RESEARCH ARTICLE

Functional Connectivity Changes Related to Cognitive and Motor Performance in Spinocerebellar Ataxia Type 2

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ABSTRACT: Background: Several neuropathological studies in spinocerebellar ataxia type 2 (SCA2) have revealed significant atrophy of the cerebellum, brainstem, sensorimotor cortex, and several regions in the frontal lobe. However, the impact of the neurodegeneration on the functional integration of the remaining tissue is unknown. To analyze the clinical impact of these functional changes, we correlated the abnormal functional connectivity found in SCA2 patients with their scores in clinical scales. To obtain the functional connectivity changes, we followed two approaches. In one we used areas with significant cerebellar gray matter atrophy as anchor seeds, and in the other we performed a whole-brain data-driven analysis.

Methods: Fourteen genetically confirmed SCA2 patients and aged-matched healthy controls participated in the study. Voxel-based morphometry and resting-state functional magnetic resonance imaging (fMRI) were done to analyze structural and functional brain changes. Independent component analysis and dual regression were used for intrinsic network comparison. Significant functional connectivity differences were correlated with the behavioral scores.

Results: Seed-based analysis found reduced functional connectivity within the cerebellum and between the cerebellum and frontal/parietal cortices. Cerebellar functional connectivity increases were found with parietal, frontal, and temporal areas. Intrinsic network analysis found a functional decrease in the cerebellar network, and increase in the default-mode and frontoparietal networks. Further analysis showed significant correlations between clinical scores and the abnormal functional connectivity strength.

Conclusion: Our findings show significant correlations between functional connectivity changes in key areas affected in SCA2 and these patients' motor and neuropsychological impairments, adding an important insight to our understanding of the pathophysiology of SCA2. © 2015 International Parkinson and Movement Disorder Society

Key Words: Spinocerebellar ataxia type 2; functional connectivity; SARA; cerebellum

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Spinocerebellar ataxias (SCAs) are a group of autosomal-dominant cerebellar ataxias that are classified according to specific genetic mutations. Among these, spinocerebellar ataxia type 2 (SCA2) is caused by an expanded CAG trinucleotide repeat in the gene *ATXN2*.[1] Patients with SCA2 exhibit a progressive cerebellar syndrome characterized by ataxic gait, cerebellar dysarthria, dysmetria, and dysdiadochokinesia.[2-5] In addition, most of the patients demonstrate other visuospatial and cognitive impairments, including slowing of saccadic eye movements.[2,6,7] Neuropathological studies have shown a reduction of overall brain size with significant atrophy of the cerebellum, brainstem, and frontal lobe.[8] Magnetic resonance imaging (MRI) analyses have confirmed the olivopontocerebellar atrophy and in some cases thalamus degeneration.[9,10] A recent study also demonstrated significant parahippocampal atrophy in these patients.[11]

However, information is lacking regarding the functional brain changes that occur as a result of the SCA2 degenerative process. Unlike other neurodegenerative diseases, only a few studies have addressed functional connectivity (FC) in the SCAs,[12-14] and none have been conducted in SCA2 to elucidate the functional abnormalities. The resting-state functional magnetic resonance imaging (rsfMRI) technique[15] emerges as a powerful tool for delineating the brain's intrinsic functional wiring architecture and has been successfully applied to study various neurodegenerative diseases and psychiatric disorders.[16,17] For example, recent studies using a seed-based approach in patients with SCA7 reported FC reductions of cerebellar, visual and motor areas, highlighting visuomotor[14] and frontocerebellar[18] deficits. At the same time, numerous studies have identified "intrinsic" large-scale brain networks that exhibit interactions at rest similar to those identified during task.[19,20] Several of these networks have been described previously,[21,22] and recent studies have reported altered network functioning in several disease states,[16,17] indicating that this marker of brain function can provide important information about neural circuit abnormalities in psychiatric and neurological disorders. In this study, we are specifically interested in exploring the abnormalities in the cerebellar network, the default mode network because of its involvement in several neurological disorders,[23,24] and the frontoparietal network, which is related to decision making and could therefore be related to the cerebellar cognitive affective syndrome.[25,26]

To further understand the neural basis of the behavioral deficits resulting from the SCA2 mutation, here we identified the FC changes in SCA2 patients and analyzed them in relation to their clinical and neuropsychological deficits. Functional connectivity changes were obtained by using a seed-based approach and the state of the intrinsic networks by means of whole brain data-driven methodology. The results showed significant correlations between FC changes and specific clinical deficits, providing a clearer understanding of the circuitry changes involved in the clinical deficits of these patients.

