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RESEARCH REPORT

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Motor and cognitive impairments in spinocerebellar ataxia type 7 and its correlations with cortical volumes

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Abstract

Spinocerebellar Ataxia Type 7 (SCA7) is a neurodegenerative disorder caused by cytosine-adenine-guanine (CAG) repeat expansion. It is clinically characterized by ataxia and visual loss. To date, little is known about SCA7 cognitive impairments and its relationship with grey matter volume (GMV) changes. The aim of this study was to explore SCA7 patients' performance in specific components of auditory-verbal neuropsychological tests and to correlate their scores with genetic mutation, severity of ataxia and GMV. We assessed verbal memory and verbal fluency proficiencies in 31 genetically confirmed SCA7 patients, and compared their results with 32 healthy matched volunteers; we also correlated CAG repeats and severity of motor symptoms with performance in the auditory-verbal tests. SCA7 patients exhibited deficiencies in several components of these cognitive tasks, which were independent of motor impairments and showed no relation to CAG repeats. Based on Resonance Images performed in 27 patients we found association between ataxia severity and GMV in "sensoriomotor" cerebellum, as well as correlations of impaired verbal memory and semantic fluency scores with GMV in association cortices, including the right parahippocampal gyrus. To our knowledge, this is the first report of deficits in the organization of semantic information and in the evocation of verbal material, as well as greater susceptibility to proactive interference in SCA7 patients. These findings bring novel information about specific cognitive abilities in SCA7 patients, particularly verbal memory and fluency, and their relation with GMV variations in circumscribed brain regions, including association cortices known to have functional relationships with the cerebellum.

KEYWORDS

autosomal dominant ataxia, cognitive impairments, motor impairments, volumetric magnetic resonance

Abbreviations: CAG, cytosine-adenine-guanine; CES-D, Center for Epidemiologic Studies Depression Scale; GMV, grey matter volume; MMSE, Mini-Mental State Examination; RAVLT-S, Rey Auditory Verbal Learning Test Spanish version; SARA, Scale for the Assessment and Rating of Ataxia; SCA7, Spinocerebellar Ataxia Type 7.

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1 | INTRODUCTION

Spinocerebellar ataxia type 7 (SCA7) is a neurodegenerative disorder characterized by cerebellar ataxia and retinal dystrophy. It is caused by a cytosine-adenine-guanine (CAG) expansion in the gene 3p21 that encodes the ataxin7 protein, and it is the only type of Spinocerebellar Ataxia (SCA)

that manifests itself in permanent blindness (Garden & La Spada, 2008). SCA7 patients show significant cerebellar and extracerebellar degeneration (Alcauter, Barrios, Diaz, & Fernandez-Ruiz, 2011) that is accompanied by functional connectivity changes in normal and atrophied structures (Hernandez-Castillo, Galvez, Morgado-Valle, & Fernandez-Ruiz, 2014; Hernandez-Castillo et al., 2013).

Despite advances in the molecular and neuropathological aspects of SCA7, there is still a dearth of information regarding the cognitive consequences of this disease. A transverse and longitudinal study with three patients mentioned the possibility of cognitive deficits in this disease (Moriarty et al., 2016; Sokolovsky, Cook, Hunt, Giunti, & Cipolotti, 2010). A study that included a more representative sample of patients also described executive dysfunctions in SCA7 patients, but its cognitive evaluation was restricted to a frontal-executive screening test in which SCA7 patients showed lower global scores compared to controls (Velázquez-Pérez et al., 2015). Although more information is needed to develop a complete characterization of the integrity of the different cognitive domains in SCA7, it should be noted that the neural bases of the cognitive impairments are even less explored.

Since most of the patients have profound motor and visual problems, one way to contribute to the characterization of their cognitive abilities is using verbal tests. For this reason, here we evaluated if patients with SCA7 show impairments in specific components of verbal fluency and auditory-verbal memory; then, once we identified those deficits, we explored if they correlated with ataxia severity, number of CAG repeats, age at onset of disease and grey matter volume (GMV) in specific cerebellar and cerebral areas as quantified with Magnetic Resonance Imaging.

2 | MATERIALS AND METHODS

2.1 | Participants

Thirty-one patients (12 female) with a molecular diagnosis of SCA7 were evaluated. Although each patient had a genetic diagnosis, nine patients did not provide the information regarding the number of CAG repetitions. Disease severity was scored according to the Scale for the Assessment and Rating of Ataxia (SARA). The SARA has eight tests including gait, stance, sitting, and speech, as well as the finger-chase test, finger nose test, fast alternating movements, and heel-shin test, yielding a total score of 0 (no ataxia) to 40 (severe ataxia) (Schmitz-Hubsch et al., 2006). The control group consisted of 32 volunteers (13 female) with no history of neurological injury or psychiatric diseases. Mini-Mental State Examination (MMSE) was applied to only include participants in the control group whose scores did not indicate cognitive impairments. Patients and controls underwent the same neuropsychological protocol, which was applied using the same standard procedure at their respective homes. All participants were native Spanish speakers and were recruited from the central region of Veracruz, Mexico (clinical and demographic data in Table 1). Experimental procedures were approved by the ethics committee of the Universidad Nacional Autónoma de México and written consent was obtained from each

