Journal of the Neurological Sciences 347 (2014) 50–58

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Parahippocampal gray matter alterations in Spinocerebellar Ataxia Type 2 identified by voxel based morphometry

Roberto E. Mercadillo [a], Víctor Galvez [b], Rosalinda Díaz [a], Carlos Roberto Hernández-Castillo [a], Aurelio Campos-Romo [c], Marie-Catherine Boll [d], Erick H. Pasaye [e], Juan Fernandez-Ruiz [a,b,f,*]

[a] Laboratorio de Neuropsicología, Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico
[b] Instituto de Neuroetología, Universidad Veracruzana, Mexico
[c] Unidad Periférica de Neurociencias, Facultad de Medicina, Universidad Nacional Autónoma de México, Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suarez", Mexico
[d] Departamento de Investigaciones Clínicas en Neurociencias, Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suarez", Mexico
[e] Unidad de Resonancia Magnética, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Mexico
[f] Facultad de Psicología, Universidad Veracruzana, Mexico

ARTICLE INFO

Article history:
Received 24 March 2014
Received in revised form 20 August 2014
Accepted 12 September 2014
Available online 19 September 2014

Keywords:
Spinocerebellar ataxia
Voxel-based morphometry
Parahippocampal gyrus
SARA

ABSTRACT

Spinocerebellar Ataxia Type 2 (SCA2) is a genetic disorder causing cerebellar degeneration that result in motor and cognitive alterations. Voxel-based morphometry (VBM) analyses have found neurodegenerative patterns associated to SCA2, but they show some discrepancies. Moreover, behavioral deficits related to non-cerebellar functions are scarcely discussed in those reports. In this work we use behavioral and cognitive tests and VBM to identify and confirm cognitive and gray matter alterations in SCA2 patients compared with control subjects. Also, we discuss the cerebellar and non-cerebellar functions affected by this disease. Our results confirmed gray matter reduction in the cerebellar vermis, pons, and insular, frontal, parietal and temporal cortices. However, our analysis also found unreported loss of gray matter in the parahippocampal gyrus bilaterally. Motor performance test ratings correlated with total gray and white matter reductions, but executive performance and clinical features such as CAG repetitions and disease progression did not show any correlation. This pattern of cerebellar and non-cerebellar morphological alterations associated with SCA2 has to be considered to fully understand the motor and non-motor deficits that include language production and comprehension and some social skill changes that occur in these patients.

1. Introduction

Spinocerebellar Ataxia Type 2 (SCA2) is a genetic disorder caused by an expanded CAG trinucleotide repeat in the gene encoding ataxin-2 [60], which causes cerebellar degeneration primarily affecting Purkinje cells, pontine nuclei and inferior olives [29,70]. Symptoms typically initiate by the 3rd or 4th decade and include several motor and visuomotor disorders, such as ataxia, dysmetria, dysarthria, dysdiadochokinesia, ophthalmoplegia, and saccade slowing [24,48,66,88,89].

The use of neuroimaging techniques in recent decades has allowed whole brain structural analyses of different neurodegenerative diseases that were difficult to perform in neuropathological studies. For example voxel-based morphometry (VBM) is based on the analysis of high-resolution magnetic resonance images of the whole brain, and it can determine different atrophy patterns in gray matter associated with neurodegenerative disorders [4]. For example, VBM analyses on various types of SCAs have been able to identify gray matter loss in many CNS regions. For example, it has identified volume reductions in the pons for SCA3 patients, in the hemispheric cerebellar lobules and vermis in SCA6 [47], and in the posterior lobe in SCA7, this last also showing alterations in non-cerebellar regions, such as the precentral and postcentral gyri, inferior and medial frontal, and the inferior parietal, parahippocampal and occipital cortices [1,35].

Regarding SCA2 patients, VBM studies have shown reduced gray matter volumes in the pons, the cerebellar vermis and cerebellar hemispheres while sparing lobules I and II, and Crus II, VII, and X [8,20,93]. VBM analyses have also identified loss of gray matter in cortical regions including the orbitofrontal cortex, the middle frontal region, the primary sensorimotor cortex, and temporomesial and insular cortices [7,8].

Other studies using VBM have compared the atrophy patterns across different SCAs. For example, it has been reported that SCA1, SCA2 and SCA3 result in atrophy of the cerebellum and brainstem in the three SCA types, although there are still some controversies regarding the relative degree of the neurodegeneration among the three mutations [21,30,36,42].

Although VBM is used to determine morphometric alterations, this technique can also be used to complement the discussion on some

* Corresponding author at: Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México, UNAM, Coyoacán, Distrito Federal 04510, Mexico. Tel.: +52 55 56232393.
E-mail address: jfr@unam.mx (J. Fernandez-Ruiz).

http://dx.doi.org/10.1016/j.jns.2014.09.018
0022-510X/

behavioral and cognitive dysfunctions. For example, SCA2 involves alterations on motor and learning processes regulated by extracerebellar structures, such as the substantia nigra, striatum, pallidum, and motor cortex [86], and atrophies in the posterior and anterior cerebellar lobes associated with SCA2 are related with executive and coordinative dysfunctions, respectively [18]. Regarding the emotional domain, cerebellar lesions impair affective recognition [22,65] and the vermis has been proposed as the limbic cerebellum to regulate emotional expressions [71]. Observations in neurological patients with morphological and functional alterations in the vermis and diagnosed with ataxia or with cerebellar cognitive affective syndrome manifest emotional fragility and several affective disorders [72,73,81,82]. In addition, some functional neuroimaging studies indicate cerebellar activity when individuals watch pictures of faces with emotional content [56] and while feeling anger, sadness, happiness, and fear [19,32]. In social cognition, the role of the cerebellum has been observed along with the activation of the hippocampus while processing socially related spaces [43] and along with the activity of the prefrontal cortex, predicts autonomic responses associated with risky social decision-making [15,16].

Behavioral and cognitive functions associated with SCA2 are diverse and alterations have been scarcely discussed in terms of non-cerebellar regions identified as atrophied. The aim of this work was to identify and confirm SCA2 brain degeneration using a VBM analysis, and to discuss the behavioral effects of the cerebellar and non-cerebellar degenerations caused by this disease. We hypothesized that the clinical feature in SCA2 patients will be correlated with a reduced brain volume, and a low performance on behavioral and cognitive tasks.

2. Materials and method

2.1. Participants

Fifteen patients with a molecular diagnosis of Spinocerebellar Ataxia Type 2 (9 women) and 15 control volunteers (7 women) without any neurological or psychiatric condition participated in this study. The Scale for Assessing and Rating Ataxia (SARA) was used as a semi-quantitative valuation comprising eight items related to gait, stance, sitting, speech, finger–chase test, nose–finger test, fast alternating movements and heel–shin test [74,92]. General characteristics of the participants are presented in Table 1. All the participants gave their informed consent after the nature of the study was explained. The research protocol was conducted according to the international standard laid down in the Declaration of Helsinki and all procedures were approved by the Health and Ethics Committees of the National Autonomous University of Mexico.

2.2. Cognitive and behavioral instruments

Both patients and control participants took the Mini-mental State Examination and the Montreal Cognitive Assessment, and performed three tasks included in The Cambridge Neuropsychological Test Automated Battery.

The Mini-mental State Examination (MMSE) is a well-known test to assess cognitive impairment in neurological patients. As the original test [26], the validated version used in Mexico is applied in 5–10 min and comprises 11 items to assess five areas: orientation, attention/concentration, immediate memory, language and visuospatial perception [59]. Scores indicate five levels of cognitive impairment: 30–27 = no impairment; 26–25 = possible impairment; 24–10 = low to moderate impairment; 9–6 = moderate to severe impairment; ≤6 = severe impairment.

