpreted with some limitations in mind. First, the cohort was part of a randomized clinical trial; therefore it is likely that our SSP group does not represent the complete spectrum of lacunar strokes in their region of residence. However, the age and vascular risk profile of our cohort is similar to the other lacunar stroke series³⁶⁻³⁹. Second, different sets of normative data were utilized for different tests, with some but not others adjusting for education, an important confounder in the SSP cohorts. Third, our MCI classifications were based on psychometric criteria rather than on clinical assessment which would have informed on previous cognitive impairment. We therefore cannot unambiguously attribute all of our MCI cases to the qualifying lacunar stroke and recognize that a proportion may already have been cognitively impaired prior to the study. Fourthly, we acknowledge that our geographical SSP groupings are insufficiently granular and do not do justice to the racial-ethnic heterogeneity of the Latin American population. There may be stroke and cognitive features associated with specific Latin American countries or racial groups (e.g., mestizos) that we have missed in our coarse analysis. Finally, as with all neuropsychological testing in which a motor response is required, the exact influence that motor limitations had on our results is unknown.

In summary, our study has shown that half of the patients from Latin America and Hispanics from US have cognitive impairment following lacunar stroke. This prevalence is comparable to the ESP cohort. While language of testing is an imperfect surrogate, our findings suggest that racial-ethnic factors do not affect the extent of the impact of lacunar stroke on cognitive function. However, these factors, through a complex mix of sociodemographics and stroke biology, may modulate the expression of the impairment, with non-amnesic rather than amnesic features in SSP. Because Spanish is the second most spoken language world-wide, there is a clear need for a Spanish neuropsychological test battery for the assessment of stroke-related cognitive impairment, with development of culturally and demographically specific norms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Patient flow chart, with Spanish-speaking participant boxes *italicized*. Shaded box represents English-speaking group with results previously published ⁸

Demographic and clinical characteristics of Spanish-speaking SPS3 participants (shaded columns published previously⁷ or not further evaluated)

Table 1

	Latin America Spanish-speaking	US Spanish-speaking	Spain Spanish-speaking	US/Canada English-speaking	Canada French-speaking	US/Canada Other language	No baseline testing
n	693	121	363	1636	111	56	40
Age, mean (sd)	65 (11)	60 (10)	64 (11)	62 (11)	62 (10)	61 (9)	63 (13)
Male, %	65	62	75	59	68	73	68
Education, %							
0-4 yrs	25	25	21	2	4	9	5
5-8 yrs	32	28	28	5	20	11	18
9-12 yrs	29	28	49	40	43	38	43
Any college	15	19	3	53	33	43	35
Modified Rankin, %							
0	9	15	27	15	18	23	18
1	55	57	41	52	57	41	50
2	22	18	25	26	21	27	25
3	14	10	7	7	5	9	8
Barthel Index 95, %	64	78	84	85	91	86	88
MMSE, raw score, median (IQR)	28 (3)	28 (4)	29 (3)	29 (2)	29 (2)	28 (5)	28 (3)
MMSE, age and education adjusted, %							
25 th percentile	6	13	8	15	6	32	13
>25 th , <75 th	48	46	30	37	41	38	48
75 th percentile	47	41	62	48	52	30	40
Motor intact upper extremities, %	17	36	51	41	38	50	48
Clinical syndrome, %							
pure motor	43	26	28	30	24	39	38
pure sensory	5	11	11	12	11	5	5

	Latin America Spanish-speaking	US Spanish-speaking	Spain Spanish-speaking	US/Canada English-speaking	Canada French-speaking	US/Canada Other language	No baseline testing
sensorimotor	33	36	35	29	25	29	35
ataxic hemi-paresis	4	9	8	12	13	14	8
dysarthria, clumsy-hand syndrome	3	2	7	7	10	7	5
hemiballism	0.3	0	0.3	0.2	0	0	0
other	11	16	11	9	17	5	10
Location of qualifying lacunar stroke, %							
Anterior	55	51	57	49	54	46	65
Thalamic	15	21	21	26	23	23	20
Posterior	31	28	23	25	23	30	15
Lateralization of qualifying lacunar stroke, %							
Right anterior or thalamic	45	49	43	47	43	41	47
Left anterior or thalamic	55	51	57	53	57	60	53
Prior symptomatic S3, %	11	16	8	10	9	2	10
Time from qualifying stroke to testing, %							n/a
< 6 weeks	43	39	22	25	23	25	
6 weeks–3 mo	27	40	42	47	39	43	
> 3 mo	29	21	36	28	38	32	