TABLE 1 Clinical and demographic characteristics of controls and SCA7 patients

	Controls		SCA 7	
	Mean (*SD*)	Median	Mean (*SD*)	Median
Age at examination (years)	40.63 (14.08)	38.50	40.94 (14.09)	38.00
Age at onset (years)			34.00 (13.13)	28.50
Disease duration (years)			7.19 (4.85)	6.00
Education (years)	8.66 (3.59)	9.00	7.05 (4.11)	6.00
Cytosine-adenine-guanine repeat length ($n = 22$)			46.32 (6.16)	45.50
Scale for the Assessment and Rating of Ataxia (global score)			14.66 (6.26)	14.00
Mini Mental State Examination	26.81 (1.31)	27.00	25.90 (1.70)	26.00
Center for Epidemiologic Studies Depression Scale	6.78 (4.48)	5.50	10.06 (8.48)	8.00

Note. SD, Standard Deviation.

participant according to the Helsinki declaration (World Medical Association, 2001).

2.2 | Neuropsychological assessment

The neuropsychological tests were chosen for their minimal reliance on visual and motor performance. The same number of tests was applied to each subject:

The Spanish version of the MMSE was administrated to explore evidence of cognitive decline through a screening test (Ostrosky-Solis, Lopez-Arango, & Ardila, 2000). The items number 9 and 11 corresponding to instruction trace and visuospatial categories were eliminated for both groups due to the visual impairment of SCA7 patients (total score: 28). As an inclusion criterion for the control group, a score below 24 was considered clinically significant.

The Rey Auditory Verbal Learning Test Spanish version (RAVLT-S) was administered to examine auditory-verbal memory and learning strategies for lists of nouns presented verbally (Miranda & Valencia, 1997). The 15-noun list (list A) was presented five times and after each time the participant had to repeat as many words as possible. After an interference trial (list B1), there was an immediate recall, a delayed recall (after 20 min) and a final trial of recognition of the list A nouns from a list of words that included nouns from list B plus 14 distractor nouns.

Based on RAVLT-S performance we calculated the following scores: (a) immediate memory span, defined as total correct words recalled in the first trial (A1); (b) immediate recall from the interference list (B1); (c) learning rate, defined as the gain of recalled nouns over five trials; (d) proactive interference, defined as the interference effect of a list of nouns previously learned over the learning of a new list; (e) retroactive interference, defined as the interference effect of learning a new list of nouns over an old list previously learned; (f) forgetting rate, defined as the loss of information acquired after 20 min; and (g) recognition memory, defined as the percentage of nouns that were correctly identified as familiar from a list containing familiar and unfamiliar nouns (Fernandes, Parreira, De Sena, Fuentes, & Vinícius, 2007).

Semantic and phonemic verbal fluency tasks were also administered. Participants were asked to say as many words as possible in 1 min that began with the letters "P", "M", and "R" for phonemic fluency, and as many animal names as possible for semantic fluency. The qualitative analyses of the verbal fluency tasks were conducted using the Spanish adaptation of the verbal fluency scoring criteria previously reported (Troyer, Moscovitch, & Winocur, 1997; Villodre et al., 2006).

In brief, we derived the following measures based on this scoring system: (a) total correct words, defined as the sum of all words produced minus repetitions and errors; (b) number of clusters. For semantic fluency, successful semantic clusters consisted of three or more successive words within the same subcategory (e.g. farm animals, pet animals or water animals). For phonemic fluency, successful phonemic clusters consisted of three or more successive words that rhyme, begin with the same first letter, have the same first sound or be homonyms; (c) mean cluster size, the sum of all clustered words divided by the total number of clusters; and (d) number of switches, the number of transitions between clustered or non-clustered words (single words).

The Pata test was administrated to assess articulation speed (Friedman et al., 2010). Participants were asked to repeat "pata" as quickly and distinctly as possible for 10 s. The test was repeated twice and the mean number of correct "pata" spoken by the participant was calculated.

Finally, the Spanish version of the Center for Epidemiologic Studies Depression Scale (CES-D) was used as indicator of depressed mood. A score above 16 was considered clinically significant, and higher scores implied the presence of more depressive features (Soler et al., 1997). Since the influence of depressive mood over cognitive performance has been previously reported (Austin, Mitchell, & Goodwin, 2001; Schwert, Aschenbrenner, Weisbrod, & Schröder, 2017), particularly in mnemonic processes (Kizilbash, Vanderploeg, & Curtiss, 2002; Strömgren, 1977), we introduced this scale in order to ensure that groups were homologated in this feature.

2.3 | Image acquisition

Twenty-seven patients agreed to participate in the imaging study. The Images were acquired at the Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz" using a 3.0-T Achieva Magnetic Resonance Imaging scanner (Phillips Medical Systems, Eindhoven, The Netherlands). The acquisition consisted of a 3-D T1 Fast Field-Echo sequence, with TR/TE of 8/3.7 ms, FOV of 256 × 256 mm; and an acquisition and reconstruction matrix of 256 × 256, resulting in an isometric resolution of $1 \times 1 \times 1$ mm^3.

