RESEARCH ARTICLE

Cognitive Impairments in Spinocerebellar Ataxia Type 10 and Their Relation to Cortical Thickness

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ABSTRACT: Background: Spinocerebellar ataxia type 10 is a neurodegenerative disorder caused by the expansion of an ATTCT pentanucleotide repeat. Its clinical features include ataxia and, in some cases, epileptic seizures. There is, however, a dearth of information about its cognitive deficits and the neural bases underpinning them.

Objectives: The objectives of this study were to characterize the performance of spinocerebellar ataxia type 10 patients in 2 cognitive domains typically affected in spinocerebellar ataxias, memory and executive function, and to correlate the identified cognitive impairments with ataxia severity and cerebral/cerebellar cortical thickness, as quantified by MRI.

Methods: Memory and executive function tests were administered to 17 genetically confirmed Mexican spinocerebellar ataxia type 10 patients, and their results were compared with 17 healthy matched volunteers. MRI was performed in 16 patients.

Results: Patients showed deficits in visual and visuospatial short-term memory, reduced storage capacity for verbal memory, and impaired monitoring, planning, and cognitive flexibility, which were ataxia independent. Patients with seizures (n = 9) and without seizures (n = 8) did not differ significantly in cognitive performance. There were significant correlations between short-term visuospatial memory impairment and posterior cerebellar lobe cortical thickness (bilateral lobule VI, IX, and right X). Cognitive flexibility deficiencies correlated with cerebral cortical thickness in the left middle frontal, cingulate, opercular, and temporal gyri. Cerebellar cortical thickness in several bilateral regions was correlated with motor impairment.

Conclusions: Patients with spinocerebellar ataxia type 10 show significant memory and executive dysfunction that can be correlated with deterioration in the posterior lobe of the cerebellum and prefrontal, cingulate, and middle temporal cortices. © 2021 International Parkinson and Movement Disorder Society

Key Words: spinocerebellar ataxia type 10; cognitive impairments; neuropsychology; cortical thickness; magnetic resonance imaging

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Spinocerebellar ataxia type 10 (SCA10) is a neurodegenerative disease caused by the expansion of a pentanucleotide repeat (ATTCT) in intron 9 of the ataxin 10 gene.[1] Pathogenic alleles range from 800 to 4500 ATTCTs,[1] whereas the normal alleles range from 9 to 32.[2] SCA10 is characterized by progressive cerebellar ataxia, dysarthria, and dysphagia.[3]

SCA10 was first clinically described in a study conducted in families of Mexican ancestry.[4] Although there are reports of SCA10 patients from North America[5] and East Asia,[6] Latin America has been pointed to as the region with the highest incidence,[7] where 2 main

TABLE 1 *Clinical and demographic features of healthy controls and SCA10 patients*

	Controls (n = 17, 7 women)		SCA10 (n = 17, 8 women)			
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Test statistic	*P*
Age at examination[a]	48.52 (10.27)	49.00 (12.00)	49.23 (9.18)	51.00 (11.00)	$t_{32} = -0.21$	0.834
Education[a]	10.82 (2.89)	12.00 (3.00)	10.23 (2.58)	9.00 (3.00)	$t_{32} = 0.62$	0.537
Age at onset of disease[a]	—	—	30.17 (7.07)	30.00 (10.00)	—	—
Disease duration[a]	—	—	19.00 (8.85)	19.00 (13.50)	—	—
ATTCT repeat length (n = 9)	—	—	2753.33 (840.18)	2861.00 (1778.00)	—	—
Scale for the Assessment and Rating of Ataxia (SARA)	—	—	17.44 (6.24)	17.00 (9.00)	—	—
Center for Epidemiologic Studies Depression Scale (CES-D)	10.26 (9.55)	5.00 (10.00)	14.33 (7.81)	12.00 (11.00)	$U = 70.50$	0.081

[a]Data given in years.
SD, standard deviation; SEM, standard error of the mean; IQR, interquartile range.

subsets of SCA10 seem to coexist: "Mexican" and "Brazilian" SCA10.

The Brazilian phenotype is associated with pure cerebellar ataxia,[8] whereas the Mexican subtype of SCA10 is characterized by the presence of seizures along with cerebellar ataxia.[4] This phenotypic heterogeneity could be related to the repeat composition of the expanded allele because the presence of ATCCT interruptions between the ATTCT and ATCCC tracts indicates a significant risk for the epilepsy phenotype.[9]

Despite advances in the molecular and neurological aspects of SCA10, to date, little is known about its cognitive consequences. Two previous studies have described cognitive impairments in Mexican and Brazilian SCA10 patients; nevertheless, the cognitive evaluations were restricted to intelligence quotient scores[4] or few isolated neuropsychological tests.[10]

In contrast, extensive neuropsychological evaluations have been conducted in other SCA subtypes describing cognitive domain–specific impairments, particularly memory and executive dysfunction.[11-14] The cognitive profiles in SCA patients have been related to a frontopontocerebellar disruption,[15-17] causing symptoms inherent to cerebellar cognitive affective syndrome.[18]

Previous studies have focused on the impact of ataxia severity on SCA10 patients' physical functioning[19,20]; however, more information is needed to delve into the consequences of cognitive impairment. Furthermore, although cerebellar and extracerebellar atrophy has been well characterized in patients with SCA10,[21,22] there is still a lack of information about the neural bases underpinning cognitive changes in these patients.

Taking into account the previous limitations, the aim of this study was to explore the performance of SCA10 patients in 2 cognitive domains typically affected in SCAs: memory and executive function. Our second objective was to correlate the identified cognitive impairments with ataxia severity, age at onset of disease, and cerebral/cerebellar cortical thickness, as quantified by MRI.