All demographic and clinical characteristics were significantly different ($p < 0.001$) across Spanish-speaking groups (unshaded columns) with the exceptions of prior symptomatic S3 ($p = 0.05$), and location ($p=0.02$) and lateralization of qualifying S3 ($p=0.5$).

Table 2

Raw and z (standard) scores by available normative data (shaded columns published previously⁷)

Test	Latin America (n=693; motor intact n=118)		US Spanish-speaking (n=121; motor intact n=44)		Spain (n=363; motor intact n=184)		Normative data used	US/Canada (n=1633; motor intact n=661)
	Raw mean (SD), median	Z-score mean (SD), median	Raw mean (SD), median	Z-score mean (SD), median	Raw mean (SD), median	Z-score mean (SD), median		Z-score mean (SD), median
CASI								
All patients	78 (14), 81	-0.6 (1.3), -0.4	81 (11), 83	-0.3 (1.0), -0.2	83 (11), 85	-0.1 (1.0), 0.06	Norms for older US Hispanics [mean (sd) age 72(7) y, mean education 8(5) y] ¹⁴	-0.70 (1.6), -0.34
Motor-intact patients	84 (12), 86	-0.1 (1.1), 0.1	81 (10), 82	-0.3 (0.9), -0.2	85 (9), 85	0.01 (0.8), 0.1		-0.45 (1.4), -0.12
CVLT							Norms by age, education, and region including Mexico/Southern United States, and Spain. ²⁵	
All patients								
Short-delay free recall	7.0 (3.6), 7	-0.7 (1.1), -0.7	7.3 (3.7), 8	-0.7 (1.1), -0.6	7.8 (3.4), 8	-0.5 (1.1), -0.4		-0.92 (1.4), -1.0
Short-delay cued recall	8.8 (3.6), 9	-0.5 (1.1), -0.5	9.2 (3.7), 10	-0.4 (1.2), -0.5	9.7 (3.2), 10	-0.2 (1.1), -0.2		-0.83 (1.3), -1.0
Long-delay free recall	7.1 (4.0), 7	-0.4 (1.0), -0.4	7.6 (3.8), 7	-0.4 (1.0), -0.4	8.4 (3.7), 9	-0.05 (1.0), -0.1		-0.83 (1.3), -1.0
Long-delay cued recall	8.7 (3.6), 9	-0.3 (0.9), -0.3	8.9 (3.5), 9	-0.4 (0.9), -0.3	9.8 (3.3), 10	-0.01 (0.9), -0.05		-0.85 (1.4), -1.0
Discriminability	82 (10), 82	-0.3 (0.7), -0.4	83 (11), 84	-0.4 (0.7), -0.4	84 (9), 84	-0.3 (0.7), -0.3		-0.65 (1.2), 0.0
Motor intact patients								
Short-delay free recall	7.8 (3.4), 8	-0.5 (1.0), -0.4	8.0 (3.0), 8.0	-0.5 (0.9), -0.5	8.0 (3.4), 8	-0.4 (1.1), -0.4		-0.82 (1.4), -1.0
Short-delay cued recall	9.5 (3.5), 10	-0.3 (1.1), -0.2	9.7 (3.3), 10	-0.3 (1.2), -0.3	9.9 (3.2), 10	-0.1 (1.1), -0.2		-0.74 (1.3), -1.0
Long-delay free recall	7.8 (4.0), 8	-0.3 (1.0), -0.4	7.8 (3.6), 8.0	-0.4 (0.9), -0.4	8.9 (3.6), 9	0.1 (1.0), 0.0		-0.78 (1.3), -1.0
Long-delay cued recall	9.5 (3.5), 9.5	-0.2 (0.9), -0.2	9.1 (3.1), 9.0	-0.3 (0.8), -0.3	10.1 (3.3), 10	0.1 (1.0), 0.1		-0.78 (1.3), -1.0
Discriminability	84 (9), 86	-0.3 (0.6), -0.3	84 (8), 84	-0.3 (0.7), -0.4	85 (8), 86	-0.1 (0.7), -0.2		-0.59 (1.2), 0.0
Block Design							Raw scores converted to scaled scores then z scores by geographic region: Spain, Mexico ^{20, 21}	
All patients	19 (11), 16	-1.1 (1.2), -1.3	20 (9), 20	-0.9 (0.9), -0.7	24 (11), 24	-0.03 (1.0), 0.0		-0.37 (1.1), -0.33
Motor-intact patients	22 (11), 20	-0.9 (1.2), -1.0	21 (9), 20	-0.9 (0.9), -0.7	24 (12), 24	0.00 (1.0), 0.0		-0.18 (1.1), -0.33
Symbol Search							Raw scores converted to scaled scores then z scores by geographic region: Spain, Mexico ^{20, 21}	
All patients	12 (8), 10	-1.2 (1.0), -1.3	14 (8), 14	-0.9 (0.9), -1.0	15 (8), 14	-0.3 (0.9), -0.3		-0.53 (1.0), -0.33
Motor-intact patients	14 (8), 13.5	-1.0 (1.1), -1.0	14 (8), 14	-0.9 (1.0), -0.7	16 (8), 15	-0.3 (0.9), -0.3		-0.31 (1.0), -0.33