The Montreal Cognitive Assessment (MoCA) evaluates mild cognitive impairment in several kinds of neurological and psychiatry patients and has been proposed as a complement for the MMSE [55]. The version in Spanish language used in Mexico (The Montreal Cognitive Assessment—MoCA©) consists in a 30-point test administered in approximately 10 min to assess visuospatial abilities, executive functions, attention/concentration/working memory, language, and orientation to time and place. A score ≥26 indicates normal cognitive functions.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) [68] consists in a computerized system to assess cognitive performance in elderly, demented, and neurological patients. Also, it has been used to study cognitive functions in psychiatric patients [37] and in healthy people across different ages [3,46,83]. The CANTAB comprises a variety of executive and memory tasks administered through a touch-sensitive screen where feedback is given in a standardized manner for all the subjects. In this study three tasks were administered: Big/Little Circle, Spatial Span, and Intra/Extra-Dimensional Shift.

The Big/Little Circle task is administered in 2 min and evaluates comprehension and learning while training the participant to follow and reverse a rule. First, the participant touches the smaller of two circles displayed in the screen. After 20 trials, the participant must touch the larger circle for 20 further trials. The outcome measures considered here were the number of errors committed and the response latency.

The Spatial Span is administered in 6 min and evaluates working memory. Each trial starts with nine white boxes displayed in the screen, some of which change in color in a variable sequence. The participant must touch the boxes that changed color in the same order they were displayed by the computer. At the beginning the participant has to choose between two boxes, but the number of boxes progresses up to nine. The test is terminated if the participant fails three consecutive trials. The outcome measures used for our study were the span length (the maximum span or box sequence successfully recalled) and the response latency.

The Intra/Extra-Dimensional Shift is administered in 7 min and is analogous to the Wisconsin Card Sorting Test. It assesses visual discrimination, attentional maintenance, shifting and flexibility of attention. The participant starts watching two simple color-filled shapes and must learn which one is correct by touching it. The complexity of the shape increases and white lines are added behind the color-filled shapes. Feedback indicates if the participant chose the correct stimuli and if the rules are changed. These shifts are initially intra-dimensional (e.g. the color filled shapes remain the only relevant dimension) but then they become extra-dimensional (e.g. the lines become the only relevant dimension). Participants have to perform six consecutive correct responses. The measures considered for our study were the number of errors and the latency.

2.3. Statistical analysis

Since demographic information, disease characteristics, and scores for the cognitive test are variable in patients and control participants

Table 1
General characteristics of the participants.

	Age (years)		Years of education		Disease evolution (months)		CAG repetitions		SARA (score)	
	$M \pm$ S.D.	Max/min	$M \pm$ S.D.	Max/min	$M \pm$ S.D.	Max/min	$M \pm$ S.D.	Max/min	$M \pm$ S.D.	Max/min
Patients	37.2 ± 15.9	65/15	6.0 ± 2.9	9/2	133.7 ± 137.7	528/2	44.2 ± 4.4	48/37	17.2 ± 8.5	33.5/2
Controls	41.7 ± 13.3	60/23	12.3 ± 3.0	16/6						

Note. M = Mean; S.D. = standard deviation; SARA = Scale for the Assessment and Rating of Ataxia.

Table 2
Estimations of the volume for the total brain tissue, gray matter and white matter for patient participating in the study.

Patients' volume estimations			
	Mean ± S.D.	Min.	Max.
Gray matter	696,292.09 ± 68,351.53	603,891.06	838,740.65
White matter	692,371.20 ± 44,637.60	607,516.37	766,386.79
Total brain	1,388,663.29 ± 107,017.38	1,232,370.20	1,603,714.80

we used the Shapiro–Wilk test to verify the data normal distribution. Only the scores for the MMSE and the MoCA for all the participants and the SARA ratings and CAG repetitions for patients presented a $p > 0.05$ indicating a normal distribution. Parametric or non-parametric test was run depending on the normal distribution of the data. Data bases and statistical analysis were performed using SPSS 17.0 software.

A Student's t-test for independent samples was used to compare the patients' and controls' MMSE and MoCA scores. A Mann–Whitney U test was used to compare the patients' and controls' scores for the CANTAB tasks. A Spearman's rank correlation coefficient was applied to evaluate the relation between the years of education and the MMSE, the MoCA and the CANTAB tests. A Mann–Whitney U test was applied comparing the women's and men's scores to analyze the effect of gender in each cognitive and behavioral task. The Spearman's coefficient was used to correlate the CAG repetitions with disease progression and scores of the CANTAB tests. The Pearson parametric quotient was used to correlate the CAG repetitions with scores for the MMSE, the MoCA and the SARA. Spearman's coefficient was also used to analyze the correlations between the SARA ratings with the patients' age, the time of disease evolution, and the scores for the CANTAB test. The Pearson coefficient was applied to analyze the correlation between the SARA ratings and the scores for the MMSE and the MoCA.

2.4. Image acquisition and analysis

Images were acquired using a 3 Tesla Philips Achieva MRI scanner (Philips Medical Systems, Eindhoven, Netherlands) at the National Institute of Psychiatry, Mexico City. A high-resolution 3D volume consisted of a T1 Fast Field-Echo sequence, with TR/TE = 8/3.7 ms, FOV 256 × 256 mm^2 and an acquisition and reconstruction matrix of 256 × 256, resulting in an isometric resolution of 1 × 1 × 1 mm^3.

To reduce patients' movements and prevent motion artifacts participants were fitted with head pads and fastened with a body sheet in the most comfortable way. Brain images for each participant were checked by an expert radiologist to verify the lack of artifacts classically observed in motion cases.

To analyze gray matter changes we used VBM [31] implemented on FSL (FMRIB Software Library) [78]. The original DICOM files were converted into NIFTI format using dcm2nii (Chris Rorden's MRIcron, copyright 2012). Voxels belonging to the neck and other non-brain tissues were eliminated using BET software and gray matter was segmented before being registered to the MNI 152 standard space using non-linear registration [2]. The images were averaged and flipped on the x-axis to create a symmetric, study-specific gray matter template. Original gray matter images were then non-linearly registered to this specific template and modulated and corrected for local expansion or contraction. The modulated images were softened by applying an isotropic Gaussian 3 mm kernel. The voxel-wise GLM was applied using a two-sample t-test corrected for multiple comparisons across space. We used a randomize permutation testing (n = 5000) for inference in VBM-style analysis and we chose the appropriate smoothing (sigma = 3 mm) for the TFCE (Threshold-Free Cluster Enhancement) based analysis. The family-wise error (FWE) rate was controlled and only corrected $1 - p$ values ≤0.095 were accepted. Cluster centroid coordinates of brain activation were estimated on the MNI template and its anatomical location and proximate Brodmann's area were identified by using the Talairach Deamon Client system [44] and fslview.

To obtain the values of the patients' brain tissue to be correlated with cognitive, behavioral and clinical measures, the brain tissue volume was normalized for each subject head size and was estimated with SIENAX which is a tool incorporated in the FSL software [77–79]. The SIENAX analysis extracts brain and skull images from the single whole-head input data [76]. The brain image is then affine-registered to the MNI152 space [38,39] using the skull image to determine the registration scaling and to obtain the volumetric scaling factor to be used as a normalized head size. Next, tissue-type segmentation with partial volume estimation was carried out [95] to calculate the total volume of brain tissue as well as estimations of gray matter volume and white matter volume (see Table 2).

Brain volume estimations had a normal distribution as indicated by the Shapiro–Wilk test. Pearson product–moment correlation was used to correlate the volume estimations of the total brain, gray matter and white matter with the CAG repetitions and with scores for the SARA, the MMSE and the MoCA test.

3. Results

Student's t-test showed that SCA2 patients have significantly lower scores than control participants in the MMSE (control: $M = 29.06 \pm$ S.D. = 2.05; patients: $M = 25.80 \pm$ S.D. = 3.42; $t_{28} = 3.16$, $p = .004$) and the MoCA (control: $M = 28.06 \pm$ S.D. = 1.62; patients: $M = 21.06 \pm$ S.D. = 6.12; $t_{28} = 4.27$, $p < .001$). Analysis of the CANTAB results showed that patients executed more incorrect responses in the Intra/Extra-Dimensional Shift ($U_{(30)} = -3.28$, $p \leq 0.001$) and passed less correct spans in the Spatial Span task ($U_{(30)} = -3.97$, $p \leq 0.001$). Also, patients took more time to choose the correct response while executing the Big Little Circle task ($U_{(30)} = -3.96$, $p \leq 0.001$), the Intra/Extra-Dimensional Shift ($U_{(30)} = -3.83$, $p \leq 0.001$) and the Spatial Span task ($U_{(30)} = -2.71$, $p = 0.007$) (see Table 3).