Patients and Methods

Subjects

Fourteen right-handed patients with a molecular diagnosis of SCA2 (9 women; mean age 37.3 ± 15.9 y; complete information in Supplemental Data Table S1) and 14 right-handed healthy volunteers age-matched to the SCA2 group (8 women; mean age 41.7 ± 12.8 y) participated in the study. The control group had no history of neurological or psychiatric disorders. All participants gave their written informed consent before entering the study. All procedures in this study were conducted in accordance with the international standards of the Helsinki Declaration of 1964 (including subsequent revisions), and in accordance with the ethical standards of the committees on human experimentation of the Universidad Nacional Autónoma de Mexico.

Clinical and Neuropsychological Measurements

The Scale for Assessing and Rating Ataxia (SARA) was used as a semiquantitative evaluation of the movement impairment, comprising eight items related to gait, stance, sitting, speech, finger-chase test, nose–finger test, fast alternating movements, and a heel–shin test.[27,28]

The Cambridge Neuropsychological Test Automated Battery[29] was used to specifically test three cognitive aspects previously reported as impaired in SCA2, specifically flexibility, planning, and movement execution and supervision.[30] Here we used the big/little circle task, which evaluates comprehension and learning while training the participant to follow and reverse a rule, and the intra/extra dimensional shift, which assesses attentional maintenance, shifting, and flexibility of attention.

Image Acquisition

All images were acquired using a 3.0-T Achieva MRI scanner (Phillips Medical Systems, Eindhoven, The Netherlands). The anatomical acquisition consisted of a three-dimensional T1 fast field-echo sequence, with TR/TE of 8/3.7 ms, field of view of 256 × 256 mm; reconstruction matrix of 256 × 256, resulting in an isometric resolution of 1 × 1 × 1 mm. Functional images were collected using an Echo Planar Imaging single-shot sequence with a TR of 2,000 ms, TE of 35 ms, and 120 whole-brain volumes with 34 slices. Final isometric resolution of the functional images was 3 × 3 × 4 mm without gaps. During

fMRI acquisition, subjects in all groups were instructed to keep their eyes closed, to think about nothing in particular, and to stay awake. Five dummy scans were performed at the beginning of each functional acquisition to allow magnetization to reach a steady state.

Resting-State Preprocessing

The rsfMRI preprocessing included brain extraction, time shifting, motion correction, spatial smoothing (6 mm full-width at half-maximum Gaussian kernel), linear trend removal, and temporal filtering (band pass, 0.01-0.08 Hz), using FSL (FMRIB Software Library (FSL), Oxford University, Oxford, UK). A regression technique was used to remove sources of variance, including white matter, cerebrospinal fluid, and global mean signal.[31] In addition, motion scrubbing was applied to scans that surrounded a minimum signal change of less than 0.5% and a frame-wise displacement of 0.5 mm.[32] All structural images were warped to the Montreal Neurological Institute MNI template, using the nonlinear registration method.[33] After rigid alignment of rsfMRI images to structural images, spatial normalization of rsfMRI images to the MNI template was achieved by using the transformation field acquired during the structural image registration.

Voxel-Based Morphometry Analysis

Voxel-based morphometry (VBM) analysis[34] was performed using FSL-VBM.[35] After smoothing the structural images with a Gaussian isotropic kernel of 2 mm sigma, a two-sample *t* test was applied. Significance was defined as $P < 0.05$ after correcting for multiple comparisons using the randomized permutation method.[36] The VBM analysis showed a high degree of gray matter atrophy in SCA2 patients compared with healthy controls (Supplemental Data Figure S1). Based on the local maxima of the resulting *t* map, a total of four regions of interest (12-mm sphere centered at the local maxima) were defined in which SCA2 patients exhibited the highest cerebellar gray matter atrophy (Table 1).

Seed-Based Functional Connectivity Analysis

Based on the VBM results, we identified the most affected cerebellar regions to use them as anchor seeds for the next procedure (Table 1). The mean time course of each defined seed was extracted by calculating the average of all voxels within the 12-mm sphere (MATLAB R2014b, The Mathworks, Inc., Natick, MA). Functional connectivity maps were created by calculating a Pearson's linear correlation between the seed's average signal and every other voxel in the brain. The FSL-VBM gray-matter probability maps smoothed with a Gaussian kernel of 4 mm were resampled to the functional images resolution (both images in MNI coordinate space), to minimize partial volume effects.[37] Before groupwise analysis, each subject's gray-matter probability map was multiplied for its functional connectivity map to reduce the effect of the gray matter loss in the patients group. A two-sample *t* test was performed between SCA2 and healthy control functional connectivity maps to detect significant differences. Functional connectivity maps were corrected for multiple comparisons at the whole brain level, setting a significance *P* value of less than 0.05, corrected using false discovery rate.[38] The average functional connectivity strength of each significant cluster was calculated. The Pearson's correlation between those functional abnormalities and the score of each clinical measurement was obtained in two separate groups. The SARA scores were correlated with motor-related connections (11 connections), and cognitive scores were correlated with cognitive-related connections (8 connections). Finally, the correlation significance was set at the *P* value <0.05 Bonferroni corrected.