Test	Latin America (n=693; motor intact n=118)		US Spanish-speaking (n=121; motor intact n=44)		Spain (n=363; motor intact n=184)		Normative data used	US/Canada (n=1633; motor intact n=661)
	Raw mean (SD), median	Z-score mean (SD), median	Raw mean (SD), median	Z-score mean (SD), median	Raw mean (SD), median	Z-score mean (SD), median		Z-score mean (SD), median
Grooved Pegboard								
All patients							Norms for age 16-70 y by sex ¹⁷	
Dominant time	172 (86), 141	-8.7(8.4), -5.7	149 (75), 126	-6.8 (7.0), -4.4	138 (69), 112	-5.5 (6.4), -3.1		-4.9 (6.7), -2.5
Non-dominant time	180 (84), 150	-7.1 (6.4), -5.0	159 (79), 130	-5.8 (6.2), -3.6	151 (73), 122	-4.8 (5.4), -2.6		-4.6 (5.8), -2.5
Motor intact patients								
Dominant time	127 (65), 105	-4.6 (6.2), -2.4	129 (60), 109	-5.0 (5.5), -3.8	128 (62), 105	-4.6 (5.8), -2.5		-2.9 (4.4), -1.6
Non-dominant time	134 (60), 115	-3.8 (4.8), -2.3	146 (76), 121	-4.7 (5.2), -3.3	136 (64), 109	-3.8 (4.7), -1.9		-3.0 (4.2), -1.6
COWA								
All patients	23 (13), 22	-0.6 (0.9), -0.6	23 (11), 22	-0.7 (0.9), -0.7	24 (13), 22	-0.5 (0.9), -0.6	Norms by age, education, and geographic by region: Mexico/Southern US, and Spain ²⁵	-0.89 (1.0), -0.96
Motor intact patients	28 (14), 27	-0.4 (0.9), -0.5	24 (11), 25	-0.7 (0.9), -0.7	26 (13), 24	-0.4 (1.0), -0.6		-0.76 (1.0), -0.79
Digit Span								
All patients	10 (3), 9	-0.5 (0.9), -0.7	10 (2), 10	-0.7 (0.7), -0.7	11 (3), 11	0.05 (0.9), 0.0	Raw scores converted to scaled scores then z scores by geographic region: Spain, Mexico ^{20,21}	-0.27 (1.2), -0.42
Motor intact patients	11 (3), 11	-0.3 (0.8), -0.3	10 (3), 10	-0.6 (0.7), -0.7	11 (3), 11	0.06 (0.9), 0.0		-0.18 (0.89), -0.33
Clox								
All patients	9.2 (3.5), 10	-1.8 (2.0), -1.3	10.3 (3.1), 11	-1.3 (1.7), -0.8	9.8 (3.0), 10	-1.5 (1.7), -1.3	Norms by age for US Hispanic sample [mean (sd) age 52(8) y, mean (sd) education 9(4) y ²⁴	-0.64 (1.2), -0.42
Motor intact patients	10.3 (3.0), 11	-1.2 (1.7), -0.8	9.9 (2.6), 10	-1.5 (1.5), -1.3	10.2 (2.7), 11	-1.3 (1.5), -1.1		-0.56 (1.2), -0.13