2.4 | Cerebral cortical volume

The reconstruction of cerebral cortical surface and volumetric segmentation were performed with the FreeSurfer image analysis suite 5.3.0 (Fischl et al., 2004). The procedure is fully automated and involves several steps including: segmentation of the white matter, tessellation of the gray/white matter junction, inflation of the folded surface tessellation patterns and automatic correction of topological defects in the resulting manifold. The resulting surface is then used as the starting point for a deformable surface algorithm designed to find the gray/white and pial surfaces with submillimeter precision. For each participant, the volume of the cortical ribbon was computed on a uniform grid. The resulting surfaces were mapped to the average inflated surface that optimally

TABLE 2 Comparative analysis of RAVLT-S (Rey Auditory Verbal Learning Test-Spanish version) and Pata test performance between controls and SCA7 patients

	Controls		SCA 7			*p*-value corrected			
	Mean (*SD*)	Median	Mean (*SD*)	Median	Uncorrected *p*-value	($q = 0.05$)	*t*-value	*U*-value	Cohen's *d*
RAVLT-S									
Immediate memory span (A1)	5.09 (1.67)	5.00	5.45 (1.89)	6.00	0.422	NS	—	438.50	$r = -0.10$
Immediate recall from the interference list (B1)	4.69 (1.61)	5.00	3.64 (1.78)	3.00	**0.018**	**0.025**	−2.43	—	$d = 0.62$
Learning rate	18.09 (7.80)	18.00	13.00 (6.53)	12.00	**0.007**	**0.012**	−2.80		$d = 0.71$
Proactive interference	1.01 (0.48)	0.93	0.69 (0.38)	0.75	**0.009**	**0.018**	—	306.00	$r = -0.33$
Retroactive interference	0.80 (0.15)	0.84	0.85 (0.22)	0.81	0.549	NS	—	452.50	$r = -0.07$
Forgetting rate	1.02 (0.20)	1.00	0.99 (0.15)	1.00	0.811	NS	—	479.00	$r = -0.03$
Recognition memory	94.14 (6.09)	96.86	89.87 (8.99)	93.18	**0.047**	NS	—	352.50	$r = -0.25$
Pata test	34.05 (6.50)	33.50	24.84 (5.90)	23.50	**<0.0001**	**0.006**	−5.88	—	$d = 1.48$

Notes. NS, not significant; SD, standard deviation.
Significant *p*-values are given in bold.

aligned sulcal and gyral features across participants, thus allowing the visualization of data across the entire cortical surface without the data being obscured by cortical folding. For each brain region identified, individual data (mm³) were extracted to calculate the correlation of cortical GMV with motor scores, MMSE scores and verbal memory and semantic fluency scores that showed significant decrease in patients. Parametric maps were threshold at $p < 0.005$.

2.5 | Cerebellar lobules volume

The GMV of the cerebellum lobules was calculated using the patch-based multi-atlas tool called CERES (CEREbellum Segmentation), available through the automated volumetric system VolBrain online web interface (http://volbrain.upv.es) (Manjón & Coupé, 2016). This method, based on an adaptation of the Optimized PatchMatch Label fusion (OPAL) (Ta, Giraud, Collins, & Coupé, 2014), works with standard resolution magnetic resonance T1-weighted images and consists of a multi-atlas patched based segmentation with a non-local label fusion technique that generated segmentations based on a library of manually segmented cases. The inclusion of a post-processing step allows to enforce regularity of the different lobule labels (Romero et al., 2016). The individual volume obtained for each cerebellar lobule (mm³) was calculated considering the relative values measured in relation to the total intracranial volume, which was subsequently correlated with ataxia severity, MMSE scores and verbal memory and semantic fluency scores that showed significant decrease in patients.

Finally, due to the key role of the cerebellar degeneration in SCA7, we also calculated the proportion of patients whose cerebellar GMV was below the expected bounds based on the age and sex of each person. The expected bounds for each cerebellar lobule were automatically provided by the CERES tool.

2.6 | Statistical analysis

Statistical comparisons between controls and patients regarding age, education level, CES-D, MMSE, RAVLT-S, and Pata scores were conducted using independent samples *t*-test or Mann–Whitney *U*-test, as appropriate. Effect size was calculated by Cohen's *d* or *r*. Comparisons of verbal fluency scores among controls and patients were evaluated by separate ANCOVA with Pata scores used as covariate to reduce the influence of articulation deficits in the analyses. Effect size was calculated by eta-square. Differences were considered significant when *p* was <0.05 with False Discovery Rate Correction ($q = 0.05$).

Spearman's Rho or Pearson correlation coefficients were used for correlation analyses between SARA scores, number of CAG repeats, age at onset, disease duration, and

TABLE 3 Comparative analysis of semantic and phonemic verbal fluency performance between controls and SCA7 patients