Materials and Methods

Participants

Seventeen Mexican patients with amolecular diagnoses of SCA10 were enrolled. As an inclusion criterion, all patients had a proven pentanucleotide (ATTCT) repeat within the expanded range, but the specific number of repeats was not determined in all cases. Nine patients reported the presence of seizures (confirmed by relatives) and 7 of them were on medications (magnesium valproate). Further detailed features of the seizures were not available. Besides the spinocerebellar ataxia, patients showed no history of acquired brain injuries and did not have contraindications to MRI. Disease severity was scored according to the Scale for the Assessment and Rating of Ataxia (SARA).[23] Seventeen age-, sex-, and education-matched healthy volunteers with no history of neurological/psychiatric diseases formed the control group (Table 1).

Exclusion criteria for both groups included age < 18 years, pregnancy, and the inability to follow basic instructions in a motor screening task. All procedures in this study were approved by the ethics committee of the Universidad Nacional Autónoma de México in accordance with the Helsinki Declaration. Written consent was obtained from each participant.

Cognitive Measures

Patients and controls were assessed with the Cambridge Neuropsychological Testing Automated Battery (CANTAB).[24] Cognitive domains evaluated included memory, executive function, and screening tests. All participants underwent all cognitive tests except for Rey Auditory Verbal Learning Test Spanish Version (RAVLT-S), verbal fluency, and PATA, which were only completed by 14 patients.

Screening Tests

Montreal Cognitive Assessment Test

The Montreal Cognitive Assessment (MoCA) is a cognitive screening measure that assesses executive function, verbal memory, visuospatial ability, attention, working memory, language, abstract reasoning, and orientation to time and place.[25] The MoCA total score (30 points) reflects global cognitive performance. A score above 25 is considered normal.

Motor Screening Task (MOT-CANTAB)

The motor screening task (MOT) provides a measure of sensorimotor impairment and lack of comprehension. Participants had to touch, as fast and accurately as possible, a flashing cross presented in changing positions on the screen.[26] The mean number of milliseconds taken to touch the cross after it appeared (mean latency) and the number of incorrect responses (total error) were used as dependent variables.The Center for Epidemiologic Studies Depression Scale (CES-D) was used as an indicator of depressed mood.[27]

Visual Memory Tests

Delayed Matching to Sample (DMS-CANTAB)

The delayed-matching sample (DMS) provides a measure of visual matching ability and short-term visual recognition memory.[28] A visual pattern was displayed on the screen, and after a short delay, 4 choice patterns appeared beneath the sample. Participants had to touch the pattern that exactly matched the sample. In some trials the sample and the choice patterns were shown simultaneously, and in others there was a delay (0, 4, or 12 seconds) before the 4 choices appeared. The number of trials with correct answers (total correct) was measured as a dependent variable. "Prob. error given error" was measured to indicate the probability of an error occurring when the previous trial was incorrect. This measure explored the cognitive mechanism that monitors for errors and recalibrates task performance accordingly.

Spatial Memory Span (SSP-CANTAB)

Spatial memory span (SSP) assesses visuospatial memory span.[29] Nine white boxes were presented, and some of them briefly changed color in a variable sequence. Participants had to touch the boxes that changed color in that same order. After each correct trial, the sequence length increased up to 9. The target variable was the longest sequence successfully recalled (span length).

Verbal Memory Test

Rey Auditory Verbal Learning Test Spanish Version (RAVLT-S)

The RAVLT-S is a 15-noun list presented 5 times (A1 to A5). After each trial participants have to repeat as many words as possible. After an interference trial, there is an immediate recall, a delayed recall (20 minutes after), and a final trial of recognition. The following scores were derived: immediate memory span (A1), learning rate, learning curve, retroactive interference, forgetting rate, and recognition memory (including false-positive and false-negative answers).[30,31]

Executive Function Tests

Intra-/Extradimensional Set Shift (IED-CANTAB)

Intra-/extradimensional set shift (IED) assesses flexibility of attention.[32] Participants observed 2 patterns displayed on a screen and had to use feedback to figure out a rule that determined which pattern was correct. After 6 correct responses, the stimuli and/or rule changed, and participants advanced to a new stage. The task included 9 stages (Supplementary Methods). In the intradimensional shift condition (IDS stage 6), participants had to switch rewards, whereas in the extradimensional shift condition (EDS stage 8), participants had to learn that reward is provided by new stimuli (perceptual dimensions). Total errors at each stage and the number of stages completed were used as dependent variables.

Stocking of Cambridge (SOC-CANTAB)

Stockingof Cambridge (SOC) is a measure of problem-solving ability.[33] Participants were asked to rearrange 3 colored balls contained in 3 stockings to match a target arrangement. They were instructed to plan their sequence of moves to accomplish the task in a specified minimum number of moves (2 to 5). In a second phase, participants copied movements that simulated the movements executed when originally solving the problem. The number of problems solved in minimum moves, the mean moves taken to solve problems, and the mean initial thinking time (difference in time taken to select the first ball for the same problem under the copy-and-follow condition) were included as dependent variables.

Spatial Working Memory (SWM-CANTAB)

Spatial working memory (SWM) is a self-ordered searching task that = requires maintenance and manipulation of visuospatial information.[34] (Supplementary Methods).

Semantic and Phonemic Verbal Fluency

Participants were required to say as many words as possible in 1 minute that began with the letters "P," "M," and "R" and as many animal names as possible. Total correct words, number of clusters, mean cluster size, and number of switches were calculated, as previously described.[35]

To assess articulation speed, participants were asked to repeat the pseudoword "PATA" for 10 seconds during 2 trials.[36] Mean score of the 2 trials was calculated for the analyses.

MRI Acquisition

Sixteen SCA10 patients agreed to participate in the MRI study. Images were acquired at the Instituto de Neurobiología of the Universidad Nacional Autónoma de México in Juriquilla, Querétaro, México, using a 3T General Electric MR750 Discovery scanner with a 32-channel head coil. The study included the acquisition of a high-resolution T1-3-D volume using a SPGR sequence, with TE/TR, 3.18/8.16 milliseconds; FOV, 256×256 mm^2; and acquisition and reconstruction matrix, 256×256, resulting in an isometric resolution of $1 \times 1 \times 1$ mm^3.