Spearman's coefficient indicated a positive correlation between years of education and MMSE scores ($r_{(30)} = .784$, $p > .001$), for the MoCA ($r_{(30)} = .686$, $p > .001$) and span length in the Spatial Span task ($r_{(30)} = .692$, $p > .001$). Negative correlations were observed with the latency for the Big/Little Circle task ($r_{(30)} = -.439$, $p = .015$), the number of errors ($r_{(30)} = -.730$, $p > .001$) and latency ($r_{(30)} = -.626$,

Table 3
Statistical description and comparison between patients and control participants for the scores obtained in the tasks included in the CANTAB test.

	Median (interquartile range)					
	BCL # incorrect responses	BCL latency (s)*	IED # incorrect responses*	IED latency (s)*	SSP passed span*	SSP latency (s)*
Patient	0	1751.8 (1090.3)	34 (24)	2374.5 (1386.2)	5 (2)	7240.6 (3223.4)
Control	0	981.28 (229.2)	17 (20)	1410.1 (832.1)	7 (2)	5425.6 (1246.2)

Note: BCL # incorrect responses = number of incorrect responses when executing the 40 trials for the Big Little Circle task; BCL latency (s) = time in seconds to choose the correct response when executing the Big Little Circle task; IED # incorrect responses = number of incorrect responses when executing the trials for the Intra/Extra-Dimensional Shift task; IED latency (s) = reaction time in seconds to respond on the trials for the Intra/Extra-Dimensional Shift; SSP passed span = last passed span for the Spatial Span task; SSP latency (s) = time in seconds to choose the correct stimuli until the last passed span.

* Represents significant statistical differences between patients and controls when applying the nonparametric Mann–Whitney U test at $p \leq 0.001$.

Table 4
Spearman's correlations between the patients' scores obtained for the cognitive and behavioral test.

							SSP latency	
						SSP passed span	1.000	SSP latency
					BCL latency	1.000	−.303	SSP passed span
				BCL incorrect responses	1.000	−.452	.389	BCL latency
			IED latency	1.000	.296	−.350	−.054	BCL incorrect responses
		IED incorrect responses	1.000	.296	.718**	−.427	.739**	IED latency
		MoCA	1.000	.176	.042	.380	−.434	.287	IED incorrect responses
	MMSE	1.000	−.270	−.485	−.212	−.442	.545*	−.555*	MoCA
SARA	1.000	.305	−.263	−.368	−.504	−.433	.346	−.413	MMSE
1.000	−.506	−.418	.226	.877**	.381	.739**	−.444	.551*	SARA

Note: The indicated value corresponds to the rho Spearman's coefficient, $N = 15$ for all cases. BCL incorrect responses = amount of incorrect responses when executing the 40 trials for the Big Little Circle task; BCL latency = time to choose the correct response when executing the Big Little Circle task; IED incorrect responses = number of incorrect responses when executing the 59 trials for the Intra/Extra-Dimensional Shift task; IED latency = reaction time to respond to the trials for the Intra/Extra-Dimensional Shift; SSP passed span = last passed span for the Spatial Span task; SSP latency = time to choose the correct answers until the last passed span; MMSE = score for the Mini-mental State Examination; MoCA = score for the Montreal Cognitive Assessment; SARA = score for the Scale for the Assessment and Rating of Ataxia.
* Indicates significant correlation at $p \leq 0.05$.
** indicates significant correlation at $p \leq 0.005$.

$p > .001$) for the Intra/Extra-Dimensional Shift, and with the latency for the Spatial Span task ($r_{(30)} = -.429$, $p = .018$). No gender differences were observed for any test.

Regarding the clinical characteristics of the patients, Spearman's coefficient did not show any correlation between the CAG repetitions and any behavioral or cognitive test.

As shown in Table 4 several correlations were observed between the behavioral and cognitive tests. Scores for the SARA correlated with most of the tests with the exception of the MoCA and the number of incorrect responses for the Intra/Extra-Dimensional Shift of the CANTAB. Scores for the MMSE did not correlate with any cognitive task but scores for the MoCA correlated with most of the tasks included in the CANTAB with the exception of the number of incorrect responses for the Intra/Extra-Dimensional Shift.

Positive correlations were observed between the patients' age and the latency for the Spatial Span task ($r_{(15)} = .592$, $p = .010$) and between the disease evolution and the latency of the three tasks included in the CANTAB test: Big Little Circle ($r_{(15)} = .541$, $p = .037$), Intra/Extra-Dimensional Shift ($r_{(15)} = .611$, $p = .016$), and Spatial Span ($r_{(15)} = .679$, $p = .005$). Also, disease progression was negatively correlated with the MMSE scores ($r_{(15)} = -.566$, $p = .028$) and with the MoCA scores ($r_{(15)} = -.749$, $p = .001$), but positively correlated with the SARA scores ($r_{(15)} = .547$, $p = .035$).

The VBM analysis showed significant loss of gray matter in the SCA2 group cerebellar vermis. Significant gray matter loss was also found in the pons of the brainstem, in the parahippocampal gyrus and insula bilaterally, and in a variety of cortical regions including the precentral, inferior frontal, middle frontal, inferior parietal and middle temporal gyri (see Table 5 and Figs. 1 and 2).

The number of CAG repetitions and the scores for the MMSE and the MoCA passed the Shapiro–Wilk test of normality. However, none of these measures correlated with the patients' gray matter, white matter or total brain volume when using the Pearson product–moment correlation. Regarding the motor impairment, SARA scores negatively correlated with the gray matter volume ($r_{(15)} = -.804$, $p \leq .001$), with the white matter volume ($r_{(15)} = -.593$, $p = .020$) and with the total brain volume ($r_{(15)} = -.761$, $p = .001$). Furthermore, a linear regression model analysis showed that SARA scores predicted the patient's three volume measurements (see Table 6).

4. Discussion and conclusions

The results of the VBM analysis showed significant bilateral degeneration in the parahippocampal gyrus. Our analyses also corroborated previous findings including significant degeneration in the cerebellar vermis and brainstem, as well as in insular, precentral, frontal, parietal and temporal cortices [17,30] as discussed below.

The most important finding of our study is the gray matter reduction in the parahippocampal gyrus, which has not previously been reported in VBM studies on SCA2. Two previous sets of results support our finding. First, previous studies in other spinocerebellar ataxias including SCA7 and SCA17 have found gray matter reductions in the parahippocampal gyrus [1,35,64]. And second, a previous finding using voxel-based FDG-PET showed a severe metabolic impairment also in the parahippocampal area in SCA2 patients when compared with SCA3 and SCA6 patients [90]. The parahippocampal gyrus has been linked to memory formation and spatial analysis of social environments that may be required to integrate incoming information with

Table 5
Neuroanatomical regions indicating a significant decrease of gray matter volume in SCA2 patients.

Lat.	Brain region	Anatomical location	Brodmann's area	Cluster size	Coordinate			1 − p (corrected)
					x	y	z	
L	Frontal lobe	Precentral gyrus	4	40	−30	−28	64	0.982
L	Frontal lobe	Middle frontal gyrus	6	222	−24	−6	48	0.989
R	Frontal lobe	Inferior frontal gyrus	45	285	34	24	8	0.996
R	Parietal lobe	Inferior parietal gyrus	40	4	−52	−28	28	0.985
L	Temporal lobe	Middle temporal gyrus	38	32	−36	4	−38	0.980
R	Sub-lobar	Insula	13	681	−40	−32	22	0.992
L	Sub-lobar	Insula	13	991	−34	24	8	0.998
R	Limbic lobe	Parahippocampal gyrus	28	6	22	−12	−8	0.985
L	Limbic lobe	Parahippocampal gyrus	28	181	−20	−14	−14	0.995
L	Brainstem	Pons	*	6	−20	−22	32	0.977
L	Post. Cerebellum	Uvula of vermis. lob. IX	*	20,680	0	−66	−34	1

Note. Coordinates represent the peak value of the cluster in accordance with the Neurological Institute of Montreal (MNI) template. Approximate Brodmann areas were obtained through the Talairach Daemon System [44].
* Indicates no Brodmann's area reported.