Verbal Fluency Tasks	Controls	SCA7						
	Mean (*SD*)	Mean (*SD*)	DOF 1	DOF 2	*F*-value	Uncorrected *p*-value	*p*-value corrected ($q = 0.05$)	Eta-square
Semantic								
Total correct words	20.59 (4.89)	16.54 (4.90)	1	60	1.534	0.220	NS	0.025
Number of semantic clusters	4.16 (1.42)	2.77 (1.09)	1	60	6.737	**0.012**	**0.012**	0.101
Mean Cluster Size	2.71 (0.92)	2.64 (1.10)	1	60	0.365	0.548	NS	0.006
Number of Switches	11.65 (4.23)	12.32 (5.49)	1	60	1.488	0.227	NS	0.024
Phonemic								
Total correct words	35.06 (12.12)	30.06 (9.90)	1	60	0.025	0.875	NS	<0.0001
Number of phonemic clusters	2.69 (1.87)	3.22 (1.93)	1	60	0.251	0.618	NS	0.004
Mean Cluster Size	2.64 (1.28)	3.00 (1.27)	1	60	0.258	0.595	NS	0.005
Number of Switches	30.50 (10.54)	24.84 (11.40)	1	60	0.187	0.667	NS	0.003

Notes. NS,: not significant; SD,: standard deviation: DOF,: degrees of freedom.
Significant *p*-values are given in bold.

neuropsychological performance. The association of cerebral and cerebellar cortical GMV with motor scores, MMSE scores and verbal memory and semantic fluency scores that showed significant decrease in patients was conducted with a partial correlation, including the age as a control variable, since it has been described age-associated changes across the cerebral cortex (Raz, 1997; Salat et al., 2004). To avoid multiple comparisons problem, all correlations were considered significant when p was <0.05 with False Discovery Rate Correction ($q = 0.05$).

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences).

3 | RESULTS

3.1 | Demographic and clinical data

Controls and patients were matched for sex, area of residence, age ($t = 0.087$, $p = 0.98$) and education level (in years) ($t = -1.65$, $p = 0.10$). Although both groups presented participants with clinically significant depressive features (four patients and two controls), the CES-D scores did not show significant differences among groups ($U = 387.00$, $p = 0.13$). All participants scored greater or equal to 24 on the MMSE, however there were significant differences among groups ($U = 335.00$, $p = 0.02$, $r = 0.28$) (Table 1).

3.2 | Cognitive data

RAVLT-S analyses showed significant differences between the control and SCA7 group in immediate recall from the interference list (B1), learning rate, proactive interference and recognition memory scores. All differences, except recognition memory, survived multiple comparison correction (Table 2). Pata scores were also significantly reduced in patients (Table 2). No differences were found for immediate memory span (A1), retroactive interference and forgetting rate.

In the semantic verbal fluency task, patients generated a smaller number of clusters compared to controls; however, the groups did not differ in total number of words produced, mean cluster size and number of switches. There were no significant effects for phonemic fluency task on any measure (Table 3).

3.3 | Cognitive performance and clinical features

Mini-Mental State Examination scores and verbal memory and fluency scores did not show significant correlations with number of CAG repeats, age at onset of disease, disease duration or motor symptoms. However, there was a negative correlation between the number of CAG repeats and the age at

onset of disease ($r = -0.63$, $p = 0.002$). There was also correlation among SARA and Pata scores ($r = -0.63$, $p < 0.001$). Both variables were associated with disease duration (SARA, $r = 0.59$, $p < 0.001$; Pata, $r = -0.50$, $p = 0.004$) but not with the number of CAG repeats or the age at onset of disease.

3.4 | Motor/cognitive performance and volumetric measures

Two of the verbal memory and verbal fluency scores identified as impaired in SCA7 patients (RAVLT-S learning rate and number of semantic clusters) showed correlations with GMV in specific association cortices; and among these structures, the right parahippocampal was the only one whose volume correlated to both scores. There were not significant correlations with any of the cerebellum lobules GMV. In contrast, the scores associated with the cerebellar motor alterations (SARA and Pata) had significant correlations with GMV in lobules VIIIB, I and II, while the lateral occipital region was the only cortical region involved (Figures 1 and 2 and Table 4). Table S1 shows the volumetric measurements corresponding to anatomical regions that exhibited significant correlations with motor scores and with impaired verbal memory and verbal fluency scores in SCA7 patients.

In line with cerebellar findings, 40.74% and 25.92% of the patients had levels of GMV below the bounds expected for their age and sex in the right and left lobule VIIIB, respectively. In contrast, only 3.70% showed significant reductions of the GMV in the left lobule I-II.

Other cerebellar lobules, which did not show significant correlations with motor alterations, also showed reduced GMV in a large proportion of patients, including the right (100%) and left (96.29%) lobule X and the right lobule IX (29.62%). A smaller proportion of patients showed GMV levels below the expected bounds in right lobule IV and left lobule VI (25.92%); left lobule IX and Crus I (22.22%); left lobule IV and right lobules VI, VIIIA, Crus I and Crus II (18.51%); right lobule VIIB (14.81%); right lobule III and left lobule VIIB, VIIIA, and Crus II (11.11%).

4 | DISCUSSION

In this study, we identified significant impairments in specific components of the auditory-verbal learning and memory, as well as in semantic verbal fluency in SCA7 patients; these deficits seem to be related to an executive control process disorder. In sum, this is one of the first studies to examine these cognitive functions in a large group of patients with SCA7 and to analyze their relationship with different disease-associated factors (GMV, length of CAG expansion, age of onset, disease duration, and ataxia severity).