Cerebral Cortical Thickness

Image preprocessing included MNI reorientation, denoising,[37] and intensity inhomogeneity corrections.[38] Cortical reconstruction processing was performed using FreeSurfer 6.0.0 (http://surfer.nmr.mgh.harvard.edu/fswiki; Supplementary Methods). All outcomes were visually inspected for accuracy, and minor manual corrections were performed. Linear relationships between cortical thickness and performance on impaired motor/cognitive tasks were evaluated. Using the Query Design Estimate Contrast included on FreeSurfer, a t test was performed at each vertex's vector through the general linear model, correcting for multiple comparisons using false discovery rate (FDR; $q < 0.05$). Age was included as a covariate because it is known to influence the trajectory of the disease and the cortical thickness.[39]

Cerebellar Cortical Thickness

The cerebellar cortical thickness was calculated with an automated process using the tool CERES (CEREbellum Segmentation) from the online automated volumetric system VolBrain (http://volbrain.upv.es).[40]

The CERES preprocessing phase included image transformation to a common geometric and intensity space. The segmentation phase consisted of several steps described elsewhere[41] and included a post-processing step allowing enforced regularity of the different cerebellar lobule labels. To determine the relationship between SCA10 patients' impaired motor/cognitive scores and cortical thickness of each cerebellar lobule, Pearson partial correlations or Spearman partial rank correlations were run while controlling for age, using FDR correction.

Statistical Analyses

Normality of the standardized residuals was evaluated with the Shapiro–Wilk test. Comparisons between SCA10 patients and controls regarding clinical features and cognitive scores were conducted using the independent-sample t test or the Mann–Whitney U test. Effect sizes were calculated by Cohen's d or r scores.

CANTAB scores with different levels of difficulty (eg, varying delay periods before memory was tested) were compared among groups with mixed analysis of variance (ANOVA), using difficulty as a within-subject factor and group (patients vs. controls) as a between-subject factor. Sphericity was proved with Mauchly's test, and when violations occurred, the Huynh–Feldt correction was applied. Significant interaction effects were further analyzed with post hoc pairwise comparisons using Bonferroni adjustment. Skewed distributions (SOC mean initial thinking time, IED total adjusted errors, and SWM total errors) were log10-transformed before statistical analysis.

Verbal fluency scores were analyzed by analysis of covariance (ANCOVA) or the Quade test, using PATA score as a covariate. Effect size for ANCOVAs and mixed ANOVAs were calculated by partial η_p^2.

A multiple-comparison correction using FDR was performed within the measures derived from MOT and from each cognitive domain (visual memory, verbal memory, and executive function). Subsequently, cognitive scores in SCA10 patients that showed significant decreases were compared in patients with and without seizures using the t test or Mann–Whitney U test, as appropriate.

Spearman's rho or Pearson correlation coefficient was used for correlation analyses between impaired motor/cognitive scores and CES-D score, age at onset, and disease duration. The multiple-correlations problem was addressed with FDR corrections. To explore the influence of age and education over the variability of cognitive scores, independent standard multiple-regression analyses were conducted for patients and controls.

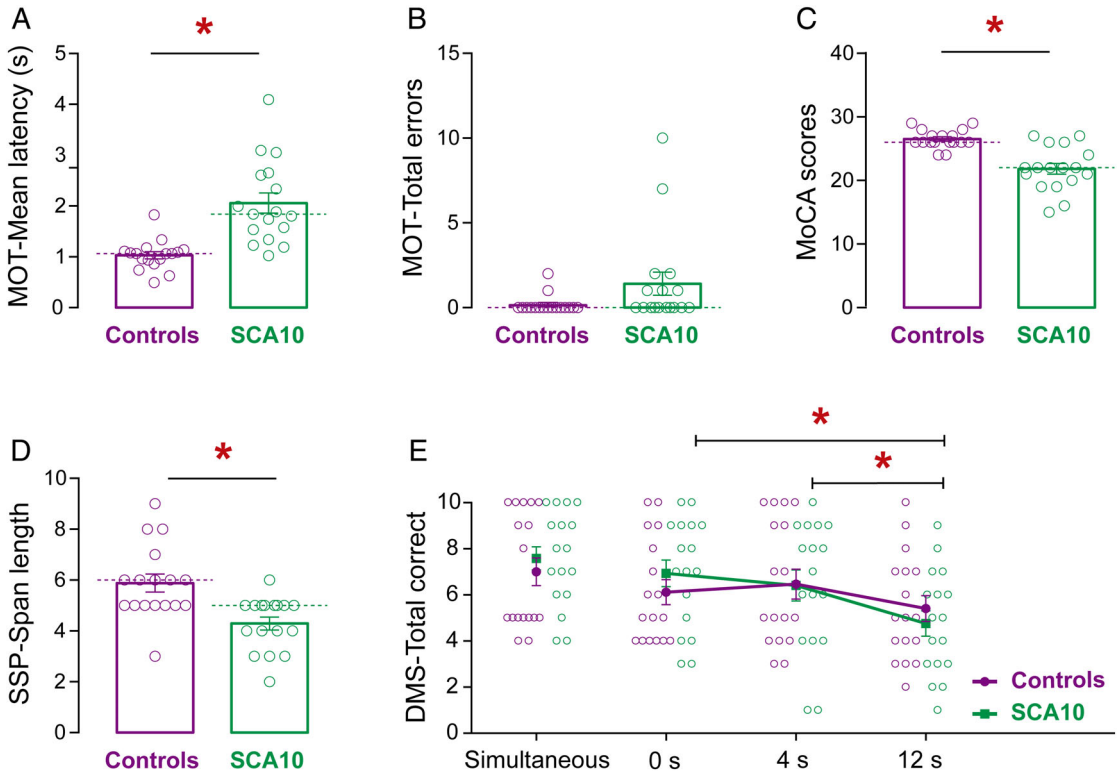

FIG. 1. Performance of controls and SCA10 patients on motor/cognitive screening and visual/visuospatial memory tests. (**A**) Mean seconds taken to touch the screen after the stimulus appeared during MOT task. (**B**) Number of incorrect responses in MOT task. (**C**) Total score in MOCA test. (**D**) Longest sequence successfully recalled in SSP task. (**E**) Number of correct answers in simultaneous and delayed trials during DMS task. Data are expressed as mean ± SEM. Dotted lines represent the median. *$P < 0.05$ significant after FDR corrections ($q = 0.05$). [Color figure can be viewed at wileyonlinelibrary.com]

All statistical analyses were performed using SPSS 25, and results were considered significant when $P < 0.05$. The FDR threshold was $q = 0.05$.