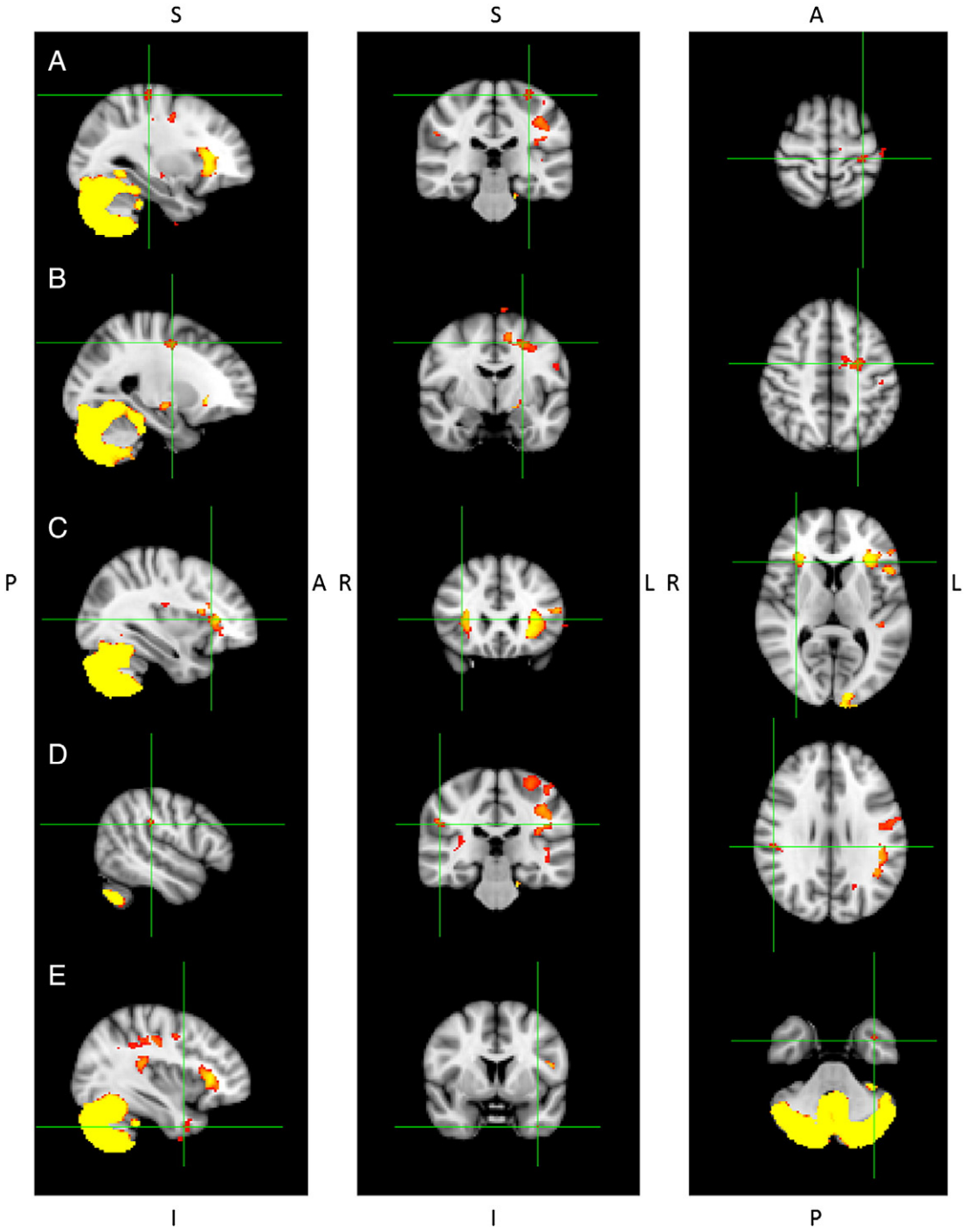

Fig 1. Sagittal, axial and coronal slices showing cortical regions with significant gray matter volume reductions in SCA2 patients. Green crosshairs indicate the local maxima differences. A. Left precentral gyrus (BA 4), B. left middle frontal gyrus (BA 6), C. right inferior frontal gyrus (BA 45), D. right inferior parietal gyrus (BA 40), E. middle temporal gyrus (BA 38). BA = Brodmann's area; S = superior face; I = inferior face, A = anterior face; P = posterior face; R = right face; L = left face.

episodic memory to perform adequate social and spatial mobilization [5,61]. These mnemonic processes implicate a network comprising high cortical functions regulating visuo-constructive skills and emotions [9] that are impaired in SCA2 patients [25]. Additionally, SCA2 patients also manifest memory complaints when remembering recent events or incorporating new information [49]. Since damage in the cerebellum influences deficits in verbal working memory, the loss in the parahippocampal region along with the cerebellar, frontal, and temporal regions observed could contribute to the low scores in the MMSE and the MoCA test involving articulatory rehearsal [62].

Reduced volume in the vermis has been previously reported in SCA2 using VBM [20,93]. This reduction may be linked to impairments on executive and coordinative functions in SCA2 patients [17] that could be explained by the fact that the vermis acts on a network comprising other cerebellar regions, such as the flocculonodular lobe, the fastigial nucleus, the globose nucleus, and the limbic regions involved in the regulation of executive decisions [34,87]. The vermis is fundamental to regulating emotional expressions [71] and its damage could be associated with the cerebellar cognitive affective syndrome and with emotional fragility and alterations in facial recognition in several SCA types [17,72,81,82].

