Cuadernos de Neuropsicología / Panamerican Journal of Neuropsychology
2022, Vol. 16 Nº 2 14 - 27

ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

ASSESSMENT OF COGNITIVE IMPAIRMENT IN LOW-RESOURCES CONTEXTS (THE VENEZUELAN EXAMPLE): ARE THE MINI-MENTAL STATUS EXAMINATION AND THE CLOCK DRAWING TEST USEFUL?

Evaluación del deterioro cognitivo en contextos de bajos recursos (el ejemplo Venezolano): ¿Son útiles el MMSE y el test del dibujo del reloj?

Avaliação do comprometimento cognitivo em contextos de poucos recursos (o exemplo venezuelano): o miniexame do estado mental e o teste do desenho do relógio são úteis?

RECIBIDO: 18 octubre 2021 ***ACEPTADO: 08 junio 2022***

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Palabras clave: evaluación, diagnóstico, cribado, validez, déficit cognitivo.

Keywords: assessment, diagnosis, screening, validity, cognitive deficit.

Palavras-chave: avaliação, diagnóstico, triagem, validade, déficit cognitivo.

A B S T R A C T

This retrospective study aimed to explore the diagnostic validity of the Mini-Mental Status Examination and the Clock Drawing Test, and a composite score of both tests while controlling for age and years of education in a Venezuelan sample, in order to determine if these tools are capable of discriminating different types of cognitive complaints. The sample included healthy controls (n=456), patients diagnosed with Alzheimer's disease (n=28), mild cognitive impairment (n=50), depression (n=30), and patients with a subjective cognitive complaint which was not corroborated by clinical and psychometric assessment (n=29). The General Linear Model and logistic regressions revealed that these tests have a moderate degree of sensitivity when discriminating between the control and Alzheimer's Disease mild groups while controlling for age and years of education, but do not assist with the differential diagnosis with the other clinical groups. The predictive validity of both tests used together is comparable to the one observed when the tests are used separately.

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ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

R E S U M E N

Este estudio retrospectivo tuvo como objetivo explorar la validez diagnóstica del MMSE y el Test del Dibujo del Reloj, y una puntuación compuesta de ambas pruebas controlando por edad y años de educación en una muestra de la población venezolana, con el fin de determinar si son capaces de discriminar diferentes tipos de quejas cognitivas. La muestra incluyó controles sanos (n=456), pacientes con diagnóstico de enfermedad de Alzheimer (n=28), deterioro cognitivo leve (n=50), depresión (n=30) y pacientes con una queja cognitiva subjetiva que no fue corroborada por evaluación clínica y psicométrica (n=29). El modelo lineal general y las regresiones logísticas revelaron que estas pruebas tienen un grado moderado de sensibilidad al discriminar entre el grupo control y el de enfermedad de Alzheimer leve mientras se controla por edad y años de educación, pero no ayudan con el diagnóstico diferencial entre los otros grupos clínicos. La validez predictiva de ambas pruebas usadas juntas es comparable a la que se observa cuando las pruebas se usan por separado.

R E S U M O

Este estudo retrospectivo teve como objetivo explorar a validade diagnóstica do Mini-Exame do Estado Mental e do Teste do Desenho do Relógio, e uma pontuação composta de ambos os testes, controlando idade e anos de escolaridade em uma amostra da população venezuelana, a fim de determinar se são capazes de discriminar diferentes tipos de queixas cognitivas. A amostra incluiu controles saudáveis (n=456), pacientes com diagnóstico de doença de Alzheimer (n=28), déficit cognitivo leve (n=50), depressão (n=30) e pacientes com queixa cognitiva subjetiva não fundamentada por avaliação clínica e psicométrica (n=29). O modelo linear geral e as regressões logísticas revelaram que esses testes têm um grau moderado de sensibilidade na discriminação entre os grupos controle e da doença de Alzheimer leve, controlando por idade e anos de escolaridade, mas não são úteis no diagnóstico diferencial entre os demais grupos clínicos. A validade preditiva de ambos os testes usados em conjunto é comparável àquela observada quando os testes são usados separadamente.

Introduction

Clinicians working in under-resourced state-provided health settings need to conduct inexpensive and fast assessments that are able to support the diagnostic processes of patients from diverse socioeconomic and educational backgrounds. The lack of resources (human and material) that often characterize countries with great levels of inequality (Coetzer & Balchin, 2014), such as Venezuela, often do not allow for specialized neuropsychological assessment, so the clinician (psychiatrist or psychologist) must select tools that are economical, quick and easy to administer, and that have optimal levels of specificity and sensitivity. The Mini Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Clock Drawing Test (CDT) (Freedman, Leach, Kaplan, Shulman, & Delis, 1994) are widely used because they are both easily administered and scored, involve short administration times, require few materials, and are non-threatening to the patient (Schramm et al., 2002). These tests are considered sensitive tools to identify cognitive decline linked to a diverse range of pathologies (Nieuwenhuis-Mark, 2010), but the general discrimination capacity of neuropsychological tests in Venezuela has been challenged (Campagna, 2015a) and highlighting the imperative of incorporating age and educational attainment as moderating factors of performance (Lam et al., 2013).

Specifically, studies indicate that the MMSE has good capacity to identify cognitive impairment, particularly when screening for dementia in diverse populations (Ansari, Naghdi, Hasson, Valizadeh, & Jalaie, 2010; Ng, Niti, Chiam, & Kua, 2007). Nevertheless, specific limitations, such as inadequate capacity for differential diagnosis and cultural variability of norms and cut-off points have been noted (Nieuwenhuis-Mark, 2010). Similarly, the CDT has been considered as an effective neuropsychological screening (Shulman, 2000) with good diagnostic validity for mild cognitive impairment (Yamamoto et al., 2004) and dementia (Jitapunkul, Worakul, & Kiatprakoth, 2000) in diverse populations.

Although the MMSE examines different cognitive functions, it has been characterized as placing more emphasis on language (Nieuwenhuis-Mark, 2010), having easy memory items with low diagnostic power and poor assessment of the visual-spatial function (Brown, Pengas, Dawson, Brown, & Clatworthy, 2009). Hence, the MMSE has a bias towards temporoparietal functions (Brown et al., 2009) and pre-frontal functions (Brodaty & Moore, 1997). The CDT has been used to assess mostly parietal functions (e.g. visual-constructive ability) (Tuokko, Hadjistavropoulos, Rae, & O'Rourke, 2000). Therefore, the CDT has been used together with the MMSE's because it provides additional discrimination power as it complements the MMSE's weaknesses (Brodaty & Moore, 1997). Together, they are considered to have high sensitivity for the diagnosis of dementia (Schramm et al., 2002).