All patients, except one with <1 year of evolution, showed a range of different impairments associated to cerebellar ataxia. In line with previous findings (Hernandez-Castillo, Galvez, Diaz, & Fernandez-Ruiz, 2016), our results showed a close relation between ataxia/dysarthria measures and cerebellum GMV, specifically with the "sensoriomotor" cerebellum, which include the anterior lobe and lobules VIIIA/B. These results are consistent with functional topography maps of the human cerebellum (Stoodley & Schmahmann, 2009; Stoodley, Valera, & Schmahmann, 2012).

Our analyses showed a widespread damage of the cerebellum that was distributed in different proportions among the cerebellar lobules, as has been previously described for SCA7 (Alcauter et al., 2011). Interestingly, some of the lobules affected in the majority of the patients (e.g. bilateral lobule X) did not showed motor correlations, probably because the deterioration resulted in a ceiling effect. In contrast, lobules that showed GMV reductions in a smaller proportion of patients (e.g. bilateral lobule VIIIB and left lobules I-II) did show a correlation with motor impairments.

Regarding the MMSE performance, none of the patients had scores below the clinical cut-off point, therefore, possibly the parameters used in this screening test were not able to detect cognitive impairments associated with SCA7. Consistent with our results, SCA1, SCA2, and SCA3 patients, who had significant deficits on verbal memory and fronto-executive tasks, also had MMSE scores considered "within normal limits" (Bürk et al., 2001). Since the MMSE lacks of fronto-executive tasks, it is likely to miss important cognitive changes during the screening evaluation of SCA7 patients and other SCAs patients.

However, performance on the MMSE was significantly lower in SCA7 than controls, which may imply signs of neuropsychological deficits not detected by the clinical cut-off points of the MMSE, but recognized through fronto-executive screening test (Velázquez-Pérez et al., 2015), or during the evaluation of specific components in extensive neuropsychological tests (Vaca-Palomares et al., 2015).

For instance, RAVLT-S performance was significantly worse in SCA7 patients. Their learning rate was reduced, but the recognition memory was spared, suggesting a deficit in retrieval (memory search functions) rather than in storage (Vakil & Blachstein, 1993). This discrepancy, coupled with the major prone to proactive interference, point to an impairment in the executive component of memory where learning per se is better preserved. Moreover, the forgetting rate reflected an efficient consolidation process and the A1 trial suggested an adequate attentional volume (Lezak, Howieson, Bliger, & Tranel, 2012).

In verbal fluency, patients showed a deficient organization of semantic information into subcategories. As the total production of words in the semantic fluency task was not