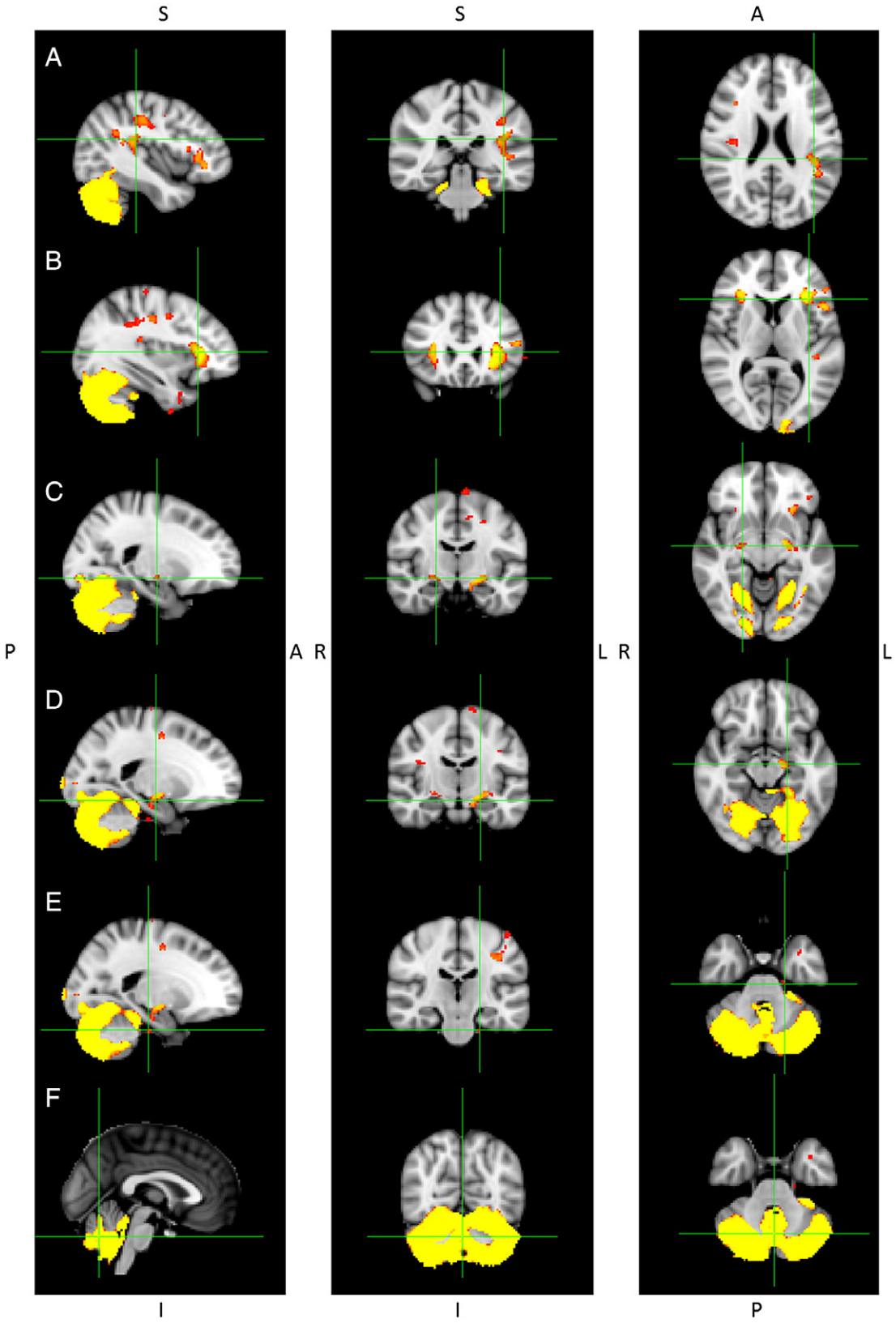

Fig 2. Sagittal, axial and coronal slices showing subcortical and cerebellar regions with significant gray matter volume reductions in SCA2 patients. Green crosshairs indicate the local maxima differences. A. Right insula (BA 13), B. left insula (BA 13), C. right parahippocampal gyrus (BA 28), D. left parahippocampal gyrus (BA 28), E. left brainstem (pons), F. left posterior cerebellum (uvula of vermis). BA = Brodmann's area; S = superior face; I = inferior face, A = anterior face; P = posterior face; R = right face; L = left face.

Our results also support previous SCA2 findings reporting the loss of cortical gray matter in the premotor cortex and the inferior frontal gyrus [21], the temporal and parietal cortices [17,30], as well as, the insula that has been associated to dystonia, myoclonus, tremor and pyramidal signs in patients with multiple system atrophy [7].

Table 6
Summary of linear regression analyses for the Scale for the Assessment and Rating of Ataxia scores predicting brain volume ($N = 15$).

SARA predictor	R^2	B	pSE B	β	*p* value
Gray matter	.647	−6406.289	1311.875	−.804	.001
White matter	.352	−3085.795	1161.000	−.593	.020
Total brain	.580	−9492.084	2242.115	−.761	.001

It has been reported that decreased activity in the left inferior frontal gyrus in Brodmann area 45 is associated with reduced body movements [67], which may occur in SCA2 progression. The inferior frontal gyrus is also necessary for language production and higher-order motor sequences [10,40,53]. The loss of gray matter in this frontal region observed in SCA2 patients may affect speech production and language processes [13,69] and could be related to the low scores in the MMSE and the MoCA test which include verbal production and repetition tasks.

The insular cortex is anatomically and functionally linked with the inferior frontal and temporal cortices, and its function is required for goal-directed behaviors, sound to speech transformations [11] and interoceptive information allowing for bodily maps and social skills [27,50,54]. The gray matter reduction in the insula may be related with speech impairments and deficits in social and perceptual guides to motor decisions and emotional attributions observed in SCA patients [17,23,28,80].

It has been proposed that the temporal pole (Brodmann area 38) plays a role in social cognition, emotional experiences and learning of linguistic concepts [57,94] when working in conjunction with the frontal cortex (Brodmann area 45), parietal cortex (Brodmann area 40) and insula [51] observed as atrophied in our study. Taking into account the role of the cerebellar vermis in emotional regulation [81], morphological alterations in the temporal pole could be related to eventual social cognitive alterations in SCA2 [28,80] affecting emotional face recognition [17].

As we hypothesized, some clinical features in SCA2 patients correlated with low performance of behavioral and cognitive tasks and with reduced brain volume, as it was the case for the SARA ratings. Nevertheless, other features such as CAG repetitions and disease evolution did not show any correlation. The use of VBM is an important tool to clarify cerebellar and non-cerebellar atrophies in SCA2 patients but findings may not always be strictly related with unique clinical manifestations, as has been proposed before [93]. Nevertheless, to assess more accurate correlations, VBM analysis could be complemented with other volumetric techniques, such as cortical regional thickness, or functional analysis using resting state to identify disrupted connectivity between reduced brain regions [35].

The pattern of cerebellar and non-cerebellar morphological alterations associated with SCA2 has to be considered to understand the deficient performances of these patients in psychiatric and neurological tests evaluating visual motor coordination, and non-motor functions such as verbal and visual memory, attention, learning abilities, language comprehension, and emotion recognition [9,17,45,85]. Besides, the influence of factors such as gender and education involving social cognition and emotion in SCA2 needs the integration of interdisciplinary phenomenological and neurobiological methodologies in order to describe in a more accurate manner the social consequences of this disease, as it has been recently made for other neuropsychiatric disorders [14,52].

In comparison with healthy participants SCA2 patients made more incorrect responses and required more time to respond in the CANTAB tests. Besides, latency was correlated with the SARA ratings and with the years of disease progression. These results confirm that SCA2 patients exhibit low performance in non-verbal task abilities such as working memory, retrieval, attention, and visuomotor learning [9,84,85] and that these cognitive abilities get worse as the motor difficulties aggravate and disease progression moves forward [41,45].

SCA2 patients exhibited lower scores than control participants in the MMSE and in the MoCA indicating cognitive impairments. In this regard, it has been reported that SCA2 patients do not show severe impairments evaluated by the MMSE but show evident deficits in other cognitive tests such as the Wechsler Adult Intelligence Scale-R and the Wisconsin Card Sorting Test [75]. In addition, scores for the MMSE and the MoCA were negatively correlated with the years of disease evolution but not with the scores for the CANTAB neither for the SARA ratings. These results may suggest that, similar to SCA14 [91] and SCA6 patients [12], the spectrum of cognitive impairing in SCA2 is diverse. So, although eventually this disease results in high cognitive process alterations [17,45,66], these alterations may not be directly related with the motor difficulties classically observed in these patients.

On the other hand, it is reported that age and education are two demographic qualities influencing the cognitive performance in SCA patients and that education may represent a protective factor [58]. In our study, age was correlated with a better performance for the Spatial Span task of the CANTAB and years of education was correlated with higher scores for the MMSE and the MoCA and with better performance of the CANTAB test for both patients and control participants. These results are important for several reasons. CANTAB tests are non-verbal tasks suitable for testing individuals with low educational levels and the MMSE is validated to be applied in samples with 5 years of education in Mexico [59]. This is relevant since most of the SCA2 participants show low socioeconomic levels probably linked to limited educational access in their places of residency, and social discrimination dynamics that we have detected in field observations during this research, similar to other medical anthropological observations made in other countries [6,33]. Therefore, although education may influence the cognitive performance in our SCA2 patients, a clear relation between both variables requires more research.

In reference to the clinical features, it has been proposed that CAG repetitions can be considered as a genotypic indicator of the evolution and behavioral and cognitive impairments in SCA1, 2, 3 and 6 [25,36,63]. Nevertheless, in our study CAG repetitions did not correlate either with the scores for the MMSE, the MoCA and the SARA test, or with the calculated gray, white and total volume of the patients' brain. These results agree with previous reports [30] and may be attributable to the small sample and the variable clinical characteristics of the patients in our study. Conversely, we found a clear correlation between the SARA ratings and the gray matter, white matter and total brain volumes. In fact, SARA scores predicted the calculated patients' brain volumes which confirm that SCA2 is a fundamental motor affection and suggest that the SARA test is a viable clinical evaluation.

Conflict of interests

The authors declare no conflict of interests.

