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ORIGINAL ARTICLE

Mapping the Cerebellar Cognitive Affective Syndrome in Patients with Chronic Cerebellar Strokes

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Abstract

The cerebellar cognitive affective syndrome (CCAS) has been consistently described in patients with acute/subacute cerebellar injuries. However, studies with chronic patients have had controversial findings that have not been explored with new cerebellar-target tests, such as the CCAS scale (CCAS-S). The objective of this research is to prove and contrast the usefulness of the CCAS-S and the Montreal Cognitive Assessment (MoCA) test to evaluate cognitive/affective impairments in patients with chronic acquired cerebellar lesions, and to map the cerebellar areas whose lesions correlated with dysfunctions in these tests. CCAS-S and MoCA were administrated to 22 patients with isolated chronic cerebellar strokes and a matched comparison group. The neural bases underpinning both tests were explored with multivariate lesion-symptom mapping (LSM) methods. MoCA and CCAS-S had an adequate test performance with efficient discrimination between patients and healthy volunteers. However, only impairments determined by the CCAS-S resulted in significant regional localization within the cerebellum. Specifically, patients with chronic cerebellar lesions in right-lateralized posterolateral regions manifested cognitive impairments inherent to CCAS. These findings concurred with the anterior-sensorimotor/posterior-cognitive dichotomy in the human cerebellum and revealed clinically intra- and cross-lobular significant regions (portions of right lobule VI, VII, Crus I-II) for verbal tasks that overlap with the "language" functional boundaries in the cerebellum. Our findings prove the usefulness of MoCA and CCAS-S to reveal cognitive impairments in patients with chronic acquired cerebellar lesions. This study extends the understanding of long-term CCAS and introduces multivariate LSM methods to identify clinically intra- and cross-lobular significant regions underpinning chronic CCAS.

Keywords Cerebellar cognitive affective syndrome · Cerebellar cognitive affective syndrome scale · Lesion-symptom mapping · Cerebellar stroke · Magnetic resonance imaging

Introduction

The role of the cerebellum in cognition and affect has been firmly established beyond its known association with motor control and motor learning [1]. In fact, the constellation of cognitive and affective symptoms that could arise from damage to the cerebellum has been epitomized as the cerebellar cognitive affective syndrome (CCAS) [2].

In the last two decades, a growing number of studies have demonstrated the occurrence of CCAS in patients with acquired cerebellar injuries [3, 4]; however, there is still uncertainty about the suitable tests that should be administrated to cerebellar patients to detect CCAS in clinical practice [5]. In response to this need, an easily applicable bedside test, the cerebellar cognitive affective syndrome scale

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(CCAS-S), has been recently developed [6]; but, despite its rapid widespread acceptance [7, 8], there is no information yet about its neural correlates or how they differ from other cognitive screening tests, such as the Montreal Cognitive Assessment (MoCA) test.

More generally, the correspondence between CCAS symptoms and lesion location after a cerebellar injury has mainly been studied comparing the cognitive performance among patients grouped based on their damaged cerebellar anatomical regions (anterior vs posterior, vermal vs hemispheric, right hemisphere vs left hemisphere) [3, 9]. A new approach was offered by Stoodley et al. [10], who conducted a univariate voxel-based lesion-symptom mapping (VBLSM) research in 18 patients with acute/subacute isolated cerebellar strokes to reveal clinically significant functional regions underpinning cognition in the cerebellum.

Previously, Richter et al. [11] had already used univariate VBLSM analysis to associate impaired performance in a verbal fluency task with damage to Crus II in 21 patients with chronic cerebellar strokes. However, it was no possible to explore the neural correlates of the long-term CCAS since this cohort of chronic cerebellar patients only showed verbal fluency impairments.

The CCAS has been consistently described in patients with acute/subacute cerebellar injuries [2, 10]. However, studies with chronic patients have had mixed findings [12, 13], representing an additional challenge for the characterization of CCAS and its neural bases. Alexander et al. [5] have concluded that cognitive impairments after focal cerebellar injuries in adults are mild or transient, and after the acute epoch, the demonstration of these deficits may require more demanding and specific evaluation instruments. Moreover, it has been suggested that the cognitive impairments after acquired cerebellar lesions tend to resolve with time [13].

Since traditional neuropsychological tests, able to detect well-delineated cognitive profiles, are often not sensitive enough to pinpoint the "subclinical" deficits that may follow cerebellar damage [14], the administration of specific tests to uncover CCAS, such as the CCAS-S, could be crucial to understand cognitive changes in patients with chronic cerebellar injuries, and the introduction of new methods to explore the neural bases underpinning these tests could complete the comprehension of long-term CCAS. For example, VBLSM methods offered new opportunities to understand the CCAS beyond the traditional lobule-based cerebellar perspective. Nevertheless, these univariate approaches pose important methodological limitations [15] that can be overcome by more sophisticated statistical methods, such as multivariate lesion-symptom mapping (LSM) approaches, which have been scarcely applied on the cerebellum [16].

Finally, it must be noted that the hypothesis of the human cerebellum organized into distinct functional subregions has been tested in a wide range of reports involving healthy volunteers [17, 18], but the lack of LSM studies using suitable neuropsychological tests and sophisticated statistical methods has interfered with the efforts to understand which of these regions are crucial to determining the presence of CCAS in patients with chronic cerebellar injuries. Furthermore, the clinical correlates of the functional parcellations of the human cerebellum via a voxelwise approach are needed to contrast if the cerebellar functional divisions are conformed to anatomical boundaries [9] or follow an organization beyond the lobular labels [19].

Based on the previous information, our present study aimed first to prove and contrast the usefulness of the CCAS-S and the MoCA test to evaluate cognitive/affective impairments in patients with an isolated chronic cerebellar stroke. Our second goal was to map the cerebellar areas whose lesions correlated with the impairments of the cognitive tests using sophisticated multivariate LSM methods.