Raw scores (mean (SD), median) are *italicized* if distribution of raw scores is not normally distributed (K-S, $p < 0.05$). Z-score mean (SD) is *italicized* if distribution of z-scores is not normally distributed (K-S $p < 0.05$). Z-score median is **bolded** if median is significantly different from 0 (Wilcoxon signed rank test, $p < 0.05$).

Table 3

Characteristics of subjects by neuropsychological status and region

	Latin America Spanish-speaking	US Spanish-speaking	Spain Spanish-speaking	US/Canada English-speaking
n with adequate tests	690	117	357	1621
Total MCI, %	51	40	29	47
MCI subtype, %				
Amnestic	8	11	10	17
Multi-domain	13	10	4	17
Non-amnestic	29	19	15	13
% with MCI by group:				
Education 9+ y only	44	33	39	45
UE motor intact only	44	46	26	42
Rankin 0-1 only	48	42	24	41
Barthel Index 95	44	39	27	45

	Latin America Spanish-speaking		US Spanish-speaking		Spain Spanish-speaking		US/Canada English-speaking	
	NCI n = 341	MCI n = 349	NCI n = 70	MCI n = 47	NCI n = 253	MCI n = 104	NCI n = 866	MCI n = 755
UE motor intact, %	19	15	31	40	54	46	44	36
Age, mean, SD	61 (9)	69 (11)	59 (9)	63 (11)	65(11)	64 (11)	62 (10)	61 (11)
Male, %	67	63	64	62	72	81	56	61
Education, %								
0-4 y	16	33	19	36	24	13	1	3
5-8 y	34	29	30	26	32	17	3	7
9-12 y	33	24	34	15	42	63	33	43
Any college	16	14	17	23	2	6	63	47
Medical history, %								
Diabetes	39	37	60	51	36	37	32	40
Hypertension	78	74	76	87	58	62	77	80
Ischemic heart disease	4	5	4	9	4	6	15	14
Stroke	10	13	16	15	8	9	8	12
TIA	4	3	3	6	5	10	5	7
Time from qualifying lacunar stroke to test, %								
< 6 weeks	40	47	40	34	20	24	24	27
6 weeks to 3 months	29	25	41	40	40	46	46	48