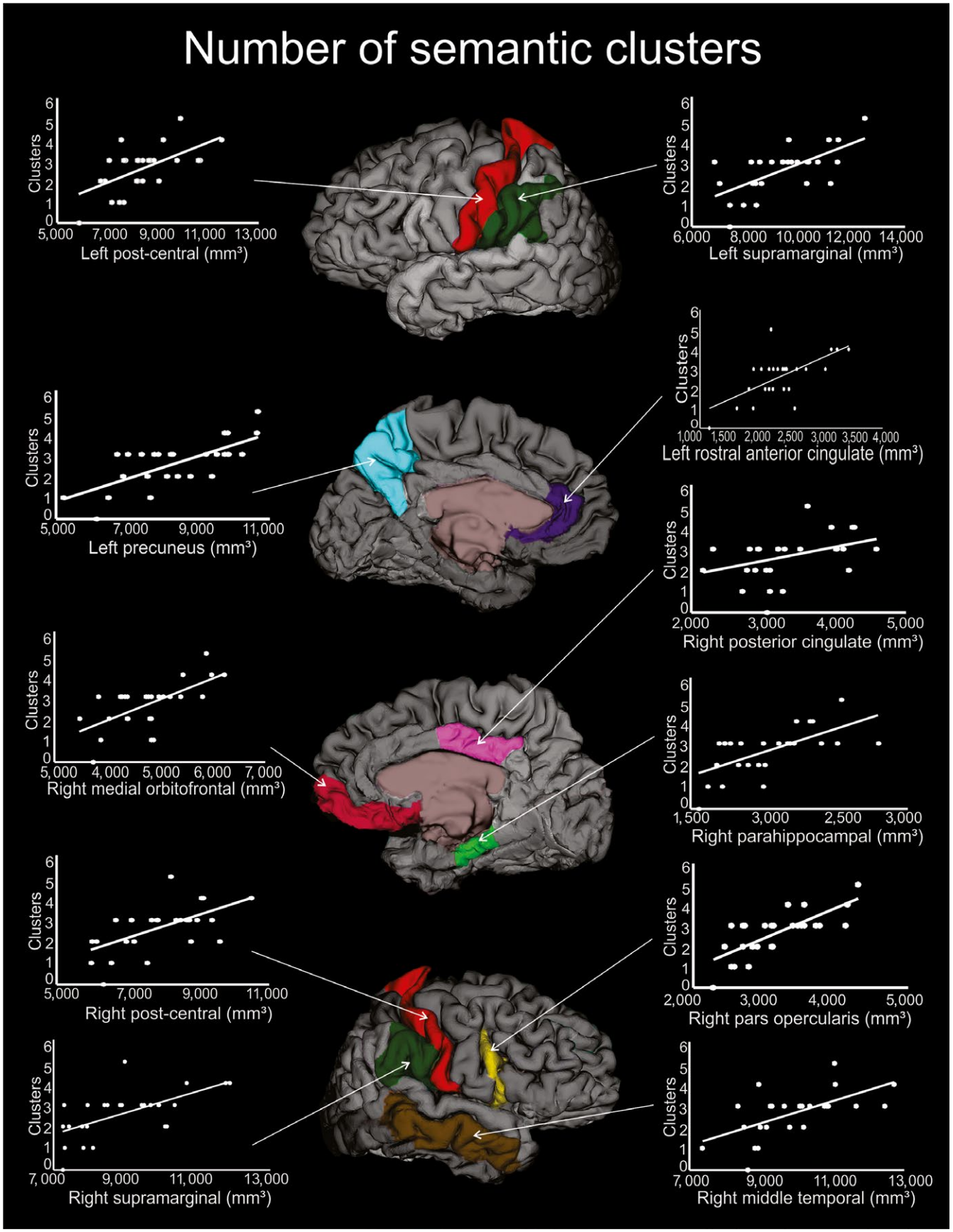

FIGURE 1 Cerebral and cerebellar regions showing significant correlation of grey matter volume with number of semantic clusters (*r* coefficients and *p*-values are shown in Table 4). [Colour figure can be viewed at wileyonlinelibrary.com]

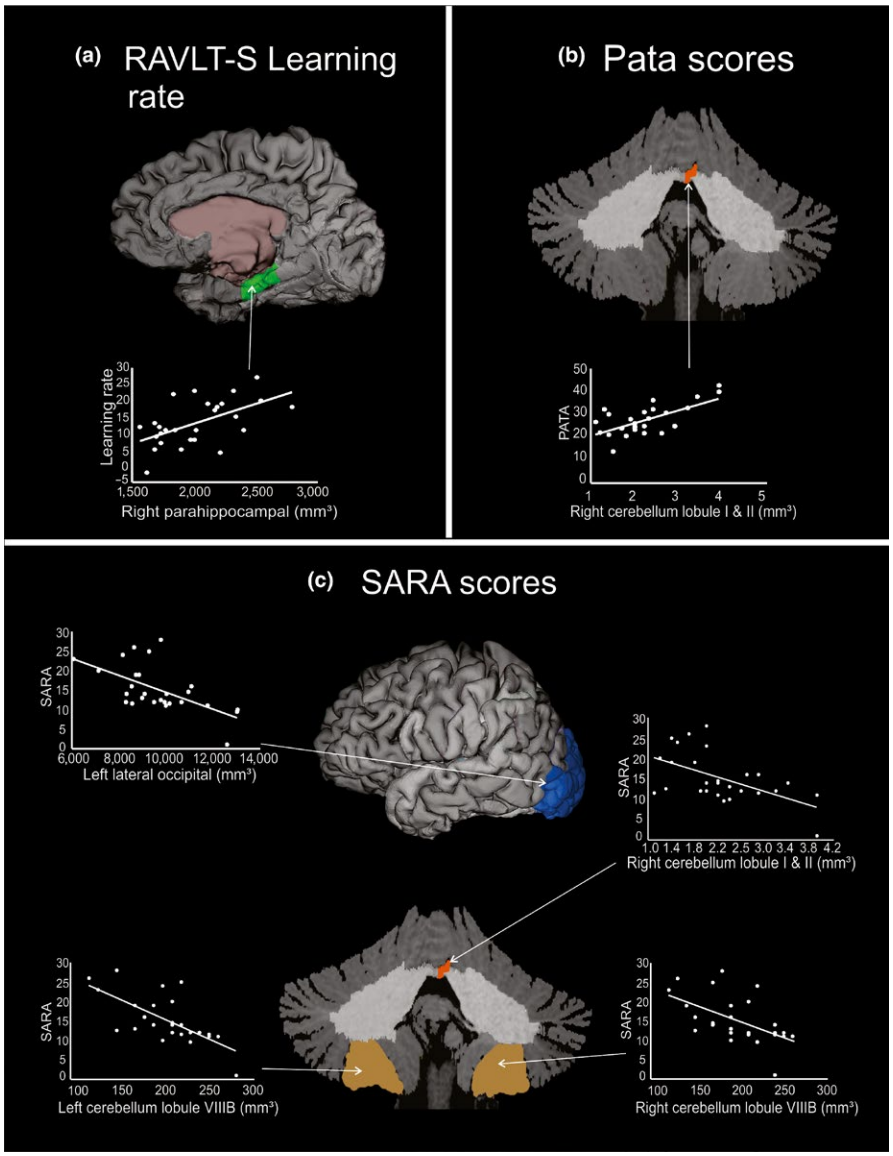

FIGURE 2 Cerebral and cerebellar regions showing significant correlation of grey matter volume with (a) RAVLT-S Learning rate, (b) Pata scores and (c) Scale for the Assessment and Rating of Ataxia scores (*r* coefficients and *p*-values are shown in Table 4). [Colour figure can be viewed at wileyonlinelibrary.com]

impaired, this deficiency may reflect dedifferentiation of the semantic network rather than disintegration of the semantic-conceptual system (Goñi et al., 2011; Rogers et al., 2004).