Methods

Participants

Medical charts of 150 patients with strokes that included the cerebellum were analyzed at the Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez (INNN-MVS). From those, twenty-four fulfilled the inclusion criteria and did not have neither contraindications for MRI nor metallic devices that could generate MRI artifacts. Of these patients, 22 with first-ever, chronic (> 4 months post-onset), ischemic ($n = 20$), or hemorrhagic isolated cerebellar strokes agreed to participate in this study (side and stroke volumes at Table 1 and Fig. 1). Only subjects with lesions restricted to the cerebellum were included. It was confirmed that patients had no pre-existing neurological/psychiatric illness and no contraindications for MRI.

The comparison group consisted of 22 healthy volunteers matched for age, sex, and education to the patient group (Table 2). All participants were right-handed. Study procedures were approved by the ethics committee of the INNN-MVS and written consent was obtained from each participant according to the Helsinki declaration.

Behavioral Assessment

All participants were evaluated with the CCAS-S, which is a brief test of mental function that queries the presence of CCAS. The scale is a 10-item battery including several cognitive tests (semantic fluency, phonemic fluency, category switching, verbal memory, digit span forward and backward, cube drawing, similarities, and Go no-Go test) and a neuropsychiatric screening. The total raw score is

Table 1 Stroke features

Patient	Sex	Stroke side	Type of stroke	Stroke volume (voxels)
1	F	Left	Ischemic	19,021
2	M	Bilateral	Ischemic	13,824
3	F	Right	Ischemic	2059
4	M	Left	Ischemic	41,613
5	M	Left	Ischemic	56,125
6	M	Left	Ischemic	40,126
7	F	Right	Ischemic	6833
8	F	Bilateral	Hemorrhagic	59,923
9	F	Bilateral	Ischemic	25,510
10	M	Right	Ischemic	31,700
11	F	Right	Ischemic	1360
12	M	Bilateral	Ischemic	1964
13	M	Left	Ischemic	15,969
14	M	Right	Hemorrhagic	6544
15	M	Right	Ischemic	23,761
16	F	Right	Ischemic	9245
17	M	Right	Ischemic	19,852
18	M	Right	Ischemic	17,726
19	M	Bilateral	Ischemic	45,912
20	M	Left	Ischemic	1083
21	M	Right	Ischemic	69,596
22	F	Right	Ischemic	16,864

F female, *M* male. Voxel size: $1 \times 1 \times 1$ mm^3

120. Each test has a threshold score leading to a pass/fail determination. Zero, one, two, and three failed test(s) were considered as a diagnosis of absence, possible, probable, and definite CCAS, respectively [6].

Since the sample was composed by native Spanish speakers and the CCAS-S has been originally published in American English, the version 1A of the scale was translated by a bilingual Spanish/English speaker and then revised by two Spanish native speakers fluent in English. The three persons involved in the translation were familiarized with neuropsychological evaluations to patients with cerebellar damages. The Spanish version of the CCAS-S was included in the Supplementary material.

The MoCA test [20] was also applied as a cognitive screening measure since it is commonly used for clinical and research purposes. The Center for Epidemiologic Studies Depression Scale was used as an indicator of depressed mood [21]. To assess articulation speed, participants were asked to repeat "PATA" for 10 s during two trials [22]. Mean score of the two trials was calculated for the analysis.

MRI Acquisition

Images from all patients were acquired at the INNN-MVS with a 3.0-T Siemens scanner (Siemens Medical Solutions, Erlangen, Germany). The acquisition included T1-3D MPRAGE sequence with TR/TE of 2.2 s/2.45 ms and T2-3D SPACE sequence with TR/TE of 3.2 s/409 ms. Both sequences with FOV of 256×256 mm, acquisition and reconstruction matrix of 256×256 mm, and isovolumetric resolution of $1 \times 1 \times 1$ mm^3.

Lesion-Symptom Mapping

Preprocessing of all images were implemented on FSL 6.0.1 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and MATLAB_R2018a (The MathWorks, Inc., MA, USA), using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/) including MNI orientation, denoising, intensity inhomogeneity correction, brain extraction, and setting the origin of the images at anterior commissure [23-25].

For each patient, the cerebellum was isolated and cropped in T1 and T2 images using SUIT 3.4 toolbox (http://www.diedrichsenlab.org/imaging/suit_function.htm#suit_isolate_seg). Then, lesion masks were drawn guided by both images using semi-automatic segmentation from ITK-SNAP 3.8.0 (http://www.itksnap.org/pmwiki/pmwiki.php). Cerebellum was normalized into SUIT atlas space [26], ignoring the lesion area plus a margin of 5 mm. Lesion masks were normalized using the same deformation parameters.

Support vector regression–based multivariate lesion-symptom mapping (SVR-LSM) [15] was conducted to investigate the neural correlates of chronic cognitive dysfunctions in patients with cerebellar strokes. SVR-LSM models the behavioral scores based on the lesion status of each cerebellar voxel (lesion/no lesion). The model assigned a weight (beta value) to each voxel of the binary lesion masks according to its contribution to the prediction of a behavioral score. Then, each beta value was evaluated via permutation testing to get a voxelwise map of statistical significance.