TABLE 1. Cerebellar seeds locations for FC analysis

Anatomical region	X	Y	Z
Left anterior culmen	−14	−38	−24
Right anterior culmen	14	−36	−22
Left posterior semi-lunar	−38	−68	−40
Right posterior semi-lunar	42	−70	−38

Seeds were placed at the cerebellar local maxima resulting from the VBM analysis. MNI coordinates in mm. FC, functional connectivity.

Independent Components Analysis

Independent components analysis (ICA) was carried out using FSL's MELODIC.[21] Preprocessing consisted of motion correction, removal of nonbrain tissue, spatial smoothing using a 5-mm full-width-at-half-maximum Gaussian kernel, and high-pass temporal filtering equivalent to 100 s (0.01 Hz). After preprocessing, the fMRI volumes were registered to the subject's high-resolution T1-weighted scan, using affine registration, and then to standard space (MNI152) images using nonlinear registration with a warp resolution of 4 mm. The data set was decomposed into 30 independent components. These components comprised several intrinsic functional networks and image artifacts such as movement, physiological noise, and cerebrospinal fluid flow. Three components of interest (cerebellar network, default mode network, and fronto-parietal control network) were selected by visual inspection based on previous literature[21,22] and by the frequency spectra of the time courses of the components.

For between-subject analyses, a voxel-wise comparison of the functional intrinsic networks was carried out using a regression technique referred to as the "dual-regression" approach.[39] Nonparametric permutation

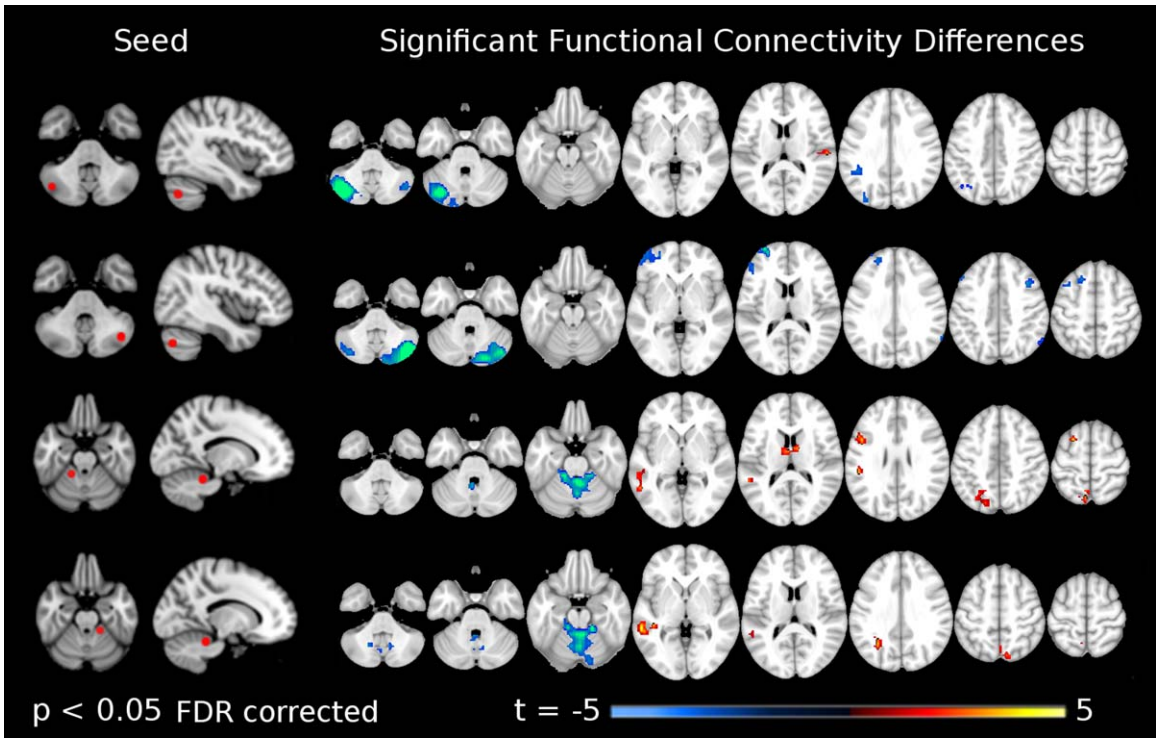

FIG. 1. Seed-based functional connectivity group differences. Parametric maps of group differences for functional connectivity related to seed in the left column. Warm colors represent increased and cold colors represent decreased functional connectivity in SCA2 patients. SCA2, spinocerebellar ataxia type 2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tests (5000 permutations) were used to detect statistically significant differences between the groups within the boundaries of the spatial maps obtained with MELODIC. Correction for multiple comparisons was performed, implementing threshold-free cluster enhancement,[40] using a significance threshold of $P < 0.05$. Because of the number of components selected, we performed a Bonferroni correction, setting the significant P value at $P < 0.016$. The regions that showed differences in functional connectivity between groups were used to extract mean functional connectivity from each individual spatial map. Finally, we calculated the Pearson's correlation between the extracted functional connectivity and the behavioral scores by setting the significance value at $P < 0.05$ Bonferroni corrected.