ISSN: 0718-4123
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The Venezuelan norms for the MMSE and CDT have been published (Campagna, 2015b; Ferreira-Correia & Campagna, 2015), but the discriminant power of these tests to diagnose cognitive impairment linked to different conditions has not been established. Therefore, this retrospective study aimed to, first, explore the association between demographic variables (age, gender, and years of education) and the MMSE and CDT scores as well as between a composite score of both tests in the Venezuelan population. Second, determine the association between the MMSE and CDT scores (separately and together) and clinical groups, while controlling for age, years of education, and their interaction. The third aim was to determine the accuracy, while controlling for the specified demographics, in which these tests can predict (separately and together) different diagnostic categories, namely Alzheimer's disease (AD mild), mild cognitive impairment (MCI), depression, and patients with subjective cognitive complaint which was not corroborated by clinical and psychometric assessment (cognitive impairment not identified [CINI]). Lastly, we explored the effects of age and years of education and their interaction in the specific items of the MMSE and CDT in a healthy control group.

Materials and methods

Participants

Patients with cognitive complaints who attended the Neuropsychology Unit at an academic hospital in the city of Caracas-Venezuela, integrated the clinical groups. Patients younger than 40 years of age, or with a previous history of neurological, psychiatric, endocrine or systemic diseases, alcohol or drug abuse were excluded from the sample. Cases with incomplete results, two or more diagnoses, and with Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982) of five or more were also excluded. Patients from the following diagnostic categories were selected for the purpose of this study:

1. *Mild Alzheimer's disease (AD mild) (GDS=4):* included patients who met the criteria outlined by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984).
2. *Mild cognitive impairment (MCI) (GDS=3):* formed by patients who met the following characteristics: memory failures corroborated by a family member without repercussions on daily living, alterations in the neuropsychological tests (excluding the MMSE and CDT) up to two standard deviations below average, and absence of dementia (Petersen, 2004).
3. *Cognitive impairment not identified (CINI) (GDS=2):* consisting of patients who came with mild complaints of memory characterized basically by benign forgetfulness, without affecting daily activities and/or not corroborated by a family member, after a neurological and neuropsychological evaluation (excluding the MMSE and CDT) no alterations were found in the neuropsychological and clinical assessments.
4. *Depression:* included patients who, after evaluation by the interdisciplinary team, did not meet the criteria for dementia or MCI, and met criteria for Major Depressive Disorder (American Psychiatric Association, 1998).

The control group included 456 subjects coming from a sample recruited for a large project of standardization of various cognitive tests in Caracas Metropolitan Area of Venezuela. The healthy participants were recruited by quota sampling (Neuman, 2014), in terms of age, years of education, gender (male and female), and socioeconomic level (Méndez-Castellano & Méndez, 1994), based on the 2001 census (Instituto Nacional de Estadística, 2001). The exclusion criteria included history of psychiatric, endocrine, immunologic, and neurological illnesses, symptoms of memory loss or other cognitive complaint, illegal substances use and abuse, legal substance abuse, and use of psychotropic medication. Special attention was given to exclude individuals with any memory problems that could be associated with early dementia or mild cognitive impairment. Informed consent was obtained from all participants before beginning the evaluation.

Procedure

We used a retrospective design (Salkind, 2010) that included two separate sources of data (clinical and controls). All the patients underwent an assessment protocol that included neurological examination and full neuropsychological evaluation, laboratory tests, and a brain scan (computerized tomography or magnetic resonance imaging). Each case was discussed in a multidisciplinary meeting (with neurologists, neuropsychologists, and psychiatrist) where the diagnosis was decided. The MMSE and CDT were administered by one of the neuropsychologists working at the unit at the hospital premises, but were not part of the diagnostic decisions.

ISSN: 0718-4123
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The control data was obtained from a standardization project conducted at the same unit, which included, in addition to the MMSE and CDT, the following tests: Benton's Temporal Orientation Test, Rey Auditory Verbal Learning Test, Controlled Oral Word Association Test, Set Test, Trail Making Test, and Attention Test. The duration of this assessment was 40 minutes approximately and it was conducted in diverse settings with appropriate testing conditions. These tests were administered by licensed psychologists or psychology students in their fifth year of training. All assessors underwent training prior data collection. Correction of assessment protocols was supervised by one of the senior neuropsychologist at the unit.

Materials

The GDS is a valid tool to assess the stages of cognitive decline linked to primary dementia (Alzheimer's disease). Patients in stage one do not display any cognitive decline, in stage two patients present with very mild cognitive decline, stage three involves mild decline, and stages four, five and six describe moderate to severe decline, respectively (Reisberg et al., 1982).

The MMSE (Folstein et al., 1975) was administered in the original version of 11 questions that evaluate the following functions: temporary orientation, spatial orientation, attention, registration, concentration, recent verbal memory, nomination, repetition, verbal comprehension, reading, writing, and constructive capacity. Scores add up to a maximum of 30 points. The MMSE was translated into Spanish and piloted. A direct translation was not adequate for item five ("*No ifs, ands, or buts*"), which was modified to "*Sin aunques, ni peros*" in order to maintain the use of conjunctions while providing a better meaning in Spanish.

For the CDT, we used the free drawn part of the method developed by Freedman et al. (1994) which involves giving the examinee a white sheet of paper and a pencil and asked to draw a clock with all the numbers and set the time to 11:10. We followed Freedman and colleague's (1994) scoring system whereby fifteen items are assessed within five categories, namely: contour (closed), numbers (all present in correct order, Arabic representation, not rotated, correctly placed, inside the contour), hands (correct representation of the hour and minutes, correct proportion), centre (drawn or inferred), and absence of additional details. One point is awarded for each correct element for a maximum of 15 points.

Sample Size

Assuming balanced groups, for the comparison of means between the groups (control, MCI, AD mild, CINI, and depression), the detection of a small, medium or large effect size (f=0.1, 0.3, 0.5 respectively) with 80% power at 5% significance level requires a sample size of 1096, 180 or 76 respectively. However, given our research design, our sample sizes are unbalanced, which means that only medium to large effect sizes can be detected, should they exist (Faul, Erdfelder, Lang, & Buchner, 2007). Sample size calculations were carried out in G*Power (Faul et al., 2007).

