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BRIEF COMMUNICATION

Specific cerebellar and cortical degeneration correlates with ataxia severity in spinocerebellar ataxia type 7

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Abstract Spinocerebellar ataxia type 7 (SCA7) is a progressive neurodegenerative disorder that is accompanied by loss of motor control and macular degeneration. Previous studies have shown cerebellar and pons atrophy as well as functional connectivity changes across the whole brain. Although different MRI modalities have been used to study the degenerative process, little is known about the relationship between the motor symptoms and cerebral atrophy. Twenty-four patients with molecular diagnosis of SCA7 where invited to participate in this study. Ataxia severity was evaluated using the scale for the assessment and rating of ataxia (SARA). Structural magnetic resonance imaging (MRI) brain images were used to obtain the grey matter volume of each participant. As expected, we found a significant negative correlation between the SARA score and the grey matter volume in distinct regions of the cerebellum in the patient group. Additionally, we found significant correlations between the ataxia degree and the degeneration of specific cortical areas in these patients. These findings provide a better understanding of the relationship between gray matter atrophy and ataxia related symptoms that result from the SCA7 mutation.

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Background

Spinocerebellar ataxia 7 (SCA7) is a neurodegenerative disorder caused by the abnormal expansion of the cytosine-adenine-guanine (CAG) trinucleotide encoding the protein ataxin7 (Garden and La Spada 2008). SCA7 is characterized by a combination of cerebellar ataxia and macular degeneration that causes permanent blindness (Michalik et al. 2004; Miller et al. 2009). Furthermore, patients may eventually develop other neurological deficits, including loss of manual dexterity, speech dysarthria, dysphagia and eye movement abnormalities (Hugosson et al. 2009). Brain atrophy associated with SCA7 has been documented in different neuropathological studies using both postmortem and imaging techniques. These techniques have identified severe neuronal loss in a broad range of cerebellar and cerebral regions, including the cerebellar cortex, the inferior olivary complex tracts, the subthalamic nucleus, the pallidum, and the substantia nigra. SCA7 is also associated with degeneration of cortical regions such as the pre/postcentral gyri, cuneus, precuneus, inferior occipital gyrus, insula, and inferior frontal gyrus (Alcauter et al. 2011; Bang et al. 2004; Döhlinger et al. 2008; Hernandez-Castillo et al. 2013; Masciullo et al. 2007). Resting state functional magnetic resonance imaging (fMRI) techniques have been used to analyze the effect of SCA7 related degeneration on functional connectivity patterns, finding synchrony changes between degenerated and non-degenerated areas across the brain (Hernandez-Castillo et al. 2013, 2014). However, there is a lack of

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information regarding the relationship between brain atrophy and the motor impairments in SCA7. Therefore, we correlated gray matter volume in specific brain areas targeted by SCA7 pathology with measures of ataxia severity using the scale for the assessment and rating of ataxia (SARA) in a large set of people with SCA7.

Methods

Participants

Twenty-four patients with a molecular diagnosis of SCA7 and a CAG expansion higher than 40 participated in this study (11 female; right-handed; mean age/SD, 39.4/14.7 years). Motor impairment was measured using the Scale for the assessment and rating of ataxia (SARA) (Schmitz-Hübsch et al. 2006). The SARA has eight items, including tests of gait, stance, sitting, and speech, as well as the finger-chase test, finger-nose test, fast alternating movements, and heel-shin test. The control group consisted of 24 healthy volunteers that were matched for age and sex to the SCA7 group (Further demographic information of the two groups can be found in supplementary Table 1). The procedures carried out were in accordance with the ethical standards of the committees on human experimentation of the Universidad Nacional Autonoma de Mexico.

Image acquisition

All images were acquired using a 3.0-T Achieva MRI scanner (Phillips Medical Systems, Eindhoven, The Netherlands) at the Instituto Nacional de Psiquiatria "Ramon de la Fuente Muñiz" in Mexico City. The high-resolution anatomical 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 1×1×1 mm.