The settings for SVR-LSM were as follows: minimum lesion overlap = 3 (at least 10% of the sample), 10,000 permutations, voxelwise $P < 0.005$, and age, education, and time post-stroke as covariates regressed out of behavioral scores. Fixed hyperparameters (cost = 30 and gamma = 5) were employed as recommended in the initial publication of SVR-LSM [15] and other studies [27, 28]. All analyses were conducted with DeMarco and Turkeltaub's toolbox [29], which was implemented in MATLAB_R2018a, relying on LibSVM [30] as the machine learning library for SVR, and SPM12 for image manipulation. This toolbox introduced a permutation-based cluster-level correction for multiple comparisons, and regressed lesion volume out of behavioral scores and lesion maps. Both improvements

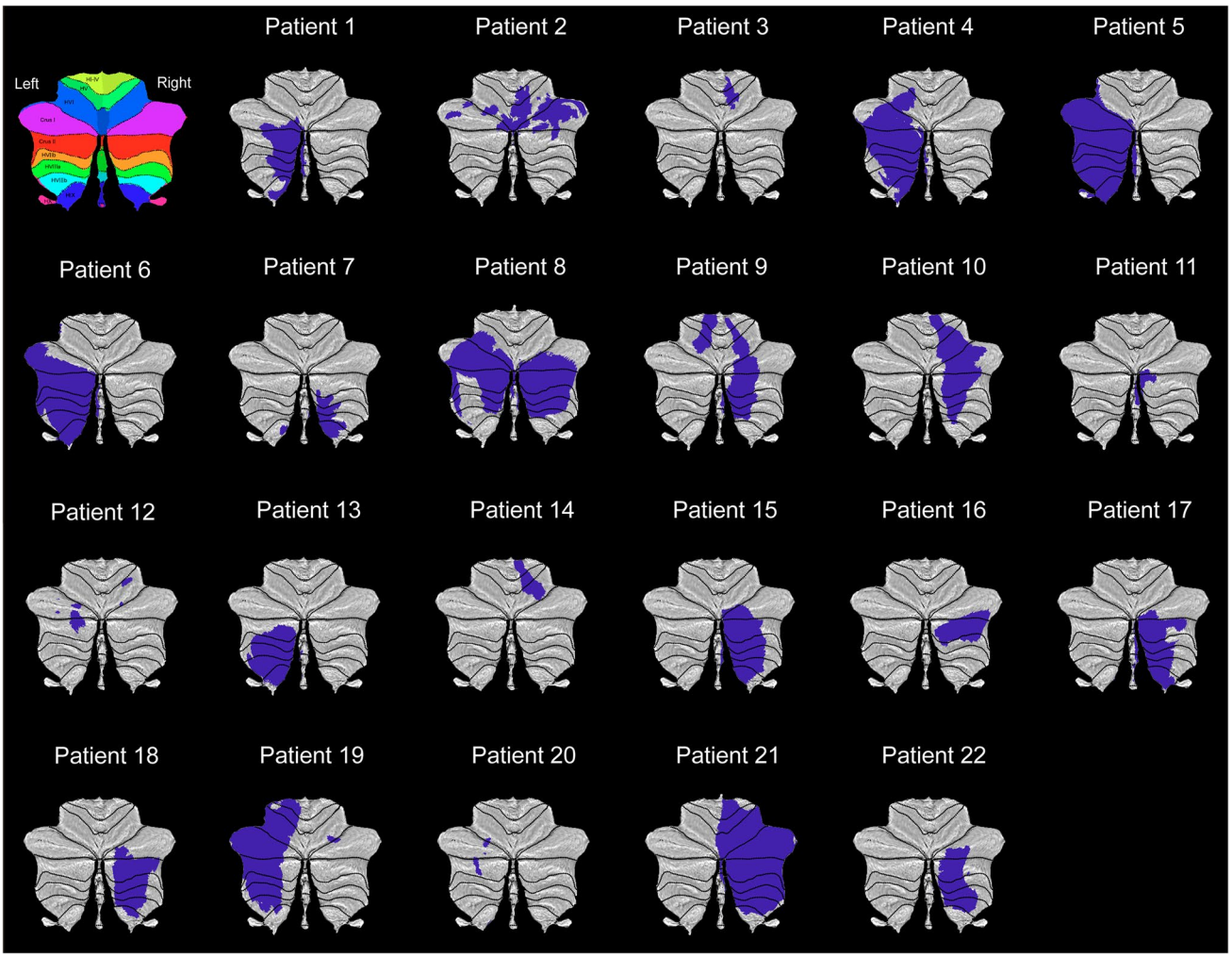

Fig. 1 Individual chronic cerebellar strokes delineated over the flat representation of the human cerebellum developed by Diedrichsen and Zotow [33]. Infarcted tissue is shaded in violet

Table 2 Clinical and demographic features of healthy volunteers (comparison group) and patients with an isolated chronic cerebellar stroke

	Comparison group ($n=22$, 8 females)		Patients ($n=22$, 8 females)		Stroke side: right ($n=11$), left ($n=6$), bilateral ($n=5$)		
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Test statistic	*P* value	Effect size
Age at examination[a]	46.77 ± 12.94	46.79 (19.35)	47.27 ± 13.10	47.37 (18.25)	$t(42) = -0.12$	0.899	$d = -0.03$
Education[a]	13.54 ± 4.28	12.00 (5.00)	13.04 ± 4.58	12.00 (7.50)	$U = 227.50$	0.729	$r = 0.05$
Depressed mood (CES-D)	8.00 ± 4.29	7.50 (6.50)	10.18 ± 7.45	8.50 (6.00)	$U = 206.00$	0.396	$r = -0.12$
Age at stroke[a]	—	—	42.09 ± 13.82	40.29 (16.05)	—	—	—
Time post-stroke[a]	—	—	5.18 ± 4.35	2.91 (7.17)	—	—	—

CES-D Center for Epidemiologic Studies Depression Scale, *SD* standard deviation, *IQR* interquartile range. [a]Data given in years

allowed to overcome the limitations of previous methodologies [29, 31]. However, since univariate methods such as VBLSM [32] are still widely used despite their limitations [15, 29], we replicated our analysis using VBLSM and an alternative multivariate toolbox [16] (with and without hyperparameters optimization), to corroborate our results (Supplementary methods). Results from all image analyses were projected into the SUIT flatmap for visualization [33].

Statistical Analyses

Normality of standardized residuals was evaluated with the Shapiro–Wilk test. Then, Student's t or Mann–Whitney U tests were conducted to compare age, education, depressed mood, PATA, MoCA, and CCAS-S scores between patients and the comparison group. Verbal fluency scores were compared among groups with ANCOVAs or Quade test using PATA scores as the covariate. Bootstrapping was performed with 10,000 samples and effect sizes were calculated by Cohen's *d*, *r* scores or eta-square, as appropriate.