Data analysis

The association between demographics (age and years of education) and the total scores of the MMSE and the CDT, as well as between the two scores, was determined by Spearman's correlation coefficient because the scores were not normally distributed. Wilcoxon's Rank Sum test was used to calculate the association between gender and each of the scores.

We explored the association between the MMSE and CDT scores (dependent variables) and age, years of education, and the interaction between age and years of education (independent variables) using a General Linear Model (GLM). Post-hoc tests were conducted using the Tukey-Kramer adjustment for multiple comparisons. A reflected log10 transformation was used to meet the assumption of the technique (transformed score = log [16-CDT] and transformed score = log [31-MMSE]).

A logistic regression was used to create predictive models for each diagnosis (vs. the control group) based ocin the test score/s, age, years of education and the interaction between age and years of education. Non-significant covariates were removed from the model to avoid over-fitting. A reflected log10 transformation of each of the MMSE and CDT scores was used, in order to transform the data to (approximate) normal distributions and thereby meet the assumptions of the technique. A predictive model for all five clinical groups, based on the two test scores (separately and in combination), age and years of education, was developed using discriminant analysis. The interaction term was removed where it was not significant. Data analysis was carried out using SAS version 9.4 for Windows. A 5% significance level was used.

ISSN: 0718-4123
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Results

Table 1 presents the descriptive characteristics of the sample in terms of demographics and MMSE and CDT scores. The correlation analysis (n=587) showed a significant (weak) negative correlation between MMSE and age (r=-0.285; p<0.001) and a positive correlation with years of education (r=0.552; p<0.0001). Similarly, the CDT score showed a significant negative but weak correlation with age (r=-0.176; p<0.0001) and a positive correlation with years of education (r=0.476; p<0.0001). Gender was not significantly associated with either the MMSE or CDT scores (p=0.17 and p=0.96, respectively). The MMSE and CDT score were positively correlated (r=0.549; p<0.0001).

Table 1.

Descriptive statistics characterizing the sample demographics and MMSE and CDT scores per diagnostic groups

		Group					
Variable	**Statistics**	**Overall (n=587)**	**Control (n=456)**	**CINI (n=24)**	**MCI (n=50)**	**AD Mild (n=28)**	**Depression (n=29)**
Age	Mean	60.53	59.4	62.5	65.4	67.9	61.1
	Std Dev	11.0	10.8	10.2	10.3	11.7	10.6
	Median	60	60	59.5	68	70	63
	Minimum	40	40	46	46	45	43
	Maximum	88	80	83	87	88	82
Gender							
Female	N (%)	326 (55.54)	238 (52.19)	13 (54.17)	34 (68.00)	16 (57.14)	25 (86.21)
Male	N (%)	261 (44.46)	218 (47.81)	11 (45.87)	16 (32.00)	12 (42.86)	4 (13.79)
Years of education	Mean	8.71	8.68	9.54	9.06	8.71	7.83
	Std Dev	5.13	5.22	5.44	4.68	4.75	4.61
	Median	9	9	9	9	9	6
	Minimum	0	0	0	0	0	0
	Maximum	26	26	19	19	18	16
MMSE score	Mean	23.34	26.60	27.08	25.80	21.82	26.82
	Std Dev	3.40	3.17	3.03	3.30	4.65	2.92
	Median	27	27	28	27	23	27
	Minimum	12	15	19	18	12	18
	Maximum	30	30	30	30	29	30
CDT score	Mean	12.59	12.73	12.29	12.20	10.68	13.13
	Std Dev	2.76	2.66	3.07	2.92	3.29	2.57
	Median	14	14	13.5	13	12	14
	Minimum	2	2	3	4	2	4
	Maximum	15	15	15	15	15	15

The effect of clinical group, age, and the age-education interaction were significant for the MMSE scores while the effect of clinical group, age, and years of education were significant for the CDT scores (Table 2). We illustrate the impact of the interactions between age and years of education in Figures 1 and 2, which show how the slope (interaction) is more accentuated in the MMSE in comparison to the CDT. Post-hoc tests showed that the estimated Least-Squares (LS) mean MMSE score for the AD mild group (LS mean=22.4 [95% CI 21.4-23.4]) was significantly lower than that of all the other groups (all p<0.0001) when controlling for age and education. The LS mean CDT score for the AD mild group (LS mean=12.0 [95% CI 10.9-12.8]) was significantly different from that of the control and depression groups when controlling for age and education. There were no other significant between-group differences in the MMSE and CDT comparisons. Figures 3 and 4 represent the LS mean of the MMSE and CDT total scores, respectively, for each group. It can be observed that the AD mild group has the lowest LS Mean.

ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

Table 2.

Summary of the two General Linear Models with the MMSE and CDT scores as dependent variables

Dependent variable	Source	DF	Type III SS	Mean Square	F Value	Pr > F
MMSE (n=585)*	Diagnostic group	4	456.9	114.5	18.5	<.0001
	Age	1	132.9	132.9	21.5	<.0001
	Years of education	1	3.1	3.1	0.5	0.48
	Interaction (age & years of education)	1	38.8	38.8	6.3	0.012
CDT (n=587)	Diagnostic group	4	8.6	2.1	5.5	0.0002
	Age	1	2.2	2.2	5.6	0.018
	Years of education	1	72.9	72.9	188.8	<.0001

