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

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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

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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.