To explore and contrast the diagnostic accuracy of the CCAS-S and MoCA test in patients with chronic cerebellar strokes, the area under the receiver operating characteristic (ROC) curves was compared among both screening tests. ROC analyses were also performed for each task included in the CCAS-S. Standard error was calculated as previously suggested [34].

Diagnostic accuracy for the CCAS-S labels of "absence," "possible," "probable," and "definite" CCAS was explored with interval likelihood ratios (LR) and chi-squared test followed by a post hoc analysis [35].

To calculate sensitivity, specificity, LR +, LR −, accuracy, and odds ratio, cut-off values were selected based on the diagnosis of absence/presence of cognitive impairments from MoCA (impaired score ≤ 25) and CCAS-S (fails ≥ 3). Comparisons between MoCA and CCAS-S regarding sensitivity among patients and specificity among healthy volunteers were conducted with the McNemar test. Pearson correlation analyses were conducted to evaluate the convergent validity among the MoCA test and the CCAS-S.

Finally, in order to explore the influence of age and education over the variability of the CCAS-S scores, independent standard multiple regression analyses were conducted for patients and the comparison group.

Statistical analyses were performed using SPSS-25 and MedCalc-18.2.1. Two-tailed $P < 0.05$ were considered significant after FDR corrections ($q = 0.05$). Also, the confidence intervals (CIs) with a 95% confidence level were reported.

Results

Cognitive Performance

Descriptive statistics for each cognitive screening test are expressed as mean ± SEM (standard error of the mean) for Student's t-test, and Median/IR (interquartile range) for Mann-Whitey U test. Statistic details are shown in Fig. 2.

Regarding total MoCA and CCAS-S scores, patients (MoCA: 25.00/3.25; CCAS-S: 88.18 ± 2.88) showed worse performance than the comparison group (MoCA: 28.00/3.00; CCAS-S: 103.54 ± 1.80). Furthermore, patients (3.36 ± 0.57) exhibit more failures in a larger number of tests included in the CCAS-S compared to the comparison group (1.09 ± 0.20) (Fig. 2A).

Individual analyses of CCAS-S's tests revealed a patients' impaired performance compared to healthy volunteers in semantic (comparison group: 22.86 ± 0.70, patients: 19.50 ± 0.93) and phonemic (comparison group: 14.68 ± 0.73, patients: 11.77 ± 0.86) fluency, category switching (comparison group: 14.50/2.00, patients: 12.50/4.50), digit span forward (comparison group: 5.63 ± 0.23, patients: 4.95 ± 0.20) and backward (comparison group: 4.00/1.25, patients: 3.50/1.00), cube drawing in response to a verbal instruction (comparison group: 15.00/0.00, patients: 15.00/3.00), similarities (comparison group: 8.00/1.00, patients: 7.00/5.00), and Go no-Go test (comparison group: 2.00/1.00, patients: 1.50/2.00) (Fig. 2B). There were no discrepancies between results from Mann–Whitney U test and bootstrapped t-tests.

Additionally, analyses of verbal fluency tasks were controlled with PATA scores because patients (29.11 ± 7.90) had a slower articulation rate ($t(42) = 3.77$, $P = 0.001$, $P_b = 0.001$, $d = 1.13$) than the comparison group (37.31 ± 1.37). These analyses showed no significant group differences for phonemic fluency ($F_{(1,41)} = 5.26$, $P = 0.027$, $q = 0.016$, $\eta_p 2 = 0.11$), semantic fluency ($F_{(1,41)} = 2.18$, $P = 0.147$, $q = 0.050$, $\eta_p 2 = 0.05$), or category switching ($F_{(1,42)} = 1.29$, $P = 0.261$, $q = 0.033$, $\eta_p 2 = 0.03$) (Supplementary Fig. 1).

Indicators of Diagnostic Accuracy in the Cognitive Screening Tests

For each test, details on impaired performance from patients and the comparison group are depicted in Fig. 3A–C. All CCAS-S scores that showed significant differences among groups had an area under the ROC curve greater than 0.5 (Fig. 3D). This means a discriminative ability between patients and the comparison group that beat chance level (semantic fluency: AUC (SE) = 0.71 (0.07), $P = 0.005$, $q = 0.031$; phonemic fluency: AUC (SE) = 0.68 (0.08), $P = 0.024$, $q = 0.043$; category switching: AUC (SE) = 0.70 (0.07), $P = 0.011$, $q = 0.037$; digit span forward: AUC (SE) = 0.66 (0.07), $P = 0.031$, $q = 0.050$; digit span backward: AUC (SE) = 0.71 (0.07), $P = 0.002$, $q = 0.025$; cube: AUC (SE) = 0.69 (0.06), $P = 0.001$, $q = 0.012$; similarities: AUC (SE) = 0.75 (0.06), $P < 0.001$, $q = 0.006$; Go No-Go: AUC (SE) = 0.70 (0.06), $P < 0.001$, $q = 0.018$).