* Two outliers removed

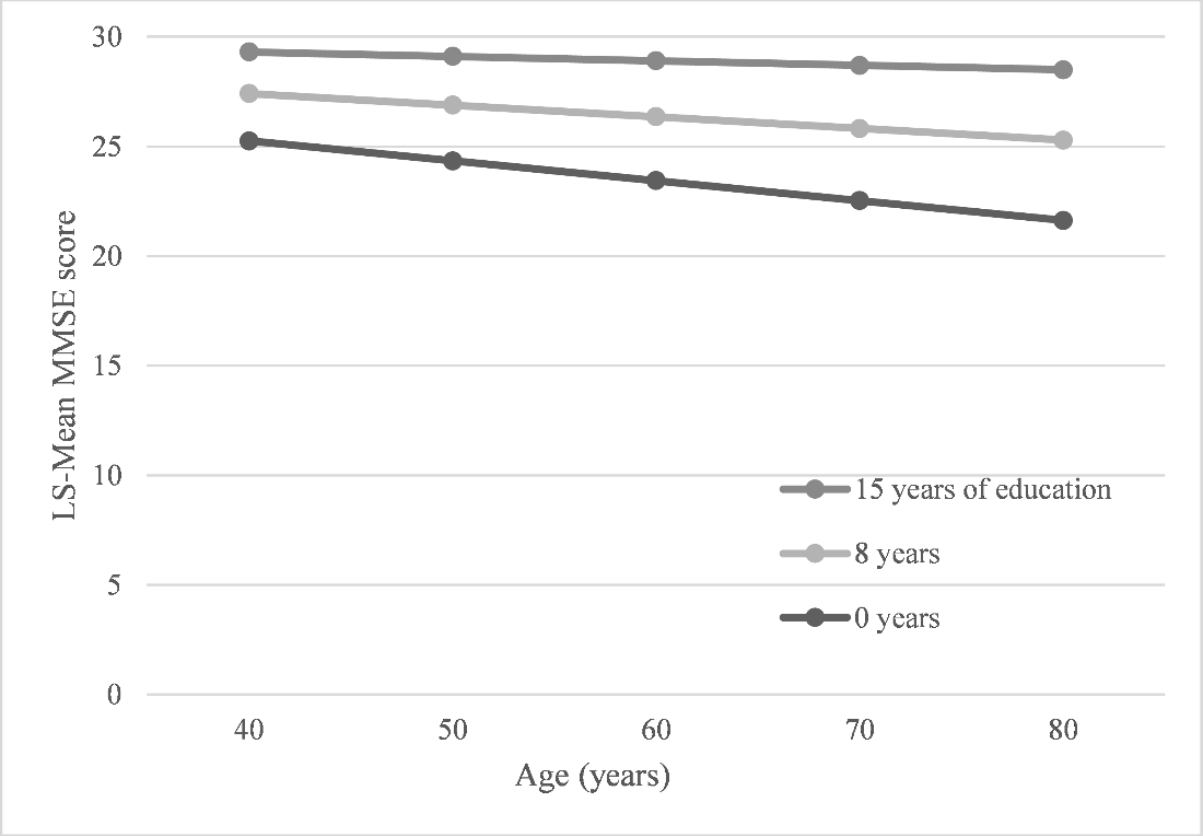

Figure 1.

The effect of the age-education interaction on MMSE scores

ISSN: 0718-4123
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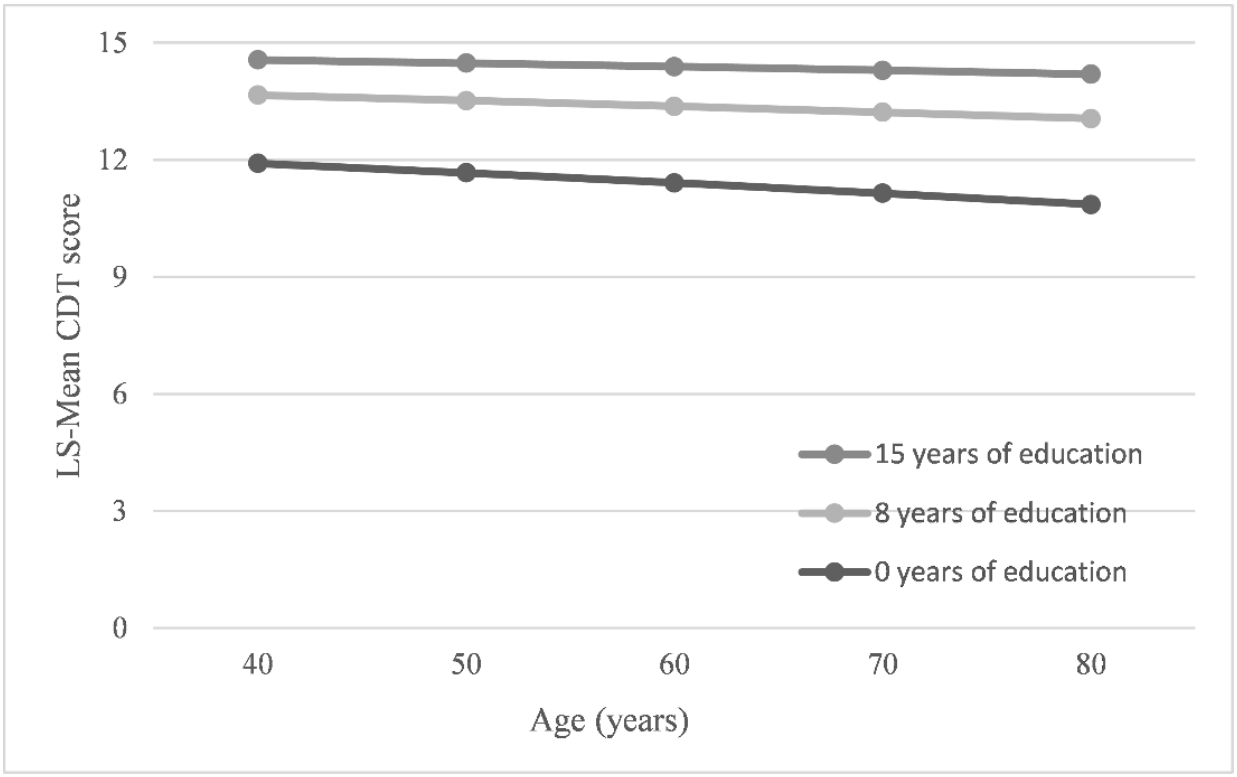