Results

Controls and patients were matched for age, education, and CES-D score (Table 1).

Cognitive Performance

Descriptive statistics are expressed as mean ± standard error of the mean (SEM) for parametric tests and median (interquartile range [IQR]) for Mann-Whitney tests.

Motor and Cognitive Screening Tests

In MOT, patients (1838.80/1192.15) performed slower ($U = 19.00$, $P < 0.001$, $q = 0.025$, $r = -0.74$) than controls (1065.11/228.30), but the pointing accuracy was similar for both groups ($U = 100.50$, $P = 0.051$, $q = 0.05$, $r = -0.33$; Fig. 1A,B). In the MoCA test, patients (21.82 ± 0.84) had lower scores ($t_{32} = -5.15$, $P < 0.001$, $d = 1.77$) than controls (26.52 ± 0.34; Fig. 1C). Of the patients, 76.47% showed scores below the clinical cutoff point (≥26).

Visual Memory Tests

Total correct answers in DMS simultaneous matching did not differ significantly between groups ($U = 138.00$, $P = 0.822$, $r = -0.03$); however, a mixed ANOVA found significant interaction among group and delayed matching ($F_{2,64} = 3.40$, $P = 0.039$, $q = 0.050$, $\eta_p^2 = 0.09$) without a significant group effect ($F_{1,32} = 0.003$, $P = 0.960$, $\eta_p^2 < 0.001$). Simple main effects revealed that patients showed poorer performance at 12 seconds delayed (4.76 ± 0.55) compared with both, 0 seconds delayed ($P < 0.001$, 6.94 ± 0.57) and 4 seconds delayed ($P = 0.003$, 6.41 ± 0.67); see Figure 1E. In SSP-span length, patients (4.2 ± 0.25) were impaired ($t_{32} = -3.65$, $P = 0.001$, $q = 0.025$, $d = 1.26$) relative to controls (5.88 ± 0.35); see Figure 1D.

Verbal Memory Test

Regarding RAVLT-S, immediate memory span did not show significant differences ($t_{26.64} = 2.51$, $P = 0.018$, $q = 0.018$, $d = 0.92$) between patients (4.00 ± 0.43) and controls (5.66 ± 0.50); see Figure 2A. The mixed ANOVA on number of items recalled from trials A1 to A5 showed a significant effect of group ($F_{1,27} = 12.07$, $P = 0.002$, $q = 0.006$,

η_p^2 = 0.30; controls, 9.52 ± 0.33; SCA10, 7.58 ± 0.36), but no interaction between group and trials ($F_{3.03,81.96}$ = 0.82, P = 0.48, η_p^2 = 0.03). This result implied that patients showed a slower learning curve than controls (Fig. 2H); however, there was no group difference in learning rate (t_{27} = −0.12, P = 0.903, q = 0.05, d = 0.04), because both groups were able to increase the information volume from trial to trial (Fig. 2B).

Patients (0.63 ± 0.07) were more prone to retroactive interference (t_{27} = −2.94, P = 0.007, q = 0.012, d = 1.08) compared with controls (0.89 ± 0.04); see Figure 2C. There was no difference among groups in the forgetting rate (U = 93.50, P = 0.612, q = 0.043, r = −0.09; Fig. 2D). Analyses revealed that patients (10.50/4.50) performed significantly worse than controls (13.00/1.00) in recognition memory (U = 54.50, P = 0.026, q = 0.031, r = −0.41; Fig. 2E), because patients made a greater number of false-negative answers (U = 52.50, P = 0.019, q = 0.025, r = −0.43; controls, 1.00/2.00; SCA10, 3.50/3.50); however, the number of false-positives did not differ among groups (U = 83.50, P = 0.310, q = 0.037, r = −0.18; Fig. 2F,G).

Executive Function

On DMS, patients (0.33/0.42) were more likely to make errors after committing a previous mistake (U = 67.00, P = 0.004, q = 0.0125, r = −0.49) compared with controls (0.14/0.10; Fig. 3A).

Regarding IED, the number of stages that reached the success criterion (6 consecutive correct responses) was significantly lower among patients compared with controls (U = 45.50, P < 0.001, q = 0.003, r = −0.64; controls: 9.00/1.00; SCA10, 7.00/0.00; Fig. 3B). To