Furthermore, total scores on MoCA (AUC/SE = 0.85/0.06) and CCAS-S (AUC/SE = 0.84/0.06) had areas under the ROC curves significantly greater than 0.5 (MoCA: $P < 0.001$, $q = 0.016$; CCAS-S: $P < 0.001$, $q = 0.033$). The comparison between ROC curves showed no significant difference between MoCA and CCAS-S

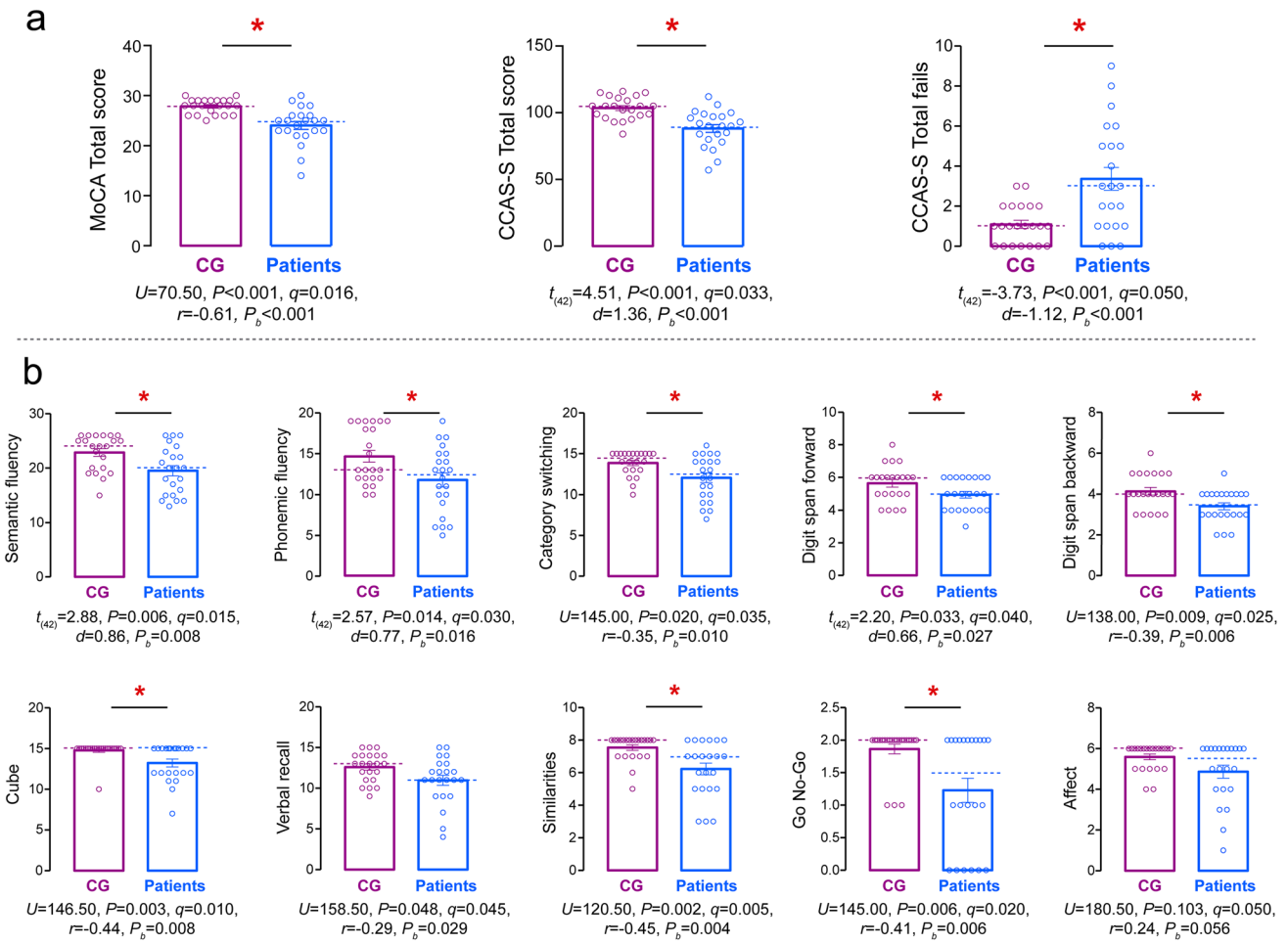

Fig. 2 Comparative analyses of MoCA and CCAS-S performance between healthy volunteers and patients with chronic cerebellar strokes. (A) Total raw scores and fails in MoCA and CCAS-S. (B) Cognitive tests included at the CCAS-S. Mean ± SEM. Median in dotted line. *$P < 0.05$ after FDR corrections ($q = 0.05$). P_b, P bootstrapped (10,000 iterations). CG, comparison group (healthy volunteers). MoCA, Montreal Cognitive Assessment. CCAS-S, Cerebellar cognitive affective syndrome scale

($P = 0.813$), which implied a similar test accuracy for both instruments (Fig. 3E). The maximum value of Youden's index J indicated the optimum cut-off point for MoCA at ≤ 25 with CI ≤ 23–≤ 26 and for CCAS-S at fails ≤ 3 with CI ≤ 1–≤ 3, coinciding with their originals cut-off points, which, consequently, was considered adequate for this cohort of patients with chronic cerebellar strokes.

There was a significant association between cerebellar strokes and diagnostic possibilities of CCAS using the CCAS-S ($\chi^2(3) = 10.57$, $P = 0.014$, Cramer's $V = 0.49$), particularly, patients were more likely than healthy volunteers ($P = 0.001$, $q = 0.012$) to had a "Definite" diagnostic of CCAS (Fig. 2F) with interval LR (CI) of 6.0 (1.51–23.74).

Diagnostics of "Possible" and "Probable" CCAS had LRs (CI) of 0.50 (0.17–1.42) and 0.60 (0.16–2.21), respectively. These results suggested that both diagnostic labels had a poor discrimination ability between patients with chronic cerebellar strokes and healthy volunteers.

Taking into account the diagnostic of absence/presence of cognitive impairments from MoCA (impaired score ≤ 25) and CCAS-S (fails ≥ 3), the number of patients classified with cognitive deficits was major than the number of healthy volunteers for both, MoCA (patients = 15, comparison group = 1, $\chi^2 = 19.25$, $P < 0.001$, Cramer's $V = 0.66$) and CCAS-S (patients = 12, comparison group = 2, $\chi^2 = 10.47$, $P < 0.001$, Cramer's $V = 0.48$).