Voxel-based morphometry

Gray matter volume measurements were performed using voxel based morphometry (VBM) (Ashburner and Friston 2000) implemented on FSL (Smith et al. 2004). First, voxels that did not represent cerebral tissue were excluded. Then, tissues were segmented into grey matter, white matter, and cerebrospinal fluid. The images corresponding to the gray matter were aligned to Neurological Institute of Montreal MNI152 standard space by means of a nonlinear co-registration. The average of these co-registered images was obtained to generate a specific standard for this study. The individual gray matter images were co-registered to this specific standard space through a non-linear co-registration, and local changes in expansion or contraction were corrected through a process known as modulation (Good et al. 2002). Smoothing was applied with a Gaussian isotropic kernel with a sigma of 2 mm. Using the FSL randomise tool, (Winkler et al. 2014) a two-sample t test was performed between the SCA7 group and controls . Significance was defined as $p<0.05$ after correcting for multiple comparisons using the randomized permutation method (Hayasaka and Nichols 2004). For the SCA7 group, whole-brain correlation maps were created by calculating the Pearson's partial correlation between the gray matter volume (GMV) and SARA scores. Since prior studies using imaging measures have described age-associated changes across the cerebral cortex (Raz 1997; Salat et al. 2004), we included the age data in the partial correlation. The standardized SCA7 GMV images were loaded in MATLAB 2014a (The Mathworks, Inc., Natick, MA) and a voxelwise partial correlation were calculated using in-house functions. Partial correlation maps were corrected for multiple comparisons by using the false discovery rate (FDR) with a p value<0.05. For every significant cluster in the final map, GMV values were extracted for each participant using a "sphere" of 15 voxels centered in the peak correlation voxel.

Results

The VBM analysis showed extensive regions of decreased brain volume in patients with SCA7 in comparison to controls, involving both neocortical and allocortical regions. As previously reported, the right anterior cerebellum showed the greatest amount of atrophy, followed by the left posterior cerebellum. Other regions showing gray matter decreases in the SCA7 group compared to controls were the cuneus, precuneus, pre/post central gyri, inferior frontal gyrus, and temporal regions (Fig. 1a).

Significant negative correlations were found between GMV and SARA scores in the SCA7 group (Table 1 and Fig. 1b). These regions include the bilateral anterior and posterior cerebellum, the left parahippocampal gyrus, bilateral precentral gyri, bilateral cingulate gyri, bilateral insula, and bilateral inferior frontal gyri. Scatter plots of the significant correlations are shown in the supplementary Fig. 1.

Discussion

In this study we analyzed the relationship between gray matter loss and SARA scores in people with SCA7. As expected, significant negative correlations between SARA scores and GMV were found in the cerebellum and precentral gyri, but also in the parahippocampal, cingulate, insular and inferior frontal cortices.