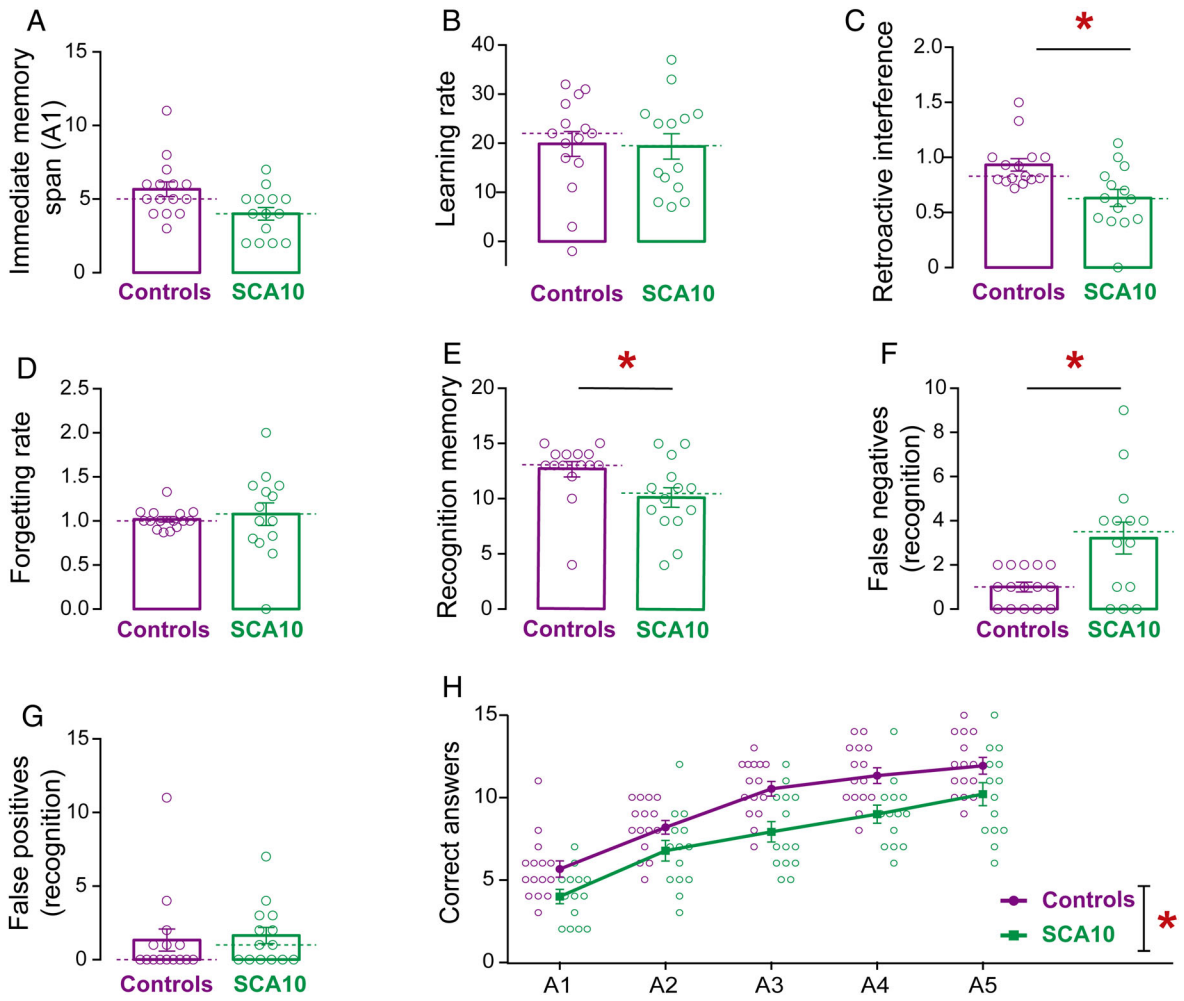

FIG. 2. Performance of controls and SCA10 patients on verbal memory test (RAVLT-S). (**A**) Total correct words recalled in first trial (A1). (**B**) Gain of recalled nouns over 5 trials. (**C**) Interference effect of a list of nouns previously learned over the learning of a new list. (**D**) Loss of information acquired after 20 minutes. (**E**) Number of nouns that were correctly identified as familiar from a list containing familiar and unfamiliar nouns. (**F**) Spurious rejections of familiar information. (**G**) Spurious recognition of unfamiliar information. (**H**) Number of correct words recalled during each coding trial (A1 to A5). Data are expressed as mean ± SEM. Dotted lines represent the median. *P < 0.05 significant after FDR corrections (q = 0.05). [Color figure can be viewed at wileyonlinelibrary.com]