Acknowledgments

This research was supported by the DGAPA—Programa de Becas Postdoctorales to REM, and DGAPA—PAPIIT IN221413 from Universidad Nacional Autonoma de Mexico, and CONACYT (102314) to JFR.

References

[1] Alcauter S, Barrios FA, Díaz R, Fernández-Ruiz J. Gray and white matter alterations in spinocerebellar ataxia type 7: an in vivo DTI and VBM study. Neuroimage 2011; 55(1):1–7. http://dx.doi.org/10.1016/j.neuroimage.2010.12.014.
[2] Andersson JLR, Jenkinson M, Smith S. Non-linear registration, aka spatial normalisation: FMRIB technical report TR07JA2; 2007.
[3] Antunes-Teixeira RA, Zachi EC, Tsubota-Roque D, Taub A, Ventura DF. Memory span measured by the spatial span tests of the Cambridge Neuropsychological Test Automated Battery in a group of Brazilian children and adolescents. Dement Neuropsychol 2011;5(2):129–34. http://dx.doi.org/10.3922/j.psns.2011.2.011.

[4] Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage 2000;11(6 Pt 1):805–21. http://dx.doi.org/10.1006/nimg.2000.0582.

[5] Axmacher N, Schmitz DP, Weinreich I, Elger CE, Fell J. Interaction of working memory and long-term memory in the medial temporal lobe. Cereb Cortex 2008;18(12):2868–78. http://dx.doi.org/10.1093/cercor/bhn045.

[6] Braithwaite J, Westbrook MT, Travaglia JF, Iedema R, Mallock N, Long D, et al. Are health systems changing in support of patient safety? A multi-methods evaluation of education, attitudes and practice. Int J Health Care Qual Assur 2007;20(7):585–601. http://dx.doi.org/10.1108/09526860710822725.

[7] Brenneis C, Boesch SM, Egger KE, Seppi K, Scherfler C, Schocke M, et al. Cortical atrophy in the cerebellar variant of multiple system atrophy: a voxel-based morphometry study. Mov Disord 2006;21(2):159–65. http://dx.doi.org/10.1002/mds.20656.

[8] Brenneis C, Bosch SM, Schocke M, Wenning GK, Poewe W. Atrophy pattern in SCA2 determined by voxel-based morphometry. Neuroreport 2003;14(14):1799–802. http://dx.doi.org/10.1097/00001756-200310060-00008.

[9] Burk K, Globas C, Bosch S, Klockgether T, Zuhlke C, Daum I, et al. Cognitive deficits in spinocerebellar ataxia type 1, 2, and 3. J Neurol 2003;250(2):207–11. http://dx.doi.org/10.1007/s00415-003-0976-5.

[10] Clerget E, Andres M, Olivier E. Deficit in complex sequence processing after a virtual lesion of left BA45. PLoS One 2013;8(6):e63722. http://dx.doi.org/10.1371/journal.pone.0063722.

[11] Cloutman LL, Binney RJ, Drakesmith M, Parker GJ, Lambon Ralph MA. The variation of function across the human insula mirrors its patterns of structural connectivity: evidence from in vivo probabilistic tractography. Neuroimage 2012;59(4):3514–21. http://dx.doi.org/10.1016/j.neuroimage.2011.11.016.

[12] Cooper FE, Grube M, Elsegood KJ, Welch JL, Kelly TP, Chinnery PF, et al. The contribution of the cerebellum to cognition in spinocerebellar ataxia type 6. Behav Neurol 2010;23(1–2):3–15. http://dx.doi.org/10.3233/BEN-2010-0265.

[13] Cooper FE, Grube M, Von Kriegstein K, Kumar S, English P, Kelly TP, et al. Distinct critical cerebellar subregions for components of verbal working memory. Neuropsychologia 2012;50(1):189–97. http://dx.doi.org/10.1016/j.neuropsychologia.2011.11.017.

[14] Couto B, Manes F, Montanes P, Matallana D, Reyes P, Velasquez M, et al. Structural neuroimaging of social cognition in progressive non-fluent aphasia and behavioral variant of frontotemporal dementia. Front Hum Neurosci 2013;7:467. http://dx.doi.org/10.3389/fnhum.2013.00467.

[15] Critchley HD, Elliott R, Mathias CJ, Dolan RJ. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. J Neurosci 2000;20(8):3033–40.

[16] Critchley HD, Rotshtein P, Nagai Y, O'Doherty J, Mathias CJ, Dolan RJ. Activity in the human brain predicting differential heart rate responses to emotional facial expressions. Neuroimage 2005;24(3):751–62. http://dx.doi.org/10.1016/j.neuroimage.2004.10.013.

[17] D'Agata F, Caroppo P, Baudino B, Caglio M, Croce M, Bergui M, et al. The recognition of facial emotions in spinocerebellar ataxia patients. Cerebellum 2011;10(3):600–10. http://dx.doi.org/10.1007/s12311-011-0276-z.

[18] D'Agata F, Caroppo P, Boghi A, Coriasco M, Caglio M, Baudino B, et al. Linking coordinative and executive dysfunctions to atrophy in spinocerebellar ataxia 2 patients. Brain Struct Funct 2011;216(3):275–88. http://dx.doi.org/10.1007/s00429-011-0310-4.

[19] Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci 2000;3(10):1049–56. http://dx.doi.org/10.1038/79871.

[20] Della Nave R, Ginestroni A, Tessa C, Cosottini M, Giannelli M, Salvatore E, et al. Brain structural damage in spinocerebellar ataxia type 2. A voxel-based morphometry study. Mov Disord 2008;23(6):899–903. http://dx.doi.org/10.1002/mds.21982.

[21] Della Nave R, Ginestroni A, Tessa C, Salvatore E, De Grandis D, Plasmati R, et al. Brain white matter damage in SCA1 and SCA2. An in vivo study using voxel-based morphometry, histogram analysis of mean diffusivity and tract-based spatial statistics. Neuroimage 2008;43(1):10–9. http://dx.doi.org/10.1016/j.neuroimage.2008.06.036.

[22] Famularo G, Corsi FM, Minisola G, De Simone C, Nicotra GC. Cerebellar tumour presenting with pathological laughter and gelastic syncope. Eur J Neurol 2007;14(8):940–3. http://dx.doi.org/10.1111/j.1468-1331.2007.01784.x.

[23] Fancellu R, Paridi D, Tomasello C, Panzeri M, Castaldo A, Genitrini S, et al. Longitudinal study of cognitive and psychiatric functions in spinocerebellar ataxia types 1 and 2. J Neurol 2013;260(12):3134–43. http://dx.doi.org/10.1007/s00415-013-7138-1.

[24] Fernández-Ruiz J, Velásquez-Perez L, Díaz R, Drucker-Colín R, Pérez-González R, Canales N, et al. Prism adaptation in spinocerebellar ataxia type 2. Neuropsychologia 2007;45(12):2692–8. http://dx.doi.org/10.1016/j.neuropsychologia.2007.04.006.

[25] Fernández M, McClain ME, Martinez RA, Snow K, Lipe H, Ravits J, et al. Late-onset SCA2: 33 CAG repeats are sufficient to cause disease. Neurology 2000;55(4):569–72. http://dx.doi.org/10.1212/WNL.55.4.569.

[26] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–98. http://dx.doi.org/10.1016/0022-3956(75)90026-6.

[27] Gallese V, Keysers C, Rizzolatti G. A unifying view of the basis of social cognition. Trends Cogn Sci 2004;8(9):396–403. http://dx.doi.org/10.1016/j.tics.2004.07.002.

[28] Garrard P, Martin NH, Giunti P, Cipolotti L. Cognitive and social cognitive functioning in spinocerebellar ataxia: a preliminary characterization. J Neurol 2008;255(3):398–405. http://dx.doi.org/10.1007/s00415-008-0680-6.

[29] Geschwind DH, Perlman S, Figueroa CP, Treiman LJ, Pulst SM. The prevalence and wide clinical spectrum of the spinocerebellar ataxia type 2 trinucleotide repeat in patients with autosomal dominant cerebellar ataxia. Am J Hum Genet 1997;60(4):842–50.