Figure 2.
The effect of the age-education interaction on CDT scores

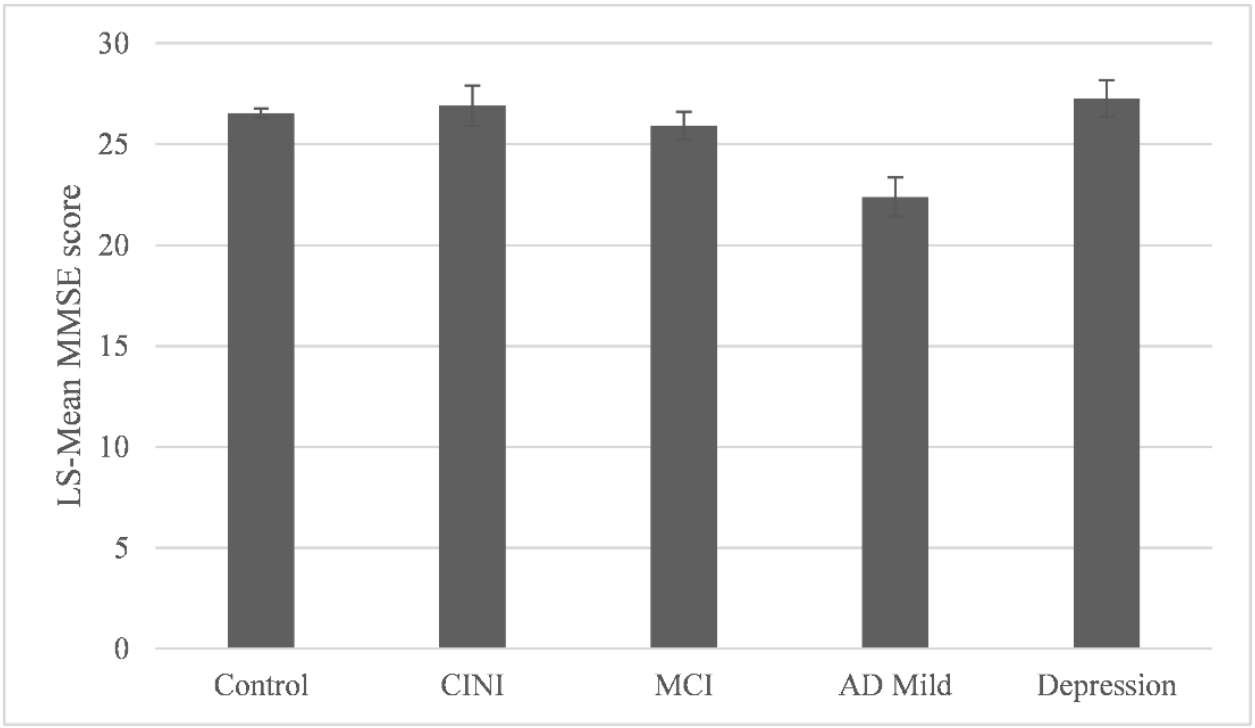

Figure 3.
MMSE Least-Square Means for each diagnostic group. n=782 (3 outliers removed based on model diagnostics). Error bars denote the 95% confidence interval for the mean

ISSN: 0718-4123
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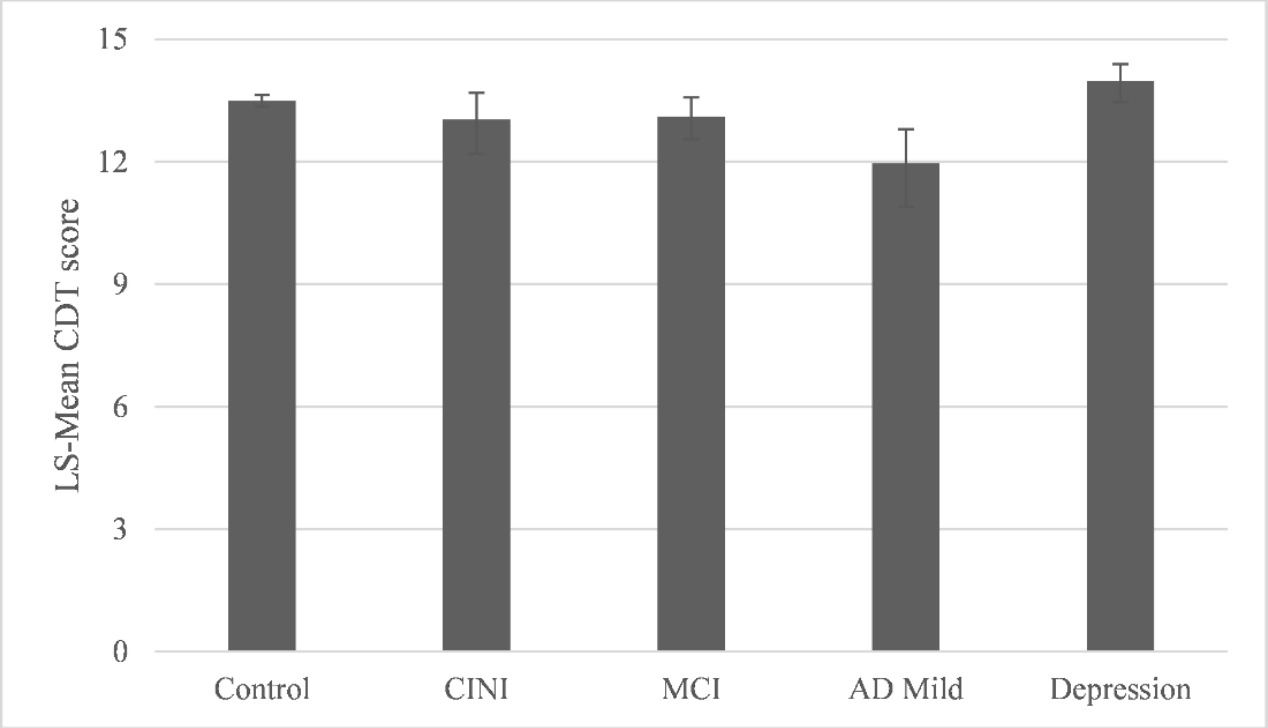

Figure 4.
CDT Least-Square Means for each diagnostic group. n=785. Error bars denote the 95% confidence interval for the mean

The mean scores stratified by age and years of education for the control sample are summarized in Table 3, and it can be observed that at all age ranges, the highest tests' means correspond to the samples with the highest educational achievements, whereas the lowest performance is observed at the oldest groups with the lowest levels of education.