Results

Seed-Based Functional Connectivity Abnormalities

Our FC analysis indicated abnormalities on each of the four seeds used. When the SCA2 group was compared with the healthy controls, a total of 19 functional connections showed significant abnormalities, including both hypo and hyper connectivity changes (Fig. 1). The largest FC decrease in the SCA2 group was found in the seeds surrounding the area of the right anterior cerebellum, and the largest FC increase was found between the right anterior cerebellum and the left middle temporal gyrus (Table 2).

Our analysis found three significant correlations between the clinical scores and the FC abnormalities in the patient group. Figure 2 illustrates the cerebral regions that showed significant FC abnormalities and a significant correlation between a clinical score and the FC strength within the cluster marked. The significant correlations were found in the functional interaction between the right posterior cerebellum and the left superior frontal gyrus, which had a positive correlation with the SARA score ($r = 0.73$, $P = 0.0026$); in the functional interaction between the left anterior cerebellum and the left superior parietal lobule, which had a negative correlation with the reaction time in the big/little circle test ($r = -0.78$, $P = 0.0011$). Finally, the functional interaction between the right anterior cerebellum and the right precuneus showed two negative correlations, one with the reaction time in the big/little circle test ($r = -0.77$, $P = 0.0010$), and one with the reaction time in the intra/extra dimensional shift test ($r = -0.74$, $P = 0.0022$).

Intrinsic Networks Abnormalities

In SCA2 patients relative to healthy controls, a significantly decreased FC within the cerebellar network was found mainly in the left posterior cerebellum (Fig. 3A). Within the default mode network, a significant increase in the FC was found in the posterior cingulate gyrus (Fig. 3B). Similarly, a significant increase in FC was found within the frontoparietal network,

TABLE 2. Significant group differences in cerebellar functional connectivity

Seed	Anatomical Region	BA	*t*	X	Y	Z
Right posterior	Right inferior semi-lunar lobule	**	−14.3	42	−70	−40
Left posterior	Left cerebellum inferior semi-lunar	**	−12.59	−38	−70	−40
Right anterior	Right anterior cerebellum culmen	**	−8.45	6	−46	−24
Left anterior	Right anterior cerebellum culmen	**	−6.98	6	−46	−24
Right posterior	Left superior frontal gyrus	10	−6.52	−34	66	8
Right posterior	Left inferior semi-lunar lobule	**	−5.35	−38	−74	−44
Right posterior	Right middle frontal gyrus	6	−4.74	38	14	44
Right posterior	Right supramarginal gyrus	40	−4.59	62	−54	36
Left posterior	Right cerebellar tonsil	**	−4.08	46	−62	−40
Right posterior	Left middle frontal gyrus	8	−4.04	−50	26	40
Right anterior	Left cerebellar tonsil	**	−4.01	−18	−62	−40
Right posterior	Left superior frontal gyrus	8	−4	−26	46	36
Left posterior	Left superior occipital gyrus	19	−3.75	−30	−82	32
Left anterior	Left superior parietal lobule	7	4.17	−6	−66	60
Left anterior	Left inferior frontal gyrus	9	4.43	−46	14	28
Left anterior	Left thalamus	**	4.44	−6	−6	16
Right anterior	Right precuneus	7	4.44	6	−74	48
Right anterior	Left precuneus	19	4.45	−30	−74	40
Left anterior	Left middle frontal gyrus	6	4.57	−22	10	60
Right anterior	Left middle temporal gyrus	21	5.13	−58	−38	0

Coordinates of each cluster's peak value (MNI space in mm). BA, Brodmann area. Highlighted rows indicate functional connections that correlate with behavioral scores.