With the absence/presence dichotomy, quantitative indicators of test performance for MoCA were as follows: sensitivity = 68.18% (CI 45.12–86.13%), specificity = 95.45% (CI 77.15–99.88%), LR + = 15.00 (CI 2.16–103.97), LR − = 0.33 (CI 0.18–0.61), accuracy = 81.81% (CI 67.28–91.80%), and odds ratio = 45.00 (CI 4.99–405.15) significantly different from 1 ($P < 0.001$, $q = 0.025$); and for CCAS-S were as follows: sensitivity = 54.54% (CI 32.21–75.61%), specificity = 90.90% (CI 70.83–98.87%), LR + = 6.00 (CI 1.51–23.74), LR − = 0.50 (CI 0.31–0.80),

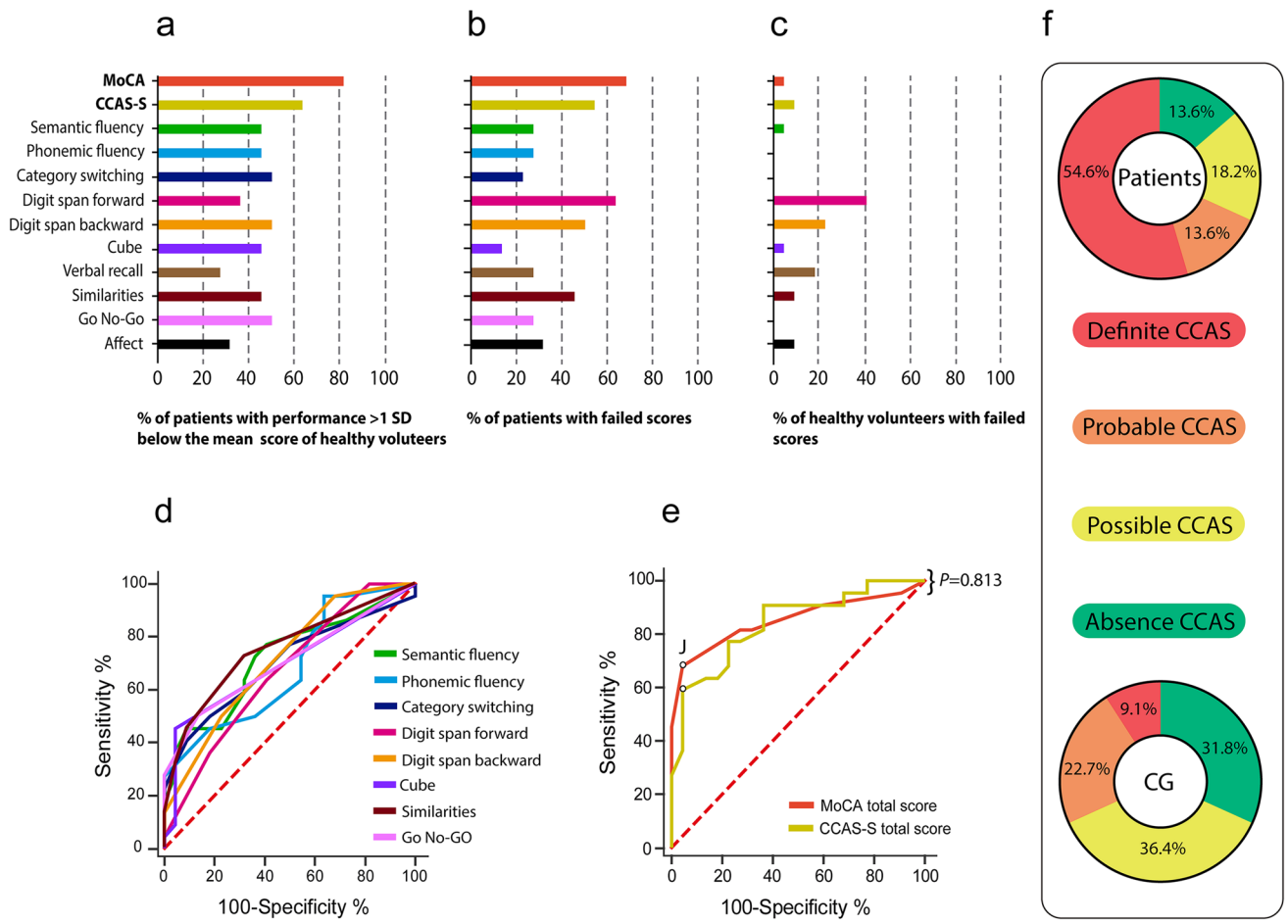

Fig. 3 Indicators of MoCA and CCAS-S performance. Percentage of patients with impaired performance on MoCA and on each test of the CCAS-S compared to (A) healthy volunteers' performance (considering performance > 1 standard deviation below the comparison group mean as indicative of deficit) and (B) cut-off points from each test. (C) Percentage of healthy volunteers with failed scores on MoCA and on each test of the CCAS-S. (D) ROC curves distinguishing between healthy volunteers and patients with chronic cerebellar strokes using each test of the CCAS-S which raw scores showed significant differences among groups. (E) Comparisons of ROC curves using MoCA and CCAS-S total scores. ROC curves plotted the true positive rate (sensitivity) in function of the false positive rate (100-specificity). Dotted red line represents an area under the curve of 0.5 and "J" point stands for the Youden index, i.e., the point with the highest combination of sensitivity and specificity. (F) Percentage of patients and healthy volunteers with the diagnostic of "Definite," "Probable," "Possible," and "Absence" of CCAS derived from the CCAS-S. CG, comparison group (healthy volunteers). MoCA, Montreal Cognitive Assessment. CCAS-S, cerebellar cognitive affective syndrome scale

accuracy = 72.72% (CI 57.21–85.04%), and odds ratio = 12.00 (CI 2.24–64.28) significantly different from 1 ($P = 0.003$, $q = 0.050$).

There were no significant differences in the comparisons between scales regarding sensitivity (P-exact = 0.250) among patients (MoCA = 68.00%, CCAS-S = 54.54%) and specificity (P-exact = 1) among healthy volunteers (MoCA = 95.45%, CCAS-S = 90.90%). Moreover, patients' total score in the MoCA test showed significant correlations with the number of failed tests ($r = -0.79$, $P < 0.001$) and the total score in the CCAS-S ($r = 0.76$, $P < 0.001$).