Table 3.
Descriptive statistics of the MMSE and CDT total scores for the control sample stratified by age and years of education

			MMSE							CDT						
Age	Years of education	N	Mean	Std Dev	Median	25th Pctl	75th Pctl	Minimum	Maximum	Mean	Std Dev	Median	25th Pctl	75th Pctl	Minimum	Maximum
40-59 years	0	22	21.6	2.5	22	20	24	18	26	8.0	3.5	7	6	11	2	15
	1-3	10	24.2	3.7	24	21	27	19	30	12.6	1.3	13	12	14	10	14
	4-6	52	27.1	2.3	27	26	29	21	30	13.0	1.8	13	12	14	8	15
	7-11	65	27.8	2.0	28	27	29	22	30	13.6	1.5	14	13	15	8	15
	12+	73	28.8	1.3	29	28	30	23	30	14.0	1.0	14	14	15	12	15
60-80 years	0	33	20.7	2.6	21	19	22	15	27	8.8	3.6	9	6	12	2	14
	1-3	16	24.5	2.8	24	23	27	19	29	10.9	2.7	11	10	13	6	15
	4-6	47	25.4	2.6	26	23	27	19	30	12.3	2.5	13	11	14	3	15
	7-11	70	27.5	2.1	28	27	29	21	30	13.3	1.9	14	13	15	8	15
	12+	68	28.0	1.6	28	27	29	23	30	13.9	1.6	14	13	15	5	15

The summary of the logistic regressions (Table 4) shows that the effects of the MMSE and CDT score were not significant for the CINI and MCI versus control group predictive model. The effect of the MMSE and CDT were significant only in the AD mild versus control model, which suggests that as the MMSE and CDT scores decrease, the odds of being part of the AD mild group instead of the control group increases. The effects of the MMSE score was not significant for the depression vs control groups, in contrast with the effects of the CDT in this specific comparison, which was significant. These findings indicate that as the CDT score decreases, the odds of being in the depression group versus control group increase. The effect of age was significant for both the CDT and the MMSE in the MCI vs control model models. The effect of age and education were significant for the MMSE and the CDT in the AD mild vs control model. The effect of age and education were significant for the CDT in the depression vs control model.

ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

When both tests scores are used together in the logistic regressions, the effects of the MMSE and CDT scores were not significant for the CINI, MCI and depression versus control group predictive model. Only in the AD mild versus control model, the effect of the MMSE is significant. The effect of age is significant in the MCI, AD mild and depression vs control models, whereas the effect of years of education is only significant in the MCI and AD mild versus control models. The interaction between age and years of education only had a significant effect on the depression versus control model.

Table 4.

Results of the logistic regression analyses of predictors for each diagnostic group versus the control group

		Analysis of Maximum Likelihood Estimates					Odds ratio estimates	
				Standard	Wald			95% Wald
Test	Model	Parameter	Estimate	Error	Chi-Square	Pr > ChiSq	Point Estimate	Confidence Limits
MMSE and CDT	CINI vs Control	Intercept	-2.91	0.40	52.86	<.0001		
		MMSE	-0.47	0.32	2.17	0.140	0.62	0.33 1.17
		CDT	0.52	0.35	2.20	0.138	1.68	0.85 3.35
	MCI vs Control	Intercept	-6.66	1.13	34.89	<.0001		
		MMSE	0.42	0.30	1.97	0.160	1.52	0.85 2.71
		CDT	0.26	0.26	0.99	0.319	1.30	0.78 2.17
		Age	0.05	0.02	9.60	0.002	1.05	1.018 1.081
		Years of Education	0.08	0.04	4.13	0.042	1.00	1.00 1.16
	AD Mild vs Control	Intercept	-14.62	2.24	42.70	<.0001		
		MMSE	3.29	0.66	24.77	<.0001	27.71	7.57 101.43
		CDT	0.47	0.39	1.50	0.221	1.62	0.76 3.47
		Age	0.05	0.02	5.14	0.023	1.06	1.02 1.10
		Years of Education	0.28	0.06	21.08	<.0001	1.32	1.18 1.49
	Depression vs Control	Intercept	-6.34	2.33	7.39	0.007		
		MMSE	-0.30	0.35	0.74	0.390	0.74	0.37 1.47
		CDT	-0.60	0.35	2.98	0.084	0.55	0.28 1.08
		Age[1]	0.08	0.04	5.20	0.023	1.02	0.98 1.06
		Years of Education[2]	0.37	0.22	2.82	0.093	0.91	0.82 1.01
		Age and Years of Education Interaction	-0.01	0.00	4.46	0.035		
MMSE	CINI vs Control	Intercept	-2.69	0.37	53.01	<.0001		
		MMSE	-0.22	0.28	0.62	0.43	0.80	0.47 1.39
	MCI vs Control	Intercept	-5.61	0.99	32.39	<.0001		
		MMSE	0.21	0.22	0.95	0.33	1.24	0.81 1.89
		Age	0.05	0.02	10.49	0.0012	1.05	1.02 1.08
	AD Mild vs Control	Intercept	-14.21	2.18	42.50	<.0001		
		MMSE	3.53	0.64	30.23	<.0001	34.20	9.71 120.47
		Age	0.05	0.02	4.97	0.026	1.05	1.01 1.10
		Years of Education	0.25	0.06	20.66	<.0001	1.28	1.15 1.43
	Depression vs Control	Intercept	-2.64	0.35	56.45	<.0001		
		MMSE	-0.09	0.25	0.14	0.71	0.91	0.55 1.50
CDT	CINI vs Control	Intercept	-3.18	0.36	76.95	<.0001		
		CDT	0.24	0.29	0.71	0.40	1.27	0.73 2.23
	MCI vs Control	Intercept	-5.62	0.98	32.62	<.0001		
		CDT	0.18	0.21	0.75	0.39	1.19	0.80 1.79
		Age	0.05	0.02	11.82	0.0006	1.05	1.02 1.09
	AD Mild vs Control	Intercept	-9.93	1.64	36.50	<.0001		
		CDT	1.33	0.35	14.42	0.0001	3.77	1.90 7.48
		Age	0.07	0.02	11.16	0.0008	1.07	1.03 1.12
		Years of Education	0.12	0.05	6.83	0.0089	1.13	1.03 1.23
	Depression vs Control	Intercept	-6.40	2.30	7.77	0.0053		
		CDT	-0.69	0.33	4.40	0.036	0.50	0.26 0.96
		Age[1]	0.08	0.04	4.81	0.0282	1.02	0.98 1.06
		Years of Education[2]	0.37	0.22	2.94	0.087	0.92	0.84 1.01
		Age and Years of Education Interaction	-0.01	0.00	4.32	0.038		

Note: DF=1

[1]= Because the interaction is significant, the odd ratios were estimated at the mean of the other variable in the interaction (age at years of education [8])

[2]=Because the interaction is significant, the odd ratios were estimated at the mean of the other variable in the interaction (years of education at age [61])

The predictive power of the four models are summarized in Table 5, which shows large confidence intervals because of the small group sizes of all the clinical groups. Specifically, in the CINI vs control model, the use of the MMSE score alone has low sensitivity and specificity and the use of the CDT score has good sensitivity (75%) but poor specificity (36%). The combined use of both scores in this model yields reasonable specificity but poor sensitivity. In MCI vs control model reveals, for the use of both tests on their own or together, good sensitivity but low specificity. Similarly, in the AD mild vs control model both tests (alone or combined) have reasonable sensitivity (noting the wide confidence limits) and good specificity. Lastly, the depression vs control model, the CDT and MMSE (separately and in conjunction) have reasonable sensitivity (noting the wide confidence

ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

limits) and low specificity. The predictive power (particularly in terms of sensitivity) of these models are affected by the small group size of the diagnostic groups.