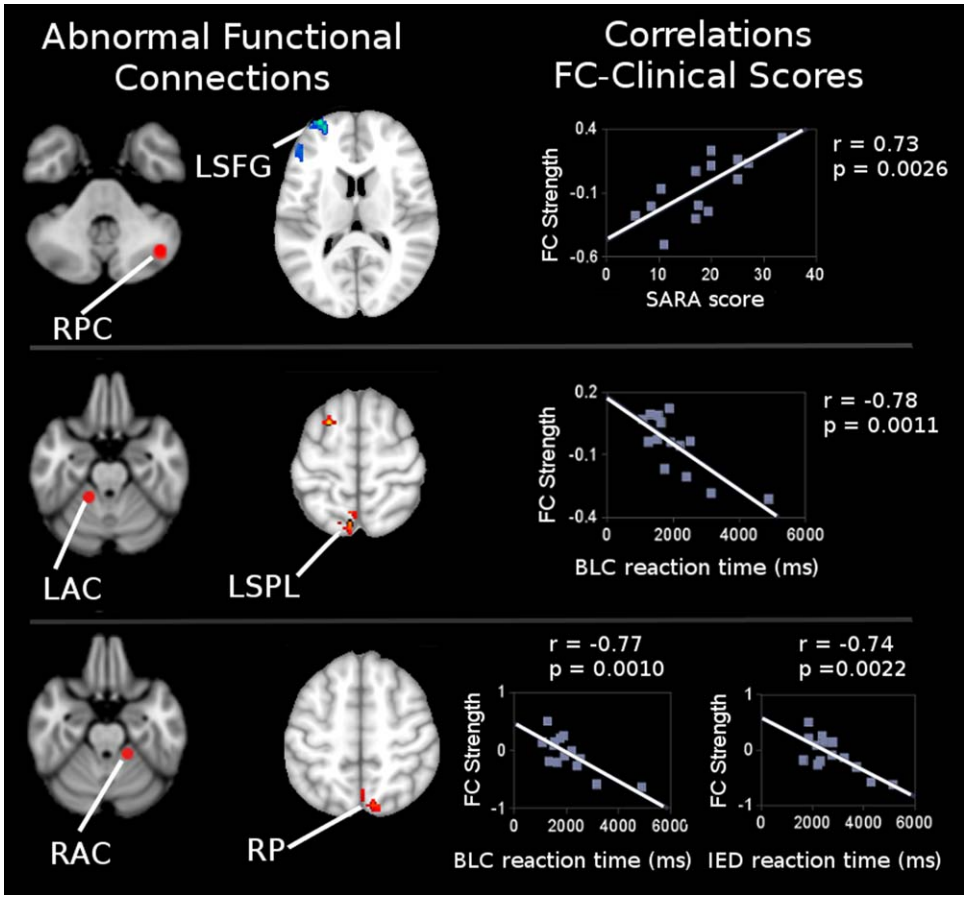

FIG. 2. Cerebellar connections showing correlation with clinical scores. Axial slices represent the seeds in the first column and the region showing a significant FC difference in the second column. Colors in the second column are the same as in Figure 1. The third column shows the significant correlations between the FC strength and the clinical scores. RPC, right posterior cerebellum; LAC, left anterior cerebellum; RAC, right anterior cerebellum; LSFG, left superior frontal gyrus; LSPL, left superior parietal lobule; RP, right precuneus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

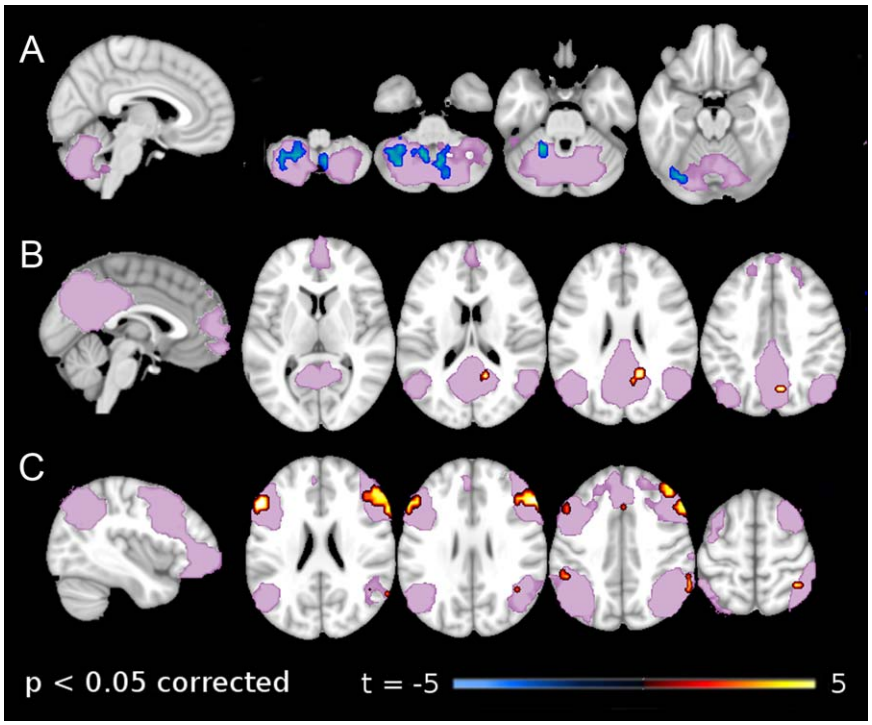

FIG. 3. Group differences in intrinsic functional networks. (**A**) Cerebellar network; (**B**) Default mode network; (**C**) Frontoparietal network. Pink color represents the group-specific network. Warm colors represent increased and cold color decreased functional connectivity within the network. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

including regions in the middle frontal gyrus and the inferior parietal lobe bilaterally (Fig. 3C).