Considering patients' performance in the CCAS-S as dependent variable, the multiple linear regression analyses showed a significant contribution of education on the variability of the total score ($\beta = 1.68$, $P = 0.007$) and the number of failed tests ($\beta = -0.37$, $P = 0.002$). Age was not a significant predictor of the CCAS-S performance. The multiple correlation coefficient from both, CCAS-S total score ($R = 0.57$, $F_{(2,19)} = 4.58$, $P = 0.024$) and CCAS-S total fails ($R = 0.65$, $F_{(1,19)} = 6.97$, $P = 0.005$), was significantly different from 0. The adjusted R^2 revealed that age and education explained 25.4% and 36.3% of the variance from the CCAS-S total score and CCAS-S total fails, respectively.

Similarly, multiple linear regression analysis within the comparison group showed that education, but not age, was a significant predictor for the CCAS-S total score ($\beta = 0.80$, $P = 0.045$; $R = 0.59$, $F_{(2,19)} = 5.28$, $P = 0.015$; Adjusted

$R^2 = 0.29$). No significant results were found when using CCAS-S total fails as dependent variable.

SVR-Lesion Symptom Mapping

Our initial topological lesion analysis revealed wide-spread coverage of the cerebellar cortex, showing a higher incidence of the stroke in Crus II, VIIb, and VIIIa in the right hemisphere (Fig. 4B).

SVR-LSM analyses showed that worse performance on the CCAS-S total score was associated with damage to the right posterior lobe of the cerebellum, particularly in the lateral portions of lobule VI and Crus I, extending into a minor portion of the right anterior lobe (Fig. 4C). SVR-LSM analyses for semantic fluency and cube drawing also produced significant clusters on lateral portions of right lobule VI and right Crus I. Similarly, category switching was impacted when damage involved lateral portions of right Crus I, Crus II, and lobule VIIb (Fig. 4C). These analyses did not reveal significant clusters associated with MoCA performance or any other task included in the CCAS-S.

These clinically significant cerebellar regions were confirmed with supplementary methodological approaches for LSM (Supplementary results). The main differences included bigger and more distributed clusters when using the alternative multivariate toolbox [15] (with and without hyperparameter optimization; Supplementary Fig. 2C-D). For semantic fluency, category switching, and cube drawing, there was an overlap with the SVR-LSM results conducted with DeMarco and Turkeltaub's toolbox [29].

Regarding VBLSM, category switching and the cube drawing produced significant regions that corresponded with the SVR-LSM results; however, more impaired cognitive tests were associated with damage to the right cerebellar hemisphere, showing smaller clusters than the observed in the multivariate analyses (Supplementary Fig. 2E).

Discussion

This study demonstrated the utility of the MoCA test and the CCAS-S to reveal cognitive impairments in patients with chronic isolated cerebellar strokes. Furthermore, multivariate LSM methods linked the presence of CCAS (identified by the CCAS-S) with chronic lesions in hemispheric regions of the right posterior cerebellar lobe. These findings concurred with the anterior-sensorimotor vs posterior-cognitive cerebellar dichotomy [17]. Beyond this anatomical-restricted functional division, the voxelwise approach provided clinical support to intra- and cross-lobular functional boundaries previously described in the human cerebellum [19].

CCAS has been widely reported after acquired cerebellar injuries [36]; however, there are contradictions about the pervasiveness and persistence of this constellation of symptoms since substantial improvement after the acute epoch has been reported [5, 11, 12]. This recovery could be explained by the resolution of cerebro-cerebellar diaschisis [37], but it could also reflect the need for suitable cerebellar-target neuropsychological tests to evaluate long-term CCAS. The results of our CCAS-S analyses confirmed that cerebellar cognitive impairments can be chronic, revealing

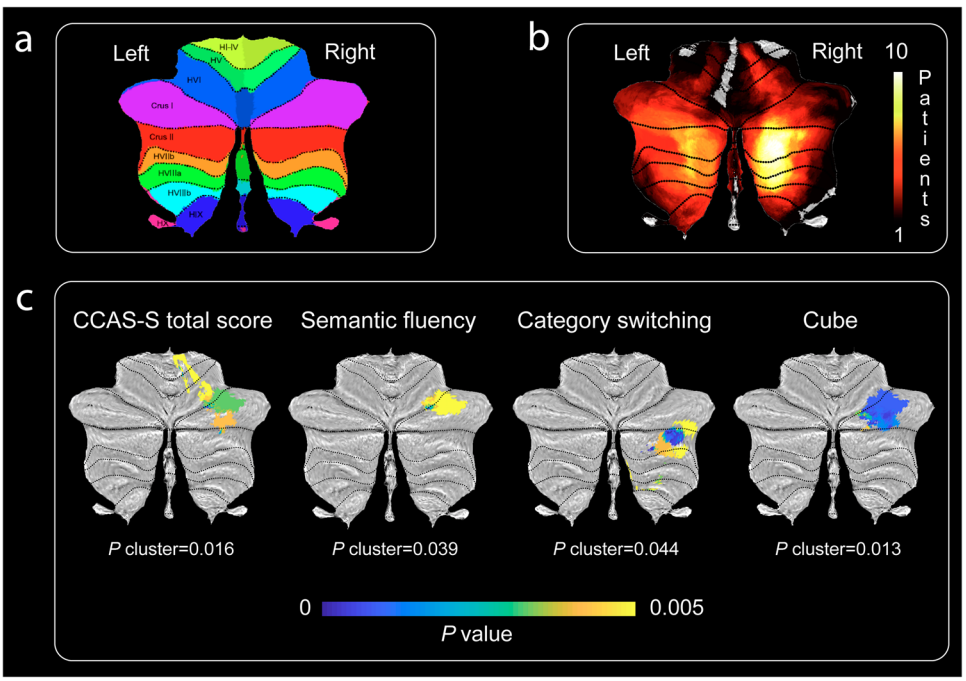

Fig. 4 Lesion symptom mapping results. (A) Flat representation of the human cerebellum developed by Diedrichsen and Zotow [33]. H stands for "Hemispheric," in contrast to the vermis portions in the middle of the flat map. (B) Lesion topography of all 22 cerebellar strokes images with the number of overlaying lesions per voxel represented by a hot color map. (C) SVR-LSM results obtained via the upgraded toolbox of DeMarco and Turkeltaub [29]. *P* values are threshold from 0 to 0.005 (violet to yellow), showing significant beta weights after permutation testing. CCAS-S, cerebellar cognitive affective syndrome scale

the necessity to include appropriate neuropsychological instruments in the long-term clinical management of these patients.