The diagnostic accuracy (controlling for age and years of education) of the MMSE, the CDT, and the MMSE with the CDT, as given by the Area Under the Receiver Operating Characteristic Curve data (AUC) is included in Table 5. It can be noted that both tests (together and separately) have an excellent discrimination power in the AD mild group, however limited by the wide confidence intervals. The discrimination power of the MMSE and CDT for the groups of MCI and depression was acceptable, but with low sensitivity as mentioned above. The MMSE and CDT have good sensitivity but poor specificity for the CINI group when used together or independently. In contrast, both tests (in all conditions) have poor sensitivity and acceptable specificity for the MCI vs control and depression vs control comparisons.

Table 5.

Summary of the predictive power for each diagnostic model for the MMSE score, the CDT score and both scores combined

		Maximise sensitivity and specificity of both tests			Maximise sensitivity and specificity of the MMSE			Maximise sensitivity and specificity of CDT	
Diagnosis	**MMSE and CDT AUC**	**% Sensitivity (CI)**	**% Specificity (CI)**	**MMSE AUC**	**% Sensitivity (CI)**	**% Specificity (CI)**	**CDT AUC**	**% Sensitivity (CI)**	**% Specificity (CI)**
CINI vs Control	0.54 (0.43-0.66)	83 (63-95)	26 (22-31)	0.54 (0.43-0.66)	75 (53-90)	36 (32-40)	0.54 (0.43-0.66)	83 (63-95)	26 (22-31)
MCI vs Control	0.66 (0.58-0.73)	54 (39-68)	72 (68-76)	0.66 (0.58-0.74)	48 (34-63)	79 (75-83)	0.66 (0.58-0.73)	54 (39-68)	72 (68-76)
AD Mild vs Control	0.78 (0.69-0.88)	71 (51-87)	81 (77-84)	0.88 (0.82-0.95)	82 (63-94)	81 (77-84)	0.78 (0.69-0.88)	71 (51-87)	81 (77-84)
Depression vs Control	0.67 (0.57-0.77)	48 (29-67)	77 (72-80)	0.51 (0.40-0.62)	24 (10-44)	84 (80-87)	0.67 (0.57-0.77)	48 (29-67)	77 (72-80)

The results of the discriminant analysis for the combined use of both tests, age and years of education, gave an overall classification accuracy of 21.1%, which is very poor. As expected, the algorithm is unable to distinguish between disease groups, and also misclassifies many control participants into disease groups (Table 6). The exception to this is that none of the participants of the AD mild group were misclassified as CINI. These findings indicate that it is not possible to distinguish between diagnosis with the use of both scores, while controlling for the significant impact of age and years of education.

Table 6.

Accuracy with which group membership can be predicted from the two scores (MMSE and CDT), age and years of education

		Predicted group membership				
Diagnostic groups	Total	Control	CINI	MCI	AD Mild	Depression
Control	456	118	81	66	63	128
	100	26	18	14	14	28
CINI	24	3	7	2	6	6
	100	13	29	8	25	25
MCI	50	4	9	6	19	12
	100	8	18	12	38	24
AD Mild	28	2	0	3	22	1
	100	7	0	11	79	4
Depression	29	8	2	3	3	13
	100	28	7	10	10	45
Total	587	135	99	80	113	160
	100	23	17	14	19	27

Note: classification accuracy of 21.1%

These results indicate that the combined use of the MMSE and CDT has a moderate degree of sensitivity when discriminating between the control and AD mild groups while controlling for age and years of education, but does not assist with the differential diagnosis between other diagnoses. This diagnostic accuracy is comparable to the one observed when the tests are used separately. The discrimination power between the control and the remaining clinical groups (MCI, depression, and CINI) is poor.

ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

Discussion

The MMSE and the CDT are commonly used screening tools because of their easy and fast administration and scoring and have good capacity to identify cognitive decline, especially when used together for diagnosing early stages of dementia (Brodaty & Moore, 1997). However, recent studies have indicated suboptimal capacity to identify and discriminate cognitive impairment in different samples (Mitchell, 2013; Seigerschmidt, Mösch, Siemen, Förstl, & Bickel, 2002) and have highlighted important cultural and demographic biases that emphasize the need for context-specific psychometric studies (Menon, Hall, Hobson, Johnson, & O'Bryant, 2012). Hence, our study aimed to explore if the CDT and MMSE are a valid tool for Venezuelan patients to identify and diagnose cognitive decline in different clinical groups that commonly offer a diagnostic challenge, namely MCI, AD mild, depression, and patients with cognitive complaints not supported by objective assessments (CINI). The latter group is of particular interest because they frequently attend neuropsychology units seeking cognitive assessment. Patients with CINI present with subjective cognitive complaints that may mask or involve a preclinical state of objective cognitive decline) (Mendonça, Alves, & Bugalho, 2016). Our sample in general, represents a group of interest given the large educational disparities which common in many countries affected by socioeconomic inequalities.

Our findings indicate that age and years of education were significantly associated with the total score of the MMSE and CDT, although the interaction between age and years of education was only found to be significant in the MMSE scores, which may indicate that the MMSE score in Venezuelan is a function of the combination of age and education, in which less education and more years of age is linked to lower performance. Significant correlations between age and education have been previously reported for the MMSE (Butman et al., 2001; Dufouil et al., 2000; González-Hernández et al., 2009) and in several scoring systems of the CDT (Bozikas, Giazkoulidou, Hatzigeorgiadou, Karavatos, & Kosmidis, 2008; Santana, Duro, Freitas, Alves, & Simões, 2013). Performance discrepancies linked to gender previously noted for the MMSE (Dufouil et al., 2000; Grigoletto, Zappalà, Anderson, & Lebowitz, 1999; Han et al., 2008) and the CDT (Seigerschmidt et al., 2002) were not supported by our results. The total scores of the MMSE and CDT are significantly correlated, which may offer support for the idea that the CDT behaves as a screening tool and is multifactorial (Shulman, Shedletsky, & Silver, 1986), however, this correlation cannot be taken as a good indicator of construct validity (Schramm et al., 2002).