For each network, the regions showing significant differences in patients compared with controls were used as network-specific regions-of-interest to extract the average FC values from the subject-specific spatial maps of all subjects. Because the regions within each network are highly correlated, we used all significant clusters within each network as a unique region-of-interest for each one. Our analysis found significant correlations between the abnormal FC within the cerebellar network and the three clinical scores used (Supplemental Data Fig. S2). Specifically, the cerebellar network abnormal FC showed a negative correlation with SARA score ($r = -0.71$, $P = 0.0038$), the intra/extradimensional shift reaction time ($r = -0.75$, $P = 0.0019$), and the big/little circle reaction time ($r = -0.84$, $P = 0.0001$). A significant positive correlation was found between the default mode network abnormal FC and the big/little circle reaction time ($r = 0.79$, $P = 0.0006$). No significant correlations were found between the frontoparietal network abnormal FC and any of the clinical scores.

Discussion

In this study, we explored the clinical impact of the SCA2 FC changes, using two different approaches. First, we obtained the abnormalities derived specifically from the cerebellar structural degeneration, and second, we found the changes in the FC of three intrinsic networks across the whole brain. Our results show significant correlations between FC changes and the severity of motor and cognitive impairments observed in SCA2 patients.

Abnormalities in Cerebellar Functional Connectivity

The cerebellum contributes to both motor and nonmotor functions and receives input from a wide variety of sources, including neocortical areas.[41] It is thought that this information is funneled into the motor system to generate and control movement.[42,43] However, previous SCA2 studies have focused on the structural deficits associated with the cerebellum, whereas potential FC abnormalities remain unknown.[3] Here we delineated for the first time the cerebellar FC abnormalities resulting from SCA2 neurodegeneration.

Our analysis showed that the largest decrease in FC was within the cerebellum, whereas the right cerebellar hemisphere showed a marked reduction in the functional interaction with its own surrounding area. Similarly, we found a significant disruption between the corresponding contralateral regions in both posterior and anterior cerebellar regions. These local disruptions could be the result of extensive cerebellar atrophy (Supplemental Data Fig. S1), suggesting that the remaining tissue could be functionally impaired, affecting the local information flow, including motor

feedback.[41] The second largest FC decrease was between the right posterior cerebellum and the left superior frontal gyrus, which could impact different cognitive operations such as self-monitoring and verbal/visuospatial memory.[44,45] Our results showed that the strength of this functional connection had a significant correlation with the SARA score. This result is supported by previous findings showing that the superior frontal gyrus plays an important role in motor function[46,47] and the regulation of intellectual function and action.[48] Interestingly, a similar disruption of the frontocerebellar network was also found in two recent studies of spinocerebellar ataxia type 7.[14,18]

Besides the hypo-connectivity changes described, our analysis also found hyper-connectivity changes between the cerebellum and specific cortical and subcortical regions. Given previous reports that an increase in FC may allow structurally atrophied brain regions to remain functional,[49-51] this enhanced connectivity between the cerebellum and structurally affected areas may reflect a compensatory mechanism; for example, patients with temporal lobe epilepsy show an increased brain activity within various structures of the memory network.[52-54] Specifically, during an autobiographical memory task, an overall reorganization was found in the hierarchical interactions between temporal, parietal, and frontal structures, showing the presence of brain plasticity in response to pathological damage induced by this disorder.[52]

Our results also showed an increase in the FC strength between the cerebellum and the parietal lobe, including the superior parietal lobule and the precuneus. The parietal lobe is involved in spatial attention/orientation and motion processing.[55] Damage to the superior parietal lobe region leads to both sensory and motor deficits,[56] supporting the idea that sensory and motor signals are combined in these areas to provide an internal estimate of the state of both the world and the body.[55] The precuneus has been involved in directing attention in space when an individual prepares and performs movements,[57,58] as well as during motor imagery and attention shifting between motor targets.[57] It is also involved in motor coordination, which requires shifting attention to different spatial locations.[59] The FC strength between the cerebellum and the superior parietal lobule showed a negative correlation with the Big Little Circle (BLC) reaction time, similar to the negative correlation of the FC strength between the cerebellum and the precuneus with BLC and Intra/Exta Dimensional Shift (IED) reaction times. In both cases the functional connection showed a negative effect, that is, patients with stronger connections showed better performance, supporting the idea of a compensatory mechanism, as has been suggested for other neurodegenerative diseases.[60]

Abnormalities in Resting-State Networks

Our analysis of intrinsic functional networks found significant group differences between SCA2 and healthy controls. The independent component analysis applied to resting state MRI data has been used in a variety of neurological disorders,[16,17] and its reliability when used with dual regression has been previously reported.[61] Here we focused on three functional networks, including the cerebellar network, the frontoparietal network, and the so-called default mode network.