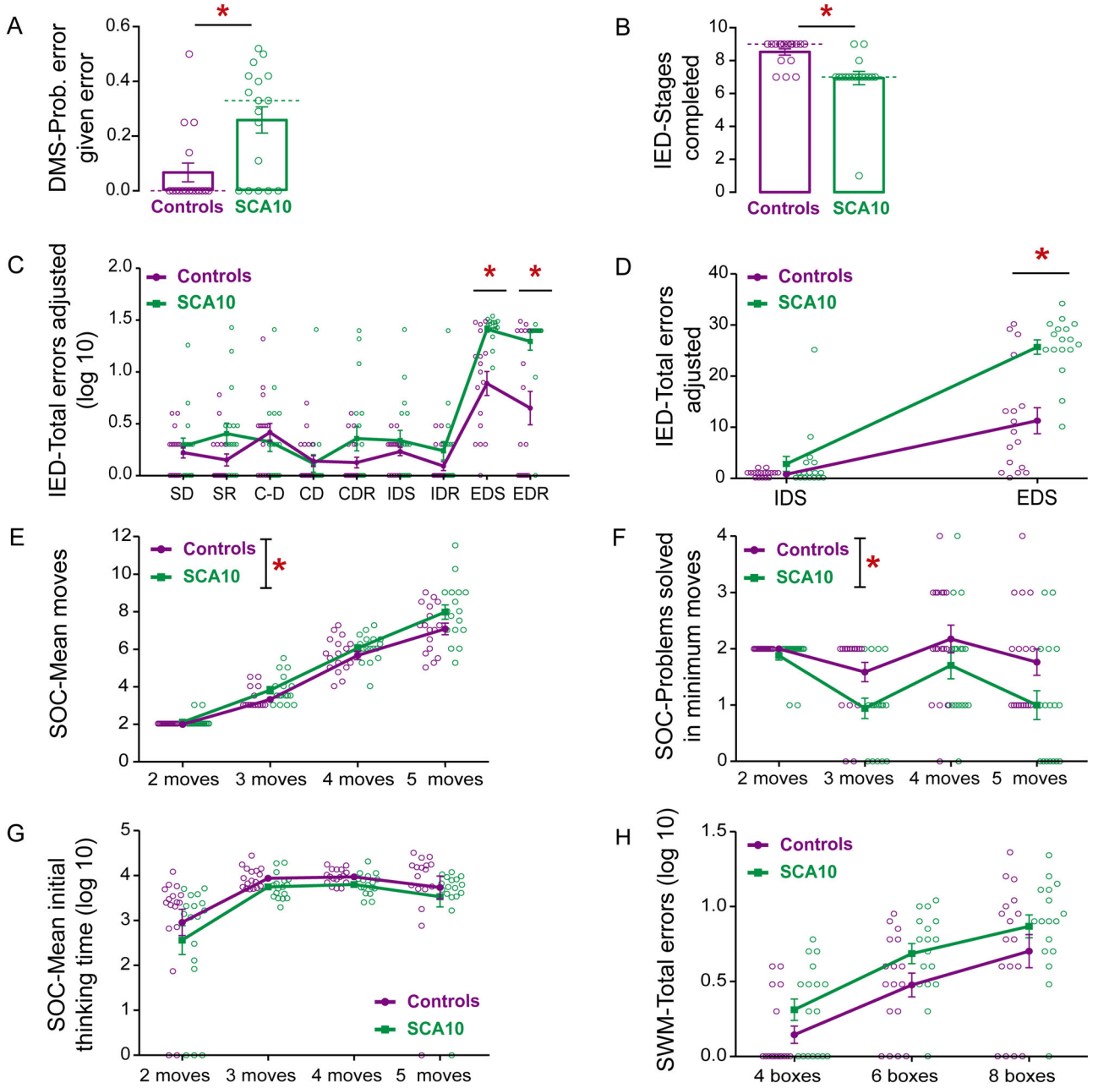

FIG. 3. Performance of controls and SCA10 patients on executive functions tests. (**A**) Probability of an error occurring when the previous trial was incorrect during DMS task. (**B**) Number of stages in which participants achieved 6 consecutive correct answers during IED task. (**C**) Number of adjusted errors (log10-transformed) at each stage of the IED task. (**D**) Number of adjusted errors in the intradimensional and extradimensional shift stages during IED task. (**E**) Mean moves taken to solve a problem at each difficulty level of the SOC task. (**F**) Number of problems solved with the minimum of movements required at each difficulty level of the SOC task. (**G**) Mean milliseconds (log10-transformed) taken to start the solution of a problem at each difficulty level of the SOC task. (**H**) Number of errors (log10-transformed) committed at each difficulty level during SWM task. Data are expressed as mean ± SEM. Dotted lines represent the median. *$P < 0.05$ significant after FDR corrections ($q = 0.05$). SD, simple discrimination; SR, simple reversal; C-D, compound discrimination; CD, compound discrimination with superimposed elements; CDR, compound discrimination reversal; IDS, intradimensional shift; IDR, intradimensional shift reversal; EDS, extradimensional shift; EDR, extradimensional shift reversal. [Color figure can be viewed at wileyonlinelibrary.com]

delve into this finding, the total adjusted errors committed across the 9 stages were analyzed by a mixed ANOVA. There was a statistically significant effect of group ($F_{1,32} = 11.06$, $P = 0.002$, $\eta_p^2 = 0.25$; controls, 0.32 ± 0.03; SCA10, 0.53 ± 0.04) and a significant interaction between group and stage ($F_{3.26,104.33} = 4.70$, $P = 0.003$, $q = 0.009$, $\eta_p^2 = 0.12$; Fig. 3C). Pairwise comparisons revealed that patients committed a greater number of errors than controls in stages 8 ($P < 0.001$; controls, 0.88 ± 0.11; SCA10, 1.41 ± 0.02) and 9 ($P < 0.001$; controls, 0.65 ± 0.16; SCA10, 1.29 ± 0.08).

Because a major number of patients could not complete stage 8 (EDS), the difference among groups on total errors in stage 9 (EDR) might be related to the adjusted score for stages not attempted because of failure. Finally, to dissociate patients' impairments at intra- and extradimensional shifting, a mixed ANOVA was conducted to compare adjusted errors in stages 6 and 8. This analysis showed a significant group × stage interaction ($F_{1,32} = 13.43$, $P = 0.001$, $q = 0.006$, $\eta_p^2 = 0.29$; Fig. 3D) because patients showed a lower performance only at the EDS ($P < 0.001$; controls, 11.29 ± 2.55; SCA10, 25.70 ± 1.42), whereas there was no group difference at the IDS ($P = 0.18$; controls, 0.82 ± 0.15; SCA10, 2.82 ± 1.47).

Mixed ANOVA on mean number of moves to solve SOC problems showed a significant group effect because patients needed more movements to accomplish the task ($F_{1,32} = 7.97$, $P = 0.008$, $q = 0.018$, $\eta_p^2 = 0.19$; controls, 4.52 ± 0.26; SCA10, 4.99 ± 0.29; Fig. 3E). No significant group × difficulty level interaction was found ($F_{1.96,62.71} = 1.14$, $P = 0.325$, $\eta_p^2 = 0.03$). A significant group effect ($F_{1,32} = 8.33$, $P = 0.007$, $q = 0.015$, $\eta_p^2 = 0.20$; controls, 1.88 ± 0.09; SCA10, 1.38 ± 0.11), but no interaction effect ($F_{3,96} = 1.26$, $P = 0.29$, $\eta_p^2 = 0.03$) was also found for number of problems solved in minimum moves, supporting the conclusion of impaired planning accuracy among patients (Fig. 3F). These results were not conditioned by impulsive behavior because there was no difference among groups for mean initial thinking time ($F_{1,32} = 3.01$, $P = 0.09$, $q = 0.031$, $\eta_p^2 = 0.08$; Fig. 3G).

In terms of visual working memory (SWM), a mixed ANOVA on total errors at set sizes 4, 6, and 8 showed neither a significant group effect ($F_{1,32} = 3.98$, $P = 0.054$, $q = 0.021$, $\eta_p^2 = 0.11$) nor an interaction effect among group and set size ($F_{2,64} = 0.09$, $P = 0.90$, $\eta_p^2 = 0.003$); see Figure 3H. Finally, there were no significant group differences for phonemic or semantic fluency (Table S1). Verbal fluency analyses were controlled for PATA scores because patients (18.88 ± 1.07) had a slower articulation rate ($t_{27} = -7.83$, $P < 0.001$, $d = 2.94$) than controls (35.60 ± 1.80).

Motor/Cognitive Performance and Seizure Presence

SCA10 patients with seizures (n = 9) and without seizures (n = 8) showed no significant differences in clinical and demographic features (Supplementary Results). Neither SARA score nor impaired cognitive score (relative to controls) differed significantly between groups (Table S2).