	Latin America Spanish-speaking		US Spanish-speaking		Spain Spanish-speaking		US/Canada English-speaking	
	NCI n = 341	MCI n = 349	NCI n = 70	MCI n = 47	NCI n = 253	MCI n = 104	NCI n = 866	MCI n = 755
> 3 months	31	28	19	26	40	30	30	26
Location of lacunar stroke, %								
Anterior	54	56	49	51	56	54	49	49
Thalamic	31	15	21	21	22	18	27	25
Posterior	15	30	30	28	21	27	23	26
Lateralization of lacunar stroke, %								
Right ant/thalamic	50	41	53	59	46	33	50	43
Left ant/thalamic	50	59	47	41	54	67	50	57
Modified Rankin, %								
0	11	8	14	17	31	18	18	11
1	56	54	56	57	43	39	55	48
2	21	23	20	15	22	32	22	31
3	12	15	10	11	4	11	5	10
Barthel Index 95, %	72	56	79	75	88	78	87	82
CASI z-score, mean (SD)	-0.03 (0.9)	-1.2 (1.3)	0.01 (0.8)	-0.8 (1.1)	0.06 (0.8)	-0.5 (1.2)	-0.03 (1.0)	-1.4 (1.8)
MMSE raw score, median, IQR	29 (3)	27 (5)	28 (3)	27 (5)	29 (3)	28 (4)	30 (2)	28 (3)
MMSE, age and education adjusted, %								
25 th percentile	4	5	10	17	6	13	8	22
>25 th , <75 th	41	54	46	51	28	36	22	44
75 th percentile	55	39	44	32	67	51	60	34

UE=upper extremity; TIA=transient ischemic attack; CASI=Cognitive Abilities Screening Instrument; MMSE=Modified Mini Mental Status Exam; IQR=interquartile range

Table 4

Multivariate models of neuropsychological status for all Spanish-speaking participants

	Odds ratio (95% CI)	
	Full Model	Final Model
Model 1: Demographic factors		
Age, per 10 yr increase	1.55 (1.37, 1.75)	1.52 (1.35, 1.71)
Male sex	1.18 (0.90, 1.54)	*
Education		
0-4 yr	1.27 (0.93, 1.74)	1.23 (0.90, 1.67)
5-8 yr	0.74 (0.55, 0.99)	0.73 (0.54, 0.97)
9-12 yr + any college	Reference group	Reference group
Time from qualifying lacunar stroke to testing		
< 6 weeks	reference group	*
6 weeks - 3 mo	0.78 (0.58, 1.05)	
> 3 mo	0.77 (0.57, 1.04)	
Region		
US/Canada	reference group	Reference group
Latin America	1.29 (0.85, 1.95)	1.31 (0.87, 1.98)
Spain	0.52 (0.33, 0.82)	0.51 (0.32, 0.79)
Model 2, Pre-stroke factors[^]		
Diabetes	0.90 (0.70, 1.16)	*
Hypertension	0.87 (0.66, 1.15)	*
Ischemic Heart disease	1.19 (0.67, 2.13)	*
Prior S3	1.24 (0.84, 1.83)	*
Model 3, Stroke-related factors[^]		
Location of infarct		*
anterior	Reference group	
thalamic	0.97 (0.69, 1.36)	
posterior	0.89 (0.67, 1.19)	
Lateralization of infarct [#]		*
left	Reference group	
right	0.67 (0.50, 0.90)	
UE motor or sensory loss or incoordination	0.90 (0.63, 1.29)	*
Barthel Index < 95	1.89 (1.41, 2.53)	1.89 (1.43, 2.50)
Rankin Score > 0	1.32 (0.85, 2.06)	*
Model 4: Pre-stroke and Stroke-related factors[^]		

	Odds ratio (95% CI)	
	Full Model	Final Model
Diabetes	0.83 (0.64, 1.08)	*
Hypertension	0.83 (0.63, 1.11)	*
Ischemic Heart disease	1.15 (0.64, 2.08)	*
Stroke	1.26 (0.84, 1.88)	*
Location of infarct		*
anterior	Reference group	
thalamic	0.99 (0.70, 1.39)	
posterior	0.92 (0.69, 1.23)	
Lateralization of infarct [#]		*
left	Reference group	
right	0.67 (0.50, 0.91)	
UE motor or sensory loss or incoordination	1.12 (0.80, 1.57)	*
Barthel Index < 95	1.96 (1.46, 2.63)	1.89 (1.43, 2.50)
Rankin Score > 0	1.34 (0.86, 2.09)	*

* not significant in model, i.e. $p > 0.01$

[#] OR for right vs. left in subgroup of patients with anterior or thalamic lesion

[^] adjusted for demographic variables in final model 1