The cerebellar network is commonly associated with a range of sensorimotor, autonomic, and cognitive functions.[62] In SCA2 patients, we found significant FC decreases within the cerebellar network, mostly in the left hemisphere. Furthermore, we found a negative correlation between the connectivity strength and SARA scores, showing the close relationship between the disruption of cerebellar FC and the motor impairment, which included the negative correlation with IED and BLC reaction time.

We found an increase of the FC of the default mode network in SCA2 patients that is restricted to the right posterior cingulate gyrus, and that correlates with the BLC reaction time. Different studies have reported synchrony increases within the default mode network in neurological disorders, such as attention deficit-hyperactivity disorder,[23] schizophrenia,[24] and traumatic brain injury,[63] where this increased connectivity may reflect an abnormality in the coordination of information processing.[64] The SCA2 patients showed a similar phenomenon, where patients with stronger default mode connectivity score had larger reaction times in the BLC task.

The fronto-parietal network also showed increased connectivity in the middle frontal gyrus. However, in contrast to the other networks, we did not find any behavioral measure that correlated with the change in this network. Further exploration should include the analysis of the relation of these changes with cognitive processes, such as reasoning, attention, inhibition, and memory, that have been associated with this netwok.[62]

Conclusion

Our FC analysis of the degenerated cerebellar areas in SCA2 revealed a number of abnormalities in the functional interaction in cerebellar, frontal, and parietal circuits. The independent component analysis showed abnormal decreased connectivity in the cerebellar network and increased connectivity in the default and frontoparietal networks. Our results showed significant correlations between specific motor and cognitive deficits and FC changes in areas closely associated with the affected processes. These results

provide a new insight in the understanding of the clinical dysfunction associated with the neuropathology of SCA2 disease.