Motor/Cognitive Performance and Clinical Features/Cortical Thickness

SCA10 patients' impaired cognitive scores did not show significant correlations with age at onset of disease, disease duration, SARA score, or CES-D score. However, SARA was significantly correlated with age at onset ($r = -0.51$, $P = 0.047$, $q = 0.050$) and disease duration ($r = 0.67$, $P = 0.003$, $q = 0.025$).

Multiple linear regression analyses within the control group showed that neither education nor age was a significant predictor for the healthy volunteers' cognitive performance. Similarly, education and age were not significantly related to the impaired cognitive scores among SCA10 patients (Supplementary Results).

Cortical thickness analyses were done to determine if SCA10 patients' deficits in cognitive tasks could be explained by specific deterioration in circumscribed cerebral/cerebellar regions. Results showed positive relationships between the number of stages completed at the IED task and left caudal middle frontal, inferior temporal, middle temporal, opercular, and cingulate gyri (Fig. 4A–D; Table S3).

Regarding cerebellar lobules, there were significant positive correlations among SSP-span length and cortical thickness of bilateral lobules VI, IX, and right lobule X (Fig. 4F). SARA score showed significant negative correlation with cortical thickness of several cerebellar lobules, as shown in Figure 4E.

Discussion

Here we administered extensive neuropsychological testing to do an initial characterization of the possible domain-specific deficits in a cohort of SCA10 patients. Results showed disturbances in visual and visuospatial short-term memory, reduced storage capacity for verbal memory, and impaired monitoring, planning, and cognitive flexibility. These cognitive changes were independent of both the presence of seizures and ataxia severity, but they were related to cerebral and cerebellar cortical thickness variation. To the best of our knowledge, this is a first effort to explore the neural underpinnings of cognitive impairments in SCA10.

The SARA revealed a variable range of impairments related to cerebellar ataxia in all patients. As previously reported,[3,21] greater severity of ataxia was associated with an earlier onset and a longer disease duration. SARA score did not show any association with cerebral cortical thickness; however, it was correlated with bilateral anterior and posterior cerebellar lobe cortical thickness, including those regions in which lower gray-matter intensity has previously been associated with higher SARA score in SCA10.[22] In the same way as other SCA subtypes, severity of ataxia seemed to be

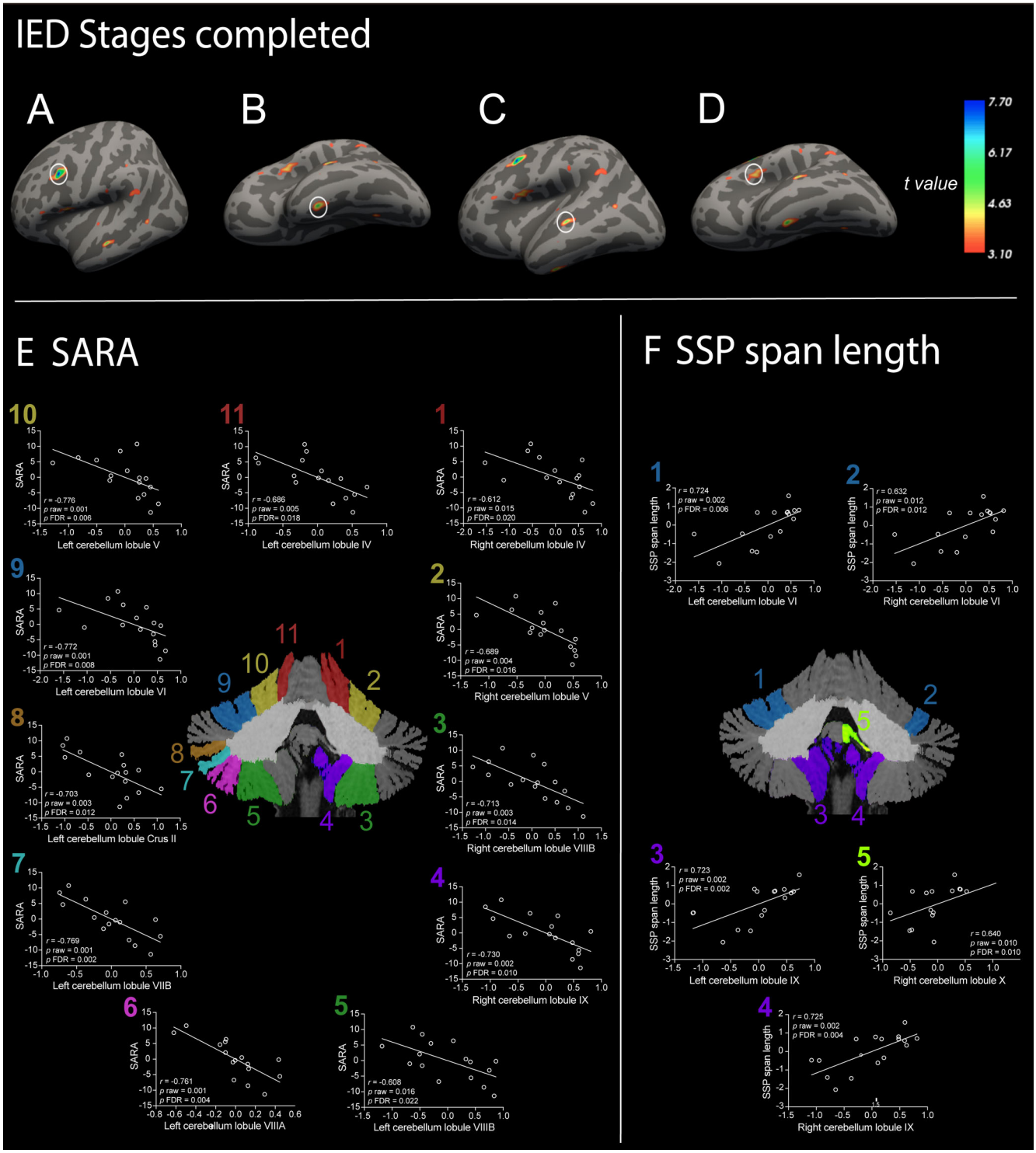

FIG. 4. Cerebral regions showing significant relationships (after FDR corrections) between cortical thickness and IED stages completed. (**A**) Left caudal middle frontal gyrus, (**B**) Left inferior temporal gyrus, (**C**) Left middle temporal gyrus. (**D**) Left opercular gyrus. The lower panel display cerebellar lobules showing significant correlations (after FDR correction) of cortical thickness with (**E**) SARA score and (**F**) span length in SSP task. *X* and *Y* axes from the scatterplots are expressed as residuals because partial correlations were adjusted considering age as a covariate. [Color figure can be viewed at wileyonlinelibrary.com]

related to the extent of cerebellar,[42,43] but not cerebral, neurodegeneration.