Although this conclusion points again to an impaired executive control process, our results failed to reveal deficits in phonemic fluency, which supposedly relies mainly on strategic search of information (Birn et al., 2010; Troyer et al., 1997). It has been suggested that semantic tasks are "easier" than phonetic tasks because the semantic associations, in contrasts to phonemic clustering, are an automatic process that prompts fluency (Ho et al., 2002). However, the broader range of options in the widespread semantic network, and the automaticity of semantic clustering, may lead to an increased noise (more competition) in semantic fluency compared to phonemic fluency (Berberian et al., 2016; Snyder & Munakata, 2008).

It has been suggested that deficits of patients with cerebellar damage on semantic fluency reflect dysfunctional executive retrieval of semantic knowledge subserved by prefrontal cerebrocerebellar circuits rather than a primary storage defect associated with medial temporal lobe pathology (Hoche, Guell, Vangel, Sherman, & Schmahmann, 2017). An insufficient executive control in SCA7 patients could interfere with the ability to maintain and deplete semantic clusters, because impairments in noise/distractors inhibition did not allow an efficient selection and accommodation of semantic activations into clusters; nevertheless, the total production of words was not impaired because the switching mechanism played a compensatory role.

Our results in SCA7 are supported by previous studies in verbal memory and fluency performance described in other SCAs (including SCA1, SCA2, SCA3, and SCA6), which deficits where underpinned by executive dysfunctions (Bürk et al., 1999, 2001, 2003; Le Pira et al., 2002; Maruff et al., 1996; Suenaga et al., 2008). In addition, our results are in accordance with the impaired frontal-executive screening

TABLE 4 Significant correlations of grey matter volume with motor scores and impaired verbal memory and fluency scores in SCA7 patients

Tests scores	Anatomical region	*r* coefficient	Uncorrected *p*-value	Corrected *p*-values ($q = 0.05$)
RAVLT-S Learning rate	Right parahippocampal gyrus	0.54	0.004	0.014
Number of semantic clusters	Left post-central gyrus	0.58	0.002	0.007
	Left precuneus	0.73	<0.0001	0.007
	Left rostral anterior cingulate gyrus	0.61	0.001	0.007
	Left supramarginal gyrus	0.63	0.001	0.007
	Right parahippocampal gyrus	0.61	0.001	0.007
	Right medial orbitofrontal gyrus	0.62	0.001	0.007
	Right middle temporal gyrus	0.59	0.001	0.007
	Right pars opercularis	0.74	<0.0001	0.007
	Right post-central gyrus	0.57	0.002	0.007
	Right posterior cingulate gyrus	0.60	0.001	0.007
	Right supramarginal gyrus	0.60	0.001	0.007
Pata test	Right cerebellum lobule I & II	0.66	<0.0001	0.007
SARA	Left lateral occipital gyrus	−0.58	0.002	0.007
	Left cerebellum lobule VIII B	−0.68	<0.0001	0.007
	Right cerebellum lobule I & II	−0.57	0.002	0.014
	Right cerebellum lobule VIII B	−0.52	0.006	0.007

Note. Volume was calculated as the average volume for each brain region as defined in FreeSurfer and CERES see Methods.

previously described in SCA7 (Velázquez-Pérez et al., 2015), suggesting a pervasive executive dysfunction in different types of SCAs.

The RAVLT-S learning rate, as well as the number of semantic clusters produced by SCA7 patients, showed a significant correlation with right parahippocampal GMV. This region, that is crucial for visuospatial processing (Aminoff, Kveraga, & Bar, 2013), has also been involved in the neuroanatomical components of a distributed system for signal processing and storage relevant to auditory-verbal memory, with a specifically right lateralization (Grasby et al., 1993). The same association among RAVLT-S impaired scores and right, but not left, parahippocampal GMV has been described in SCA3 (Lopes et al., 2013).

Furthermore, the GMV in the parahippocampal gyrus has also been associated to the severity of motor symptoms in SCA7 (Hernandez-Castillo et al., 2016). This could be related to the functional connectivity detrimental changes between the parahippocampal cortex and the cerebellum showed by SCA7 patients (Alcauter et al., 2011; Hernandez-Castillo et al., 2013). It should be noted that the degeneration of parahippocampal gyrus found in SCA7 is common to other SCAs (Hernandez-Castillo et al., 2013; Ishikawa et al., 1999; Mercadillo et al., 2014), so its involvement in motor and cognitive symptoms of these diseases should be studied further.

The number of semantic clusters generated by SCA7 patients correlated with variations in the GMV of anatomic brain areas that belong to a neural system responsible for the storage and retrieval of semantic information, and which are known to receive multimodal and supramodal inputs (Binder, Desai, Graves, & Conant, 2009). These results included volumetric variability of: a) left and right supramarginal gyrus, which have a bilateral representation in the semantic system (Binder et al., 2009) and has been related to the categorization of semantic information (Chou et al., 2006; Lau, Phillips, & Poeppel, 2008); b) left anterior rostral cingulate gyrus, involved in the internal generation of *willed* responses (Frith, Friston, Liddle, & Frackowiak, 1991), and in this sense crucial for the speech self-monitoring (Christoffels, Formisano, & Schiller, 2007). These functions are supported by its important connections with the prefrontal cortex (Pandya, Van Hoesen, & Mesulam, 1981); c) left precuneus, linked to processes of visual imagery (Hassabis, Kumaran, & Maguire, 2007; Johnson, Mitchell, Raye, D'esposito, & Johnson, 2007), which could serve as support in the organization of semantic groups containing tangible information.