References

1. Pulst S-M, Nechiporuk A, Nechiporuk T, et al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat Genet 1996;14:269-276.
2. Takahashi T, Katada S, Onodera O. Polyglutamine diseases: where does toxicity come from? what is toxicity? where are we going? J Mol Cell Biol 2010;2:180-191.
3. Velázquez-Pérez L, Rodríguez-Labrada R, García-Rodríguez JC, Almaguer-Mederos LE, Cruz-Mariño T, Laffita-Mesa JM. A comprehensive review of spinocerebellar ataxia type 2 in Cuba. Cerebellum 2011;10:184-198.
4. Auburger GWJ. Spinocerebellar ataxia type 2. Handb Clin Neurol 2012;103:423-436.
5. Manto M-U. The wide spectrum of spinocerebellar ataxias (SCAs). Cerebellum 2005;4:2-6.
6. Fernandez-Ruiz J, Velásquez-Perez L, Díaz R, et al. Prism adaptation in spinocerebellar ataxia type 2. Neuropsychologia 2007;45: 2692-2698.
7. Vaca-Palomares I, Díaz R, Rodríguez-Labrada R, et al. Spinocerebellar ataxia type 2 neurodegeneration differentially affects error-based and strategic-based visuomotor learning. Cerebellum 2013; 12:848-855.
8. Estrada R, Galarraga J, Orozco G, Nodarse A, Auburger G. Spinocerebellar ataxia 2 (SCA2): morphometric analyses in 11 autopsies. Acta Neuropathol 1999;97:306-310.
9. Brenneis C, Bösch SM, Schocke M, Wenning GK, Poewe W. Atrophy pattern in SCA2 determined by voxel-based morphometry. Neuroreport. 2003;14:1799-1802.
10. Della Nave R, Ginestroni A, Tessa C, et al. Brain structural damage in spinocerebellar ataxia type 2: a voxel-based morphometry study. Mov Disord 2008;23:899-903.
11. Mercadillo RE, Galvez V, Díaz R, et al. Parahippocampal gray matter alterations in spinocerebellar ataxia type 2 identified by voxel based morphometry. J Neurol Sci 2014;347:50-58.
12. Solodkin A, Peri E, Chen EE, Ben-Jacob E, Gomez CM. Loss of intrinsic organization of cerebellar networks in spinocerebellar ataxia type 1: correlates with disease severity and duration. The Cerebellum 2010;10:218-232.
13. Reetz K, Dogan I, Rolfs A, et al. Investigating function and connectivity of morphometric findings: exemplified on cerebellar atrophy in spinocerebellar ataxia 17 (SCA17). Neuroimage 2012;62: 1354-1366.
14. Hernandez-Castillo CR, Alcauter S, Galvez V, et al. Disruption of visual and motor connectivity in spinocerebellar ataxia type 7. Mov Disord 2013;28:1708-1716.
15. Biswal B, Zerrin Yetkin F, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995;34:537-541.
16. Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. Curr Opin Neurol 2008;21:424-430.
17. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. Neuron 2009;62:42-52.
18. Hernandez-Castillo CR, Galvez V, Morgado-Valle C, Fernandez-Ruiz J. Whole-brain connectivity analysis and classification of spinocerebellar ataxia type 7 by functional MRI. Cerebellum & Ataxias 2014;1:2.
19. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 2003;100:253-258.
20. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009;106:13040-13045.
21. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci. 2005;360:1001-1013.
22. Damoiseaux JS, Rombouts SARB, Barkhof F, et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 2006;103:13848-13853.
23. Tian L, Jiang T, Wang Y, et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett 2006; 400:39-43.
24. Jafri MJ, Pearlson GD, Stevens M, Calhoun VD. A method for functional network connectivity among spatially independent resting-state components in schizophrenia. Neuroimage 2008;39: 1666-1681.
25. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol 2008;100:3328-3342.
26. Manto M, Mariën P. Schmahmann's syndrome: identification of the third cornerstone of clinical ataxiology. Cerebellum & Ataxias 2015;2:2.
27. Schmitz-Hübsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006;66:1717-1720.
28. Weyer A, Abele M, Schmitz-Hübsch T, et al. Reliability and validity of the scale for the assessment and rating of ataxia: a study in 64 ataxia patients. Mov Disord 2007;22:1633-1637.
29. Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J R Soc Med 1992;85: 399-402.
30. Burk K. Cognitive deficits in spinocerebellar ataxia 2. Brain 1999; 122:769-777.
31. Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci U S A 2006;103:10046-10051.
32. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59:2142-2154.
33. 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;17:825-841.
34. Ashburner J, Friston KJ. Voxel-based morphometry: the methods. Neuroimage 2000;11:805-821.
35. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23(Suppl 1):S208-S219.
36. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;15:1-25.
37. Oakes TR, Fox AS, Johnstone T, Chung MK, Kalin N, Davidson RJ. Integrating VBM into the general linear model with voxelwise anatomical covariates. Neuroimage 2007;34:500-508.
38. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc 1995;57:289-300.
39. Filippini N, MacIntosh BJ, Hough MG, et al. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. Proc Natl Acad Sci U S A 2009;106:7209-7214.
40. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009;44:83-98.
41. Middleton FA, Strick PL. The cerebellum: an overview. Trends Cogn Sci 1998;2:305-306.
42. Desmond JE, Fiez JA. Neuroimaging studies of the cerebellum: language, learning and memory. Trends Cogn Sci 1998;2:355-362.
43. Schmahmann JD. Dysmetria of thought: clinical consequences of cerebellar dysfunction on cognition and affect. Trends Cogn Sci 1998;2:362-371.
44. Cao Y, D'Olhaberriague L, Vikingstad EM, Levine SR, Welch KM. Pilot study of functional MRI to assess cerebral activation of motor function after poststroke hemiparesis. Stroke 1998;29:112-122.
45. O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H. Distinct and overlapping functional zones in the

cerebellum defined by resting state functional connectivity. Cereb Cortex 2010;20:953-965.

46. Nagahama Y, Okada T, Katsumi Y, et al. Transient neural activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features. Neuroimage 1999;10: 193-199.
47. Oh A, Vidal J, Taylor MJ, Pang EW. Neuromagnetic correlates of intra- and extra-dimensional set-shifting. Brain Cogn 2014;86:90-97.
48. MacDonald AW. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 2000;288:1835-1838.
49. Qiu A, Tuan TA, Woon PS, Abdul-Rahman MF, Graham S, Sim K. Hippocampal-cortical structural connectivity disruptions in schizophrenia: an integrated perspective from hippocampal shape, cortical thickness, and integrity of white matter bundles. Neuroimage 2010;52:1181-1189.
50. Liang P, Wang Z, Yang Y, Jia X, Li K. Functional disconnection and compensation in mild cognitive impairment: evidence from DLPFC connectivity using resting-state fMRI. PLoS One. 2011;6: e22153.
51. Rytsar R, Fornari E, Frackowiak RS, Ghika JA, Knyazeva MG. Inhibition in early Alzheimer's disease: an fMRI-based study of effective connectivity. Neuroimage 2011;57:1131-1139.
52. Addis DR, Moscovitch M, McAndrews MP. Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy. Brain 2007;130:2327-2342.
53. Powell HWR, Richardson MP, Symms MR, et al