Regarding cognitive performance, our findings suggested that MoCA was useful for detecting signs of cognitive decline in SCA10. Because the MOT task proved that SCA10 patients showed adequate comprehension of the instructions and adequate pointing accuracy when using a touch screen, it was possible to

assess their cognitive status using more complex computerized neuropsychological tests.

DMS simultaneous matching partially ruled out the presence of basic visual perception impairments in SCA10 patients. However, in the delayed-matching condition, patients showed a poor performance at 12 seconds delayed. These results suggested a decline in visual memory when longer retention times were required. In contrast, visual memory traces were not affected at 0 or 4 seconds delayed, which reinforces the idea of deficits in short-term visual recognition memory with preserved perceptual processes.[28] SCA10 patients also showed impaired performance in SSP, which involves short-term visuospatial storage, and when the memory load increases, executive control.[44] In sum, DMS and SSP results demonstrated that visual memory impairments in SCA10 patients implicated both visual and visuospatial short-term capacity.

In contrast, short-term verbal memory was not affected in SCA10. The slower but ascending learning curve suggested that patients preserved their verbal learning capacity (encoding new information through trials and retrieving it in the long term), whereas the greater number of false-negative recognitions suggested that the storage capacity was reduced, slowing down the learning process.[45]

Regarding executive function, we found that SCA10 patients showed deficits in error monitoring. In the IED task, patients showed an adequate performance in the reversal learning condition because they responded to the rewards having been switched; however, patients failed when the task switch involved purely cognitive stimuli. This dissociation suggested a preserved reward-related inhibitory control (relying on orbitofrontal cortex) and impaired inhibitory control related to stimulus sensory dimensions (relying on lateral prefrontal cortex); the latter had a negative impact on attentional shift.[46] Planning, which is another executive function typically associated with the lateral prefrontal cortex,[47] was also affected in SCA10 patients because they performed an "on-line" trial-and-error problem solving with no evidence of impulsive behavior.

In contrast to Moro et al,[10] this study did not show verbal fluency impairment in SCA10. This could be explained by our applying articulatory speed corrections to the verbal fluency analyses.

In sum, the cognitive findings in this cohort of SCA10 patients resembled the memory and executive impairments typically described in other SCAs subtypes.[11,14,48] These impairments are consistent with cerebellar cognitive affective syndrome (CCAS), which arises from damage to the posterior cerebellar lobe.[49] In line with CCAS visuospatial and executive manifestations, the SSP task was related to cortical thickness variations in the bilateral posterior cerebellar lobe, including lobule VI, which have been related to visual working memory in the cerebellar functional organization proposed by King et al.[50]

Regarding the possible neural basis of the cognitive deficits, we found that cognitive flexibility impairments in the IED task were correlated with cortical thickness in the lateral prefrontal cortex, the anterior cingulate cortex, and the opercular region, which have been involved in the neural correlates of attentional shift.[46,51] These findings were left-lateralized, as previously described for standard versions of attentional shift tasks.[52] Also, there were significant correlations with cortical thickness in the left inferior and middle temporal gyri. It should be noted that the critical role of temporal cortex morphology in individual differences in cognitive flexibility has been reported previously.[53]

On the other hand, the lack of correlation among cognitive impairment and SARA score suggests that cognitive deficits of SCA10 patients were independent of the ataxia severity. Previous studies have reported contradictory findings regarding the association between motor and cognitive deficits in SCA patients. For example, whereas some studies have shown independence between motor and cognitive decline in SCA1,[54] SCA3,[13] SCA6,[17] and SCA7,[48] other studies found significant correlations between motor and cognitive scores in SCA2.[55,56]

These mixed findings could be related to the study designs' heterogeneity and differences in the cognitive assessments strategies; however, evidence showing that motor and cognitive functions might be involved with different progression rates is concordant with the differentiable patterns of cerebellar degenerations for each SCA, which disproportionally affect motor and cognitive cerebellar regions.[57]

In relation to the presence of seizures in this cohort, similar cognitive performance was found in patients with and without seizures; however, detailed information on the features of seizure type, frequency, and response to treatment was not available. Therefore, seizures were treated only as a dichotomous variable (present vs absent), which constitutes an important limitation of this study.

Furthermore, our relatively small sample size could be considered another limitation of this study; however, it should be noted that SCA10 is listed as a rare disease. Future studies should include larger SCA10 samples with patients from diverse ethnic origins, which would allow enrichment of the cognitive characterization of this disease. In this regard, collaboration among international research institutes will be critical.

In conclusion, this study offered a novel characterization of the cognitive profile in SCA10, including memory and executive impairment. Cognitive changes in SCA10 patients were related for first time with cortical thickness variations in the bilateral posterior cerebellum, left cingulate, temporal, and prefrontal regions. These findings have relevant implications for constructing a complete clinical picture of SCA10.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

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Author Roles

A.C.P., I.V.P., and J.F.R. conceived and designed the study. A.C.P., I.V.P., D.L.T., C.R.H.C., R.D., G.R.G., and J.F.R. contributed to the acquisition and analysis of the data. A.C.P., I.V.P., C.R.H.C., and J.F.R. participated in the drafting and final approval of the manuscript.