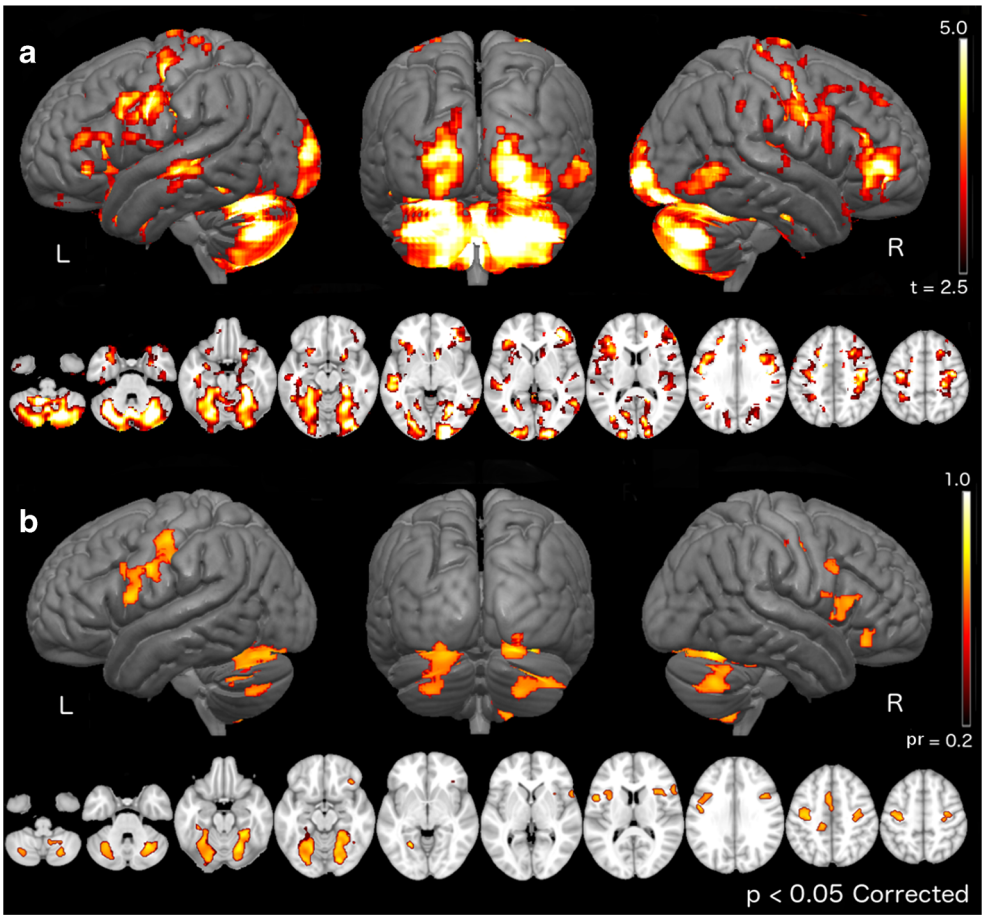

Fig. 1 Comparison of brain regions showing gray matter atrophy and SARA-GMV correlation. **a** Significant *gray* matter atrophy in patients compared with controls; **b** significant partial correlations between patients' GMV and SARA controlling for age. *Warm colors* indicate for **a**) the *t* value and **b**) the Pearson's partial correlation coefficient pr value. Parametric maps corrected at $p<0.05$ (see Methods)

Table 1 Significant correlations between gray matter volume and SARA score

Anatomical region	X	Y	Z	pr	BA
Right anterior cerebellum culmen	22	−62	−22	−0.817	–
Left parahippocampal gyrus	−24	−56	−4	−0.805	19
Left precentral gyrus	−46	−4	32	−0.799	6
Right cingulate gyrus	4	20	40	−0.793	32
Right insula	36	18	8	−0.773	13
Right precentral gyrus	32	−12	52	−0.761	4
Left anterior cerebellum culmen	−30	−52	−18	−0.759	–
Right precentral gyrus	60	12	4	−0.742	44
Right posterior cerebellum tonsil	24	−52	−46	−0.740	–
Right inferior frontal gyrus	38	30	−14	−0.725	47
Left cingulate gyrus	−14	−34	38	−0.724	–
Right inferior frontal gyrus	54	10	26	−0.723	9
Left insula	−32	8	12	−0.696	13
Left posterior cerebellum semi-lunar	−30	−68	−44	−0.640	–

Coordinates for peak correlations in MNI space in mm. Anatomical regions and BA were obtained using Talairach daemon

BA Brodmann Area

$p<0.05$ FDR corrected

The cerebellum, which is fundamental for movement and balance (Middleton and Strick 1998), is the most structurally affected region in SCA7 (Alcauter et al. 2011; Horton et al. 2013). Different studies have shown motor deficits after damage to the cerebellum (Schmahmann 2014). A number of SCAs studies including SCA1 and SCA7 have reported that the extent of cerebellar neurodegeneration correlates with a variety of clinical motor features, like ataxia scores and extrapyramidal signs (Goel et al. 2011; Lasek et al. 2006; Reetz et al. 2011). Our results show a significant correlation between ataxia severity and decreased GMV in the anterior and posterior cerebellar hemispheres, bilaterally. Previous studies have measure the amount of cerebellar atrophy in SCA7 (Alcauter et al. 2011; Hernandez-Castillo et al. 2013), but our results show for the first time the close relationship between cerebellar volume and the motor impairment in people with SCA7.