[30] Goel G, Pal PK, Ravishankar S, Venkatasubramanian G, Jayakumar PN, Krishna N, et al. Gray matter volume deficits in spinocerebellar ataxia: an optimized voxel based morphometric study. Parkinsonism Relat Disord 2011;17(7):521–7. http://dx.doi.org/10.1016/j.parkreldis.2011.04.008.

[31] Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14(1 Pt 1):21–36. http://dx.doi.org/10.1006/nimg.2001.0786.

[32] Habel U, Koch K, Pauly K, Kellermann T, Reske M, Backes V, et al. The influence of olfactory-induced negative emotion on verbal working memory: individual differences in neurobehavioral findings. Brain Res 2007;1152:158–70. http://dx.doi.org/10.1016/j.brainres.2007.03.048.

[33] Hamui-Sutton L. Las narrativas del padecer: una ventana a la realidad social. Cuicuilco 2011;18(52):51–70.

[34] Hernáez-Goñi P, Tirapu-Ustárroz J, Iglesias-Fernández L, Luna-Lario P. Participación del cerebelo en la regulación del afecto, la emoción y la conducta. Rev Neurol 2010;51(10):597–609.

[35] Hernández-Castillo CR, Alcauter S, Galvez V, Barrios FA, Yescas P, Ochoa A, et al. Disruption of visual and motor connectivity in spinocerebellar ataxia type 7. Mov Disord 2013;28(12):1708–16. http://dx.doi.org/10.1002/mds.25618.

[36] Jacobi H, Reetz K, du Montcel ST, Bauer P, Mariotti C, Nanetti L, et al. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. Lancet Neurol 2013;12(7):650–8. http://dx.doi.org/10.1016/S1474-4422(13)70104-2.

[37] Jazbec S, Pantelis C, Robbins T, Weickert T, Weinberger DR, Goldberg TE. Intra-dimensional/extra-dimensional set-shifting performance in schizophrenia: impact of distractors. Schizophr Res 2007;89(1–3):339–49. http://dx.doi.org/10.1016/j.schres.2006.08.014.

[38] Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17(2):825–41. http://dx.doi.org/10.1016/s1053-8119(02)91132-8.

[39] Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. Med Image Anal 2001;5(2):143–56. http://dx.doi.org/10.1016/s1361-8415(01)00036-6.

[40] Katzev M, Tuscher O, Hennig J, Weiller C, Kaller CP. Revisiting the functional specialization of left inferior frontal gyrus in phonological and semantic fluency: the crucial role of task demands and individual ability. J Neurosci 2013;33(18):7837–45. http://dx.doi.org/10.1523/JNEUROSCI.3147-12.2013.

[41] Kawai Y, Suenaga M, Watanabe H, Sobue G. Cognitive impairment in spinocerebellar degeneration. Eur Neurol 2009;61(5):257–68. http://dx.doi.org/10.1159/000206850.

[42] Klockgether T, Skalej M, Wedekind D, Luft AR, Welte D, Schulz JB, et al. Autosomal dominant cerebellar ataxia type I. MRI-based volumetry of posterior fossa structures and basal ganglia in spinocerebellar ataxia types 1, 2 and 3. Brain 1998;121(Pt 9):1687–93.

[43] Kumaran D, Maguire EA. The human hippocampus: cognitive maps or relational memory? J Neurosci 2005;25(31):7254–9. http://dx.doi.org/10.1523/JNEUROSCI.1103-05.2005.

[44] Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al. Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 2000;10(3):120–31. http://dx.doi.org/10.1002/1097-0193(200007)10:3<120::AID-HBM30>3.0.CO;2-8.

[45] Le Pira F, Zappala G, Saponara R, Domina E, Restivo D, Reggio E, et al. Cognitive findings in spinocerebellar ataxia type 2: relationship to genetic and clinical variables. J Neurol Sci 2002;201(1–2):53–7. http://dx.doi.org/10.1016/S0022-510X(02)00194-6.

[46] Luciana M, Nelson CA. Assessment of neuropsychological function through use of the Cambridge Neuropsychological Testing Automated Battery: performance in 4 to 12-year-old children. Dev Neuropsychol 2002;22:595–624. http://dx.doi.org/10.1207/S15326942DN2203_3.

[47] Lukas C, Hahn HK, Bellenberg B, Hellwig K, Globas C, Schimrigk SK, et al. Spinal cord atrophy in spinocerebellar ataxia type 3 and 6: impact on clinical disability. J Neurol 2008;255(8):1244–9. http://dx.doi.org/10.1007/s00415-008-0907-6.

[48] Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). Cerebellum 2005;4(1):2–6. http://dx.doi.org/10.1080/14734220510007914.

[49] McMurtray AM, Clark DG, Flood MK, Perlman S, Mendez MF. Depressive and memory symptoms as presenting features of spinocerebellar ataxia. J Neuropsychiatry Clin Neurosci 2006;18(3):420–2. http://dx.doi.org/10.1176/appi.neuropsych.18.3.420.

[50] Meltzoff AN. 'Like me': a foundation for social cognition. Dev Sci 2007;10(1):126–34. http://dx.doi.org/10.1111/j.1467-7687.2007.00574.x.

[51] Mercadillo RE, Díaz JL, Pasaye EH, Barrios FA. Perception of suffering and compassion experience: brain gender disparities. Brain Cogn 2011;76(1):5–14. http://dx.doi.org/10.1016/j.bandc.2011.03.019.

[52] Mercadillo RE, Trujillo C, Sanchez-Cortazar J, Barrios FA. In ADHD patients performing the Counting Stroop task: a social neuroscience approach. Psychol Rep 2012;111(2):652–68. http://dx.doi.org/10.2466/15.10.19.PR0.111.5.652-668.

[53] Morgan AT, Masterton R, Pigdon L, Connelly A, Liegeois FJ. Functional magnetic resonance imaging of chronic dysarthric speech after childhood brain injury: reliance on a left-hemisphere compensatory network. Brain 2013;136(Pt 2):646–57. http://dx.doi.org/10.1093/brain/aws355.

[54] Mutschler I, Reinbold C, Wankerl J, Seifritz E, Ball T. Structural basis of empathy and the domain general region in the anterior insular cortex. Front Hum Neurosci 2013;7:177. http://dx.doi.org/10.3389/fnhum.2013.00177.

[55] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695–9. http://dx.doi.org/10.1111/j.1532-5415.2005.53221.x.

[56] Nomi JS, Scherfeld D, Friederichs S, Schafer R, Franz M, Wittsack HJ, et al. On the neural networks of empathy: a principal component analysis of an fMRI study. Behav Brain Funct 2008;4:41. http://dx.doi.org/10.1186/1744-9081-4-41.