When controlling for the effects of age, years of education and their interaction, significant differences in the MMSE LS mean were identified between the AD mild and the CIDI, MCI, depression and control groups. The CDT LS mean for the AD mild group was also significantly different from that of the control and depression groups when controlling for the relevant covariates. As expected, the AD mild group had significantly lower scores on both tests when compared to controls. Therefore, the MMSE and CDT may be better suited for the identification of cognitive decline in mild to moderate dementia (Brodaty & Moore, 1997; Duro et al., 2019).

In order to investigate the predictive power of the MMSE and CDT, we explored the specificity and sensitivity of the total scores of these tests, when taking into consideration the covariates. We wanted to know whether a particular score could predict a specific diagnosis while taking into consideration age and years of education, as well as their interaction. The discriminant analysis indicates that the power of prediction of these tests is quite poor for the case of our sample. The results indicate a high risk of misclassifying patients when using these tests.

More specifically, our study supports the notion that the MMSE works best for more severe forms of cognitive decline (Nieuwenhuis-Mark, 2010). In contrast to our results, the MMSE had excellent sensitivity and specificity to diagnose dementia in several studies from other non-English speaking countries, including Peru (Soto-Añari & Belón-Hercilla, 2017), Iran (Seyedian et al., 2008), Japan (Maki et al., 2000), Israel (Werner, Heinik, Mendel, Reicher, & Bleich, 1999), and Turkey (Yildiz et al., 2016). Language and cultural diversity does not seem to play a role on the predictive validity of the MMSE to diagnose dementia, therefore, the discrepancies between our findings and these studies could be attributed to the demographic heterogeneity of our sample.

The CDT has been characterised as an excellent screening test for dementia (Shulman, 2000), which has been supported by several studies in non-English speaking countries such as Peru (Custodio, García, Montesinos, Lira, & Bendezú, 2011), Mexico (Aguilar-Navarro et al., 2018), and Thailand (Jitapunkul et al., 2000). Venezuela is the exception as our findings reveal only fair sensitivity with wide confidence interval and good specificity. As with the MMSE, it is possible that our results may have been limited by sample heterogeneity, especially with regards to educational level. In alignment with our results, it has been noted that the CDT is not a valid tool to diagnose dementia in elderly people with low levels of education (Lourenço, Ribeiro-Filho, Moreira, Paradela, & Miranda, 2008) or for the detection of questionable dementia (Seigerschmidt et al., 2002), therefore, emphasis in clinical assessment and comparisons with previous levels of performance should be placed in patients in these

ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

categories. It is worth noting that the combined use of the CDT and MMSE did not provide an advantage in the diagnosis of mild AD, as previously suggested (Brodaty & Moore, 1997).

Our results suggest that the CDT is not a good screening instrument for MCI for our sample as it is not sensitive to milder forms of neuropsychological decline. The idea that the CDT can be used as a screening test for MCI and early identification of dementia (Yamamoto et al., 2004) has been challenged in the literature (Duro et al., 2019; Nishiwaki et al., 2004; Ravaglia et al., 2005). Similar evidence is found in the MMSE literature, which suggests that the MSSE is not adequate for the detection of MCI (Hoops et al., 2009) as it is for dementia (Pinto et al., 2018). In addition, our results suggest that the MMSE and the CDT are not appropriate to diagnose cognitive decline linked to depression (Rajji et al., 2009), despite reports indicating that performance in these tests may be affected by depressive mood (Feola et al., 2013). The use of only one CDT administration and scoring system represents a limitation in our study. The lack of psychometric equivalence between different CDT methods (Brodaty & Moore, 1997; Seigerschmidt et al., 2002; Yamamoto et al., 2004), specifically in terms of the predictive accuracy for the diagnosis of dementia (Storey, Rowland, Basic, & Conforti, 2001; Tuokko et al., 2000), reduces the generalization of our findings. In agreement with our results, poor predictive power has been previously reported for the CDT and the MMSE, in particular for less severe forms of neuropsychological impairment, such as MCI (Arevalo-Rodriguez et al., 2015; Duro et al., 2019). In general, our work supports the claim that the MMSE is not an adequate tool to diagnose cognitive deficits (Mitchell, 2013). Our results indicate that the MMSE and the CDT have a fair to good positive predictive value for the identification of cognitive impairment in MCI, AD mild and depression, but a very poor negative predictive value for MCI, CINI, and depression, in particular, with a low accuracy for diagnostic classification. Therefore, our results do not support the idea that the combined use of the MMSE and the CDT improves their psychometric value, as it has been suggested (Heinik, Solomesh, Bleich, & Berkman, 2003; Schramm et al., 2002; Zhou & Jia, 2008). Moreover, it does not support the good discrimination capacity of the MSME and the CDT previously recorded for psychogeriatric patients with low levels of education (Marcopulos, Gripshover, Broshek, McLain, & McLain, 1999).

In conclusion, the MMSE and the CDT may be suitable tools to screen cognitive impairment and potentially assist with the diagnosis of AD mild if age and years of education are taken into account. The combined use of this tools does not play a major role in the discrimination between pathologies, so clinicians must complement their assessment (e.g. additional neuropsychological tests, mood and behavioural scales, and collateral data) when diagnosing patients with co-morbidities or questionable cognitive symptomatology.

This study also highlights the importance of establishing the diagnostic validity of neuropsychological tests in contexts characterised by cultural diversity, and educational and socioeconomic inequalities, which is the case of Venezuela and many other Latin-American countries. Practitioners must be mindful of the controversies surrounding the predictive value of commonly used neuropsychological tests and aware of the potential diagnostic errors that may take place when using tools that have not been psychometrically evaluated for the specific communities in which they are used. Specifically, psychologist assessing Venezuelan patients should aim to select tests that have been adapted, validated, and normed, using representative samples and taking into consideration age and level of education.

Considering our results within the context of the available literature, the generalizability of our findings is limited due to the heterogeneity of the sample in terms of age and years of education. Larger samples that are better matched for these variables can offer further insight on the potential and limitations of the MMSE and the CDT in clinical settings characterized by high educational variability and may assist with the identification of cut-off-points.

Acknowledgment: We are grateful to Dr Petra Gaylard for her assistance with the statistical analyses.

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ISSN: 0718-4123
DOI: 10.7714/CNPS/16.2.202

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ISSN: 0718-4123
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