A number of cortical areas where GMV correlated with the SARA score could reflect the motor deficits in gait and general movement in people with SCA7 (Martin 2012). As expected, based on previous volumetric studies, volume of the precentral gyrus showed significant correlation with higher SARA scores in the SCA7 group. Another region where GMV correlated with SARA scores was the anterior cingulate cortex. This region has been related to emotional self-control,

focused problem solving, error recognition, and adaptive response to changing conditions, and is also known to have numerous projections to motor systems (Allman et al. 2006). The motor areas of the cingulate cortex have connections not only to the spinal cord and red nucleus, but also to the primary motor cortex and the supplementary motor area (Devinsky et al. 1995). Patients with lesions in this area often show deficits in spontaneous initiation of movement and speech, as well as inability to suppress externally triggered motor subroutines (Paus et al. 2001). Like the cingulate and primary motor cortices, insula GMV also correlated with SARA scores. Structurally, the anterior insular cortex is connected with limbic and paralimbic regions including the anterior cingulate area and anterior inferior frontal cortex, whereas the posterior insula cortex is more densely connected with posterior temporal, parietal, and frontal areas including somatosensory, motor, and premotor cortices (Cerliani et al. 2012; Jakab et al. 2012). Moreover, the insula also supports pre-articulatory functions of speech motor control such as the "programming" of vocal tract gestures (Ackermann and Riecker 2004). Another region where GMV correlates with SARA scores was the inferior frontal cortex. This area contributes to different cognitive processes including decision making, response inhibition, stimulus-based switching of attention (Freedman 1998; Szatkowska et al. 2007), as well as performance on go/no go tasks (Aron et al. 2003). Aside from response inhibition (Swick et al. 2008), the left inferior frontal gyrus is extremely important for language production and verb comprehension (Costafreda et al. 2006). Overall, loss of gray matter volume in these areas probably represents an advanced stage of the neurodegenerative process, the clinical consequences of which are gait, speech, and coordination deficits that worsen with disease progression.

The significant correlation between SARA scores and GMV found in the left parahippocampal gyrus was unexpected. This area has been associated with many cognitive processes, including visuospatial processing and episodic memory (Aminoff et al. 2013). For example, the parahippocampal gyrus is involved in the visuospatial storage of stimulus representations across long delays (Maguire et al. 2003) and in the production of allocentric sense of position. Lesions in this region can lead to topographical disorientation (Aguirre et al. 1996; Bohbot et al. 1998). Taking into account that the parahippocampal area is affected in different subtypes of SCAs such SCA2, SCA6, SCA7 (Hernandez-Castillo et al. 2013; Ishikawa et al. 1999; Mercadillo et al. 2014) and that it has been related to the progression of motor symptoms in SCA17 (Reetz et al. 2010), we believe that its possible involvement in the ataxia severity should be explored further.

Finally, it is important to note that significant decreases in GMV in the SCA7 group compared to controls were found in other brain regions including the occipital, parietal and temporal cortices (Fig. 1a). However, in those cases GMV loss did not correlate with SARA scores (Fig. 1b), suggesting that not all the areas that degenerate during the SCA7 course are related to ataxia severity.

Conclusion

Our results show specific brain regions where GMV correlates with the severity of ataxia in SCA7. All of these regions, with the exception of the parahippocampal cortex, are closely related to movement coordination and speech deficits that patients with SCA7 usually develop. Our results provide novel and relevant information for the understanding of SCA7.

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Conflict of Interest Carlos R. Hernandez-Castillo, Victor Galvez, Rosalinda Diaz, and Juan Fernandez-Ruiz declare that they have no conflicts of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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