[57] Olson IR, Plotzker A, Ezzyat Y. The enigmatic temporal pole: a review of findings on social and emotional processing. Brain 2007;130(Pt 7):1718–31. http://dx.doi.org/10.1093/brain/awm052.
[58] Orsi L, D'Agata F, Caroppo P, Franco A, Caglio MM, Avidano F, et al. Neuropsychological picture of 33 spinocerebellar ataxia cases. J Clin Exp Neuropsychol 2011;33(3):315–25. http://dx.doi.org/10.1080/13803395.2010.518139.
[59] Ostrosky-Solís F, López-Arango G, Ardila A. Sensitivity and specificity of the Mini-Mental State Examination in a Spanish-speaking population. Appl Neuropsychol 2000;7(1):25–31. http://dx.doi.org/10.1207/S15324826AN0701_4.
[60] Pulst SM, Nechiporuk A, Nechiporuk T, Gispert S, Chen XN, Lopes-Cendes I, et al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat Genet 1996;14(3):269–76.
[61] Qin S, Rijpkema M, Tendolkar I, Piekema C, Hermans EJ, Binder M, et al. Dissecting medial temporal lobe contributions to item and associative memory formation. Neuroimage 2009;46(3):874–81. http://dx.doi.org/10.1016/j.neuroimage.2009.02.039.
[62] Ravizza SM, McCormick CA, Schlerf JE, Justus T, Ivry RB, Fiez JA. Cerebellar damage produces selective deficits in verbal working memory. Brain 2006;129(Pt 2):306–20. http://dx.doi.org/10.1093/brain/awh730.
[63] Reetz K, Costa AS, Mirzazade S, Lehmann A, Juzek A, Rakowicz M, et al. Genotype-specific patterns of atrophy progression are more sensitive than clinical decline in SCA1, SCA3 and SCA6. Brain 2013;136:905–17. http://dx.doi.org/10.1093/brain/aws369.
[64] Reetz K, Lencer R, Hagenah JM, Gaser C, Tadic V, Walter U, et al. Structural changes associated with progression of motor deficits in spinocerebellar ataxia 17. Cerebellum 2010;9(2):210–7. http://dx.doi.org/10.1007/s12311-009-0150-4.
[65] Richter S, Schoch B, Kaiser O, Groetschel H, Dimitrova A, Hein-Kropp C, et al. Behavioral and affective changes in children and adolescents with chronic cerebellar lesions. Neurosci Lett 2005;381(1–2):102–7. http://dx.doi.org/10.1016/j.neulet.2005.02.011.
[66] Rodríguez-Labrada R, Velázquez-Pérez L, Seigfried C, Canales-Ochoa N, Auburger G, Medrano-Montero J, et al. Saccadic latency is prolonged in spinocerebellar ataxia type 2 and correlates with the frontal-executive dysfunctions. Neurol Sci 2011;306(1–2):103–7. http://dx.doi.org/10.1016/j.jns.2011.03.033.
[67] Rosano C, Aizenstein H, Cochran J, Saxton J, De Kosky S, Newman AB, et al. Functional neuroimaging indicators of successful executive control in the oldest old. Neuroimage 2005;28(4):881–9. http://dx.doi.org/10.1016/j.neuroimage.2005.05.059.
[68] Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB. J R Soc Med 1992;85:399–402.
[69] Schalling E, Hartelius L. Speech in spinocerebellar ataxia. Brain Lang 2013;127(3):317–22. http://dx.doi.org/10.1016/j.bandl.2013.10.002.
[70] Scherzed W, Brunt ER, Heinsen H, de Vos RA, Seidel K, Burk K, et al. Pathoanatomy of cerebellar degeneration in spinocerebellar ataxia type 2 (SCA2) and type 3 (SCA3). Cerebellum 2012;11(3):749–60. http://dx.doi.org/10.1007/s12311-011-0340-8.
[71] Schmahmann JD. An emerging concept. The cerebellar contribution to higher function. Arch Neurol 1991;48:1178–87.
[72] Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci 2004;16(3):367–78. http://dx.doi.org/10.1176/appi.neuropsych.16.3.367.
[73] Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998;121(Pt 4):561–79. http://dx.doi.org/10.1093/brain/121.4.561.
[74] Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006;66(11):1717–20. http://dx.doi.org/10.1212/01.wnl.0000219042.60538.92.
[75] Shimohata T, Matsuzawa Y, Tanaka K, Onodera O, Tanaka K, Nishizawa M. Evaluation of two patients with SCA2 with frontal lobe dysfunction using brain SPECT with three-dimensional stereotactic surface projections (3D-SSP). Rinsho Shinkeigaku 2005;45(1):22–6.
[76] Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17(3):143–55. http://dx.doi.org/10.1002/hbm.10062.
[77] Smith SM, De Stefano N, Jenkinson M, Matthews PM. Normalised accurate measurement of longitudinal brain change. J Comput Assist Tomogr 2001;25(3):466–75. http://dx.doi.org/10.1016/S1053-8119(00)91589-1.
[78] Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23(Suppl. 1):S208–19. http://dx.doi.org/10.1016/j.neuroimage.2004.07.051.
[79] Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17(1):479–89. http://dx.doi.org/10.1006/nimg.2002.1040.
[80] Sokolovsky N, Cook A, Hunt H, Giunti P, Cipolotti L. A preliminary characterisation of cognition and social cognition in spinocerebellar ataxia types 2, 1, and 7. Behav Neurol 2010;23(1–2):17–29. http://dx.doi.org/10.3233/BEN-2010-0270.
[81] Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 2009;44:489–501. http://dx.doi.org/10.1016/j.neuroimage.2008.08.039.
[82] Tedesco AM, Chiricozzi FR, Clausi S, Lupo M, Molinari M, Leggio MG. The cerebellar cognitive profile. Brain 2011;134(Pt 12):3672–86. http://dx.doi.org/10.1093/brain/awr266.
[83] Tsubota-Roque D, Antunes-Teixeira RA, Zachi EC, Ventura DF. The use of the Cambridge Neuropsychological Test Automated Battery (CANTAB) in neuropsychological assessment: application in Brazilian research with control children and adults with neurological disorders. Psychol Neurosci 2011;4(2):255–65. http://dx.doi.org/10.3922/j.psns.2011.2.011.
[84] Vaca-Palomares I, Diaz R, Rodríguez-Labrada R, Medrano-Montero J, Vázquez-Mojena Y, Velázquez-Pérez L, et al. Spinocerebellar ataxia type 2 neurodegeneration differentially affects error-based and strategic-based visuomotor learning. Cerebellum 2013;12(6):848–55. http://dx.doi.org/10.1007/s12311-013-0496-5.
[85] Valis M, Masopust J, Bažant J, Říhová Z, Kalnická D, Urban A, et al. Cognitive changes in spinocerebellar ataxia type 2. Neuro Endocrinol Lett 2011;32(3):354–9.
[86] van Gaalen J, Giunti P, van de Warrenburg BP. Movement disorders in spinocerebellar ataxias. Mov Disord 2010;26(5):792–800. http://dx.doi.org/10.1002/mds.23584.
[87] van Harskamp NJ, Rudge P, Cipolotti L. Cognitive and social impairments in patients with superficial siderosis. Brain 2005;128(Pt 5):1082–92. http://dx.doi.org/10.1093/brain/awh487.
[88] Velázquez-Pérez L, Rodríguez-Labrada R, Canales-Ochoa N, Sánchez-Cruz G, Fernández-Ruiz J, Montero JM, et al. Progression markers of spinocerebellar ataxia 2. A twenty years neurophysiological follow up study. J Neurol Sci 2010;290(1):22–6. http://dx.doi.org/10.1016/j.jns.2009.12.013.
[89] Wadia NH, Swami RK. A new form of heredo-familial spinocerebellar degeneration with slow eye movements (nine families). Brain 1971;94(2):359–74. http://dx.doi.org/10.1093/brain/94.2.359.
[90] Wang PS, Liu RS, Yang BH, Soong BW. Regional patterns of cerebral glucose metabolism in spinocerebellar ataxia type 2, 3 and 6: a voxel-based FDG-positron emission tomography analysis. J Neurol 2007;254(7):838–45. http://dx.doi.org/10.1007/s00415-006-0383-9.
[91] Wedding IM, Koht J, Dietrichs E, Landro NI, Tallaksen CM. Cognition is only minimally impaired in spinocerebellar ataxia type 14 (SCA14): a neuropsychological study of ten Norwegian subjects compared to intrafamilial controls and population norm. BMC Neurol 2013;13:186. http://dx.doi.org/10.1186/1471-2377-13-186.
[92] Yabe I, Matsushima M, Soma H, Basri R, Sasaki H. Usefulness of the Scale for Assessment and Rating of Ataxia (SARA). J Neurol Sci 2008;266(1–2):164–6. http://dx.doi.org/10.1016/j.jns.2007.09.021.
[93] Ying SH, Choi SI, Perlman SL, Baloh RW, Zee DS, Toga AW. Pontine and cerebellar atrophy correlate with clinical disability in SCA2. Neurology 2006;66(3):424–6. http://dx.doi.org/10.1212/01.wnl.0000196464.47508.00.
[94] Zahn R, Moll J, Krueger F, Huey ED, Garrido G, Grafman J. Social concepts are represented in the superior anterior temporal cortex. Proc Natl Acad Sci U S A 2007;104(15):6430–5. http://dx.doi.org/10.1073/pnas.0607061104.
[95] Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging 2001;20(1):45–57. http://dx.doi.org/10.1109/42.906424.