We also found significant correlations with medial paralimbic regions (parahippocampal and posterior cingulate gyrus) which have strong connections with the hippocampal formation (Binder et al., 2009). Other regions with significant correlations were pars opercularis, relevant for phonological-articulatory processing (Popescu et al., 2017), and middle temporal gyrus, essential for lexical evocation (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004). Despite these areas belong to the left-lateralized semantic

network (Binder et al., 2009) our correlations were "contradictorily" right-lateralized.

These "contradictorily" findings may be interpreted considering the cerebral GMV variations either as a secondary effect resulting from cerebellar deafferentation (Boni et al., 1992) or as result of a primary degenerative process related to SCA7. Regarding the cerebellar deafferentation explanation, we should note that most part of the cerebello-cerebral projections are crossed (Ramnani, 2006), and thus, focal cerebellar lesions are usually accompanied by functional changes of contralateral cerebral cortex, which received projections from the damaged cerebellar regions (Sönmezoğlu, Sperling, Henriksen, Tfelt-Hansen, & Lassen, 1993).

Nevertheless, previous studies have also reported bilateral structural alterations in cerebral grey matter density and in white matter tracts as a result of unilateral cerebellar lesions (Clausi et al., 2009; Olivito et al., 2017). This may explain why cognitive dysfunctions, possibly linked to a primary damage in a specific side of the cerebellum, can also be associated to structural changes in ipsilateral cerebral regions that seem to be opposed to the cortical lateralization of the cognitive process evaluated.

Taking into account the cerebral GMV variations as result of a primary degenerative process related to SCA7, we should consider that the involvement of homotopic regions in the right hemisphere may be playing a compensatory role in the functions that the left hemisphere cannot longer perform on its own. So that, a greater volume in these regions would lead to the possibility of a greater compensatory deployment, whereas the arrival at a determined threshold of degeneration in the dominant left hemisphere would only reflect dysfunction in the task.

Supporting this possibility, changes in lateralization as a compensatory mechanism has been described in Alzheimer Disease (Fallgatter et al., 1997), Mild Cognitive Impairment (Yeung et al., 2016) and Schizophrenia (Sommer, Ramsey, & Kahn, 2001; Weiss et al., 2004); whereas the increased of right hemisphere GMV in classical left-lateralized language areas has been associated with better language comprehension in aphasic patients (Lukic et al., 2017). However, compensatory reorganization of cognitive functions in SCA7 should be explored further, since other mechanisms as increased functional connectivity has been suggested (Hernandez-Castillo et al., 2013).

In sum, the volumetric correlations suggest an inefficient processing of the information integrated by association cortices. Although this information is fundamental to higher functions such as planning, reasoning and problem solving, we cannot rule out that a disconnection syndrome of the cerebro-cerebellar circuitry also underpinned cognitive deficits in SCA7 patients. This is mainly because the anatomic regions which volumetric changes correlated with verbal memory and verbal fluency deficits are not only known to be atrophic in SCA7 patients (Alcauter et al., 2011), but also some of them showed abnormal functional connectivity pattern with the cerebellum (i.e. parahippocampal gyrus, inferior frontal gyrus, precuneus and inferior parietal gyrus) (Hernandez-Castillo et al., 2013, 2014).

The decrease of executive functions in pure cerebellar syndromes and SCAs with a more widespread damage (including the frontal lobe) has been related to the interruption of the fronto-ponto-cerebellar pathway, in which the cerebellum is the main hub impaired (Le Pira et al., 2002; Reetz et al., 2018; Schmahmann & Sherman, 1998; Suenaga et al., 2008). Either way, it is possible that we failed to find associations of verbal memory and verbal fluency impairments with the cerebellum GMV because, as the most structurally affected region in SCA7, we expected that a more homogenous and advanced changes across individuals would "wash out" correlations in group analysis.

Finally, in accordance with the genetic anticipation phenomenon (Durr, 2010), we found that onset at younger ages was related to a major number of CAG repetitions; and also it leads to a major severity in motor symptoms, which seems to progress independently from the cognitive symptoms evaluated by this research. Although motor symptoms were related to disease progression, the total score of SARA was not related to the mutation size, which is not usually observed in other cohorts of polyglutamine SCAs. This lack of correlation may be caused by the sample size and the absence of some quantitative data on the CAG repeats. In this regard, we cannot assure that motor performance or verbal memory and fluency scores in SCA7 depends on different factors than gene dosage.

In conclusion, our results bring novel information about specific cognitive abilities in SCA7 patients, particularly impairments in verbal memory and verbal fluency tasks related to a defective executive control. Although these findings were correlated with GMV variations in circumscribe brain regions, the contribution of cerebral-cerebellar connections deserves further investigation.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA ACCESSIBILITY

All data underlying the reported findings are included in the article or in supplementary data files. Raw data are available on request.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to conception and design of research; acquisition, analysis and interpretation of data; draft and revise the article and final approval of the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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