As a warning for the CCAS-S, our results suggest that tasks with verbal fluency requirements should be corrected in case of potential dysarthria since articulation speed obscured group differences in category switching and semantic and phonemic fluency.

Regarding the CCAS-S specificity, two healthy volunteers were classified as "definite CCAS." Thus, in contrast to previous reports [8], we are not concerned about the specificity of the scale. Nevertheless, "possible" and "probable" diagnostics had a significant number of false positives, a scale feature that had already been discussed [6]. Also, our results showed that years of education, but not age, had a significant influence over the CCAS-S performance, which is partially concordant with the findings of previous results [8]. However, it should be noted that patients and healthy volunteers were matched for age and education.

On the other hand, there was an adequate convergent validity between the MoCA tests, one of the most widely used cognitive screening test, and the CCAS-S. Although MoCA has been described as inadequate to detect CCAS [6], we found that both, CCAS-S and MoCA, reliably differentiated patients with chronic cerebellar strokes from healthy volunteers. However, only impairments determined by the CCAS-S resulted in significant regional localization within the cerebellum.

Since the MoCA test was not design to assess the CCAS, it includes subtests not directly related to cerebellar impairments (such as naming and orientation); thus, it was expected that its overall performance would not be associated with the lesions' localization within the cerebellum, although its total score could be affected by the cognitive deficits that arise from the cerebellar damage.

In contrast, the CCAS-S include the assessment of cerebellar-related functions, not contemplated in the MoCA test, such as flexibility and response inhibition [38] (category switching and Go No-Go), self-direction of behavior [39] (cube drawing in response to a verbal instruction), and affect [40]. This could explain why the deficits in the overall performance of the CCAS-S, unlike the MoCA, were associated with damage to specific cerebellar regions. In fact, the tests from the CCAS-S, which showed association with the lesions' localization within the cerebellum, are subscores not included in the MoCA test (semantic fluency, category switching, and cube drawing in response to a verbal instruction).

Regarding the neural correlates of the CCAS-S, overall cognitive impairments and impairments on tasks with language requirements involved damage to right-lateralized posterolateral cerebellar regions. Beyond this crude anatomical-functional relation, widely described in previous reports [3, 9], our findings also identified intra- and cross-lobular significant functional regions which lesions were associated to impairments in specific cognitive tasks from the CCAS-S. For semantic fluency, these included portions of Crus I and lobule VI, which overlap with the "verbal fluency region" in the cerebellar functional organization proposed by King et al. [19]. In relation to the switching category, our analyses produced significant clusters on portions of right Crus II, lobule VI, and lobule VII, which coincided with functional regions associated with divided attention, language processing, and verbal fluency [19]. It should be noted that this functional parcellation of the human cerebellum was developed with healthy volunteers and it is not conformed to the cerebellar anatomical lobular boundaries [19].

Damage to the right cerebellar hemisphere has been related to language deficits [36] and general impairments in cognitive performance [5, 41, 42]. The latter not only could be associated with atrophic changes in left cerebral cortices conditioned by right-lateralized cerebellar insults [42], but also could reflect the impact of language disorders over neuropsychological test performance [6].

In line with the functional boundaries proposed by King et al. [19], the cube drawing task was also affected when lesions involved right-lateralized regions related to language processes and verbal fluency. In the cube drawing task from the CCAS-S, participants are asked to first draw the cube from detailed verbal instructions. The design of this task was based on the idea that cerebellar patients may have more difficulties using metalinguistic abilities to self-directing their own drawing of a cube in response to verbal instructions than they would when copying a cube, that is a more constrained and visually-guided task [6].

Based on the design of this task, it was expected a direct relation between lesions in "language" cerebellar functional regions and an impaired performance in the cube drawing. This relation is also supported by the findings of Guell et al. [39], who reported that cerebellar patients had impaired metalinguistics abilities which could preclude the self-direction/self-organization of behavior and, as a consequence, negatively impacting the general cognitive performance. This could also explain why the overall performance in the CCAS-S was also linked to lesions in "language" functional regions of the right cerebellar hemisphere. However, to confirm our results, future studies should include a larger number of patients to increase the coverage of the topological lesion analysis of the cerebellum. Also, a complete cognitive profile should be considered.

Conclusions

In sum, our findings provide strong evidence for the presence of cognitive impairments in patients with chronic acquired cerebellar lesions. We conclude that both, the MoCA test

and the CCAS-S, efficiently identify cognitive dysfunctions that arise from a long-term CCAS; however, only the CCAS-S shows a correspondence with the cerebellar lesions' locations, particularly with right-lateralized lesions in posterolateral portions of the cerebellum. Our study identifies for the first time clinically intra- and cross-lobular significant functional regions underpinning chronic CCAS and provides clinical support to functional boundaries of the human cerebellum not conformed to lobular anatomical boundaries. As such, we think that these results are an important reference for future studies involving the use of the CCAS-S.

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Declarations

Ethical Approval Study procedures were approved by the ethics committee of the Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez."

Statement of Informed Statement Written consent was obtained from each participant according to the Helsinki declaration.

Conflict of Interest The authors declare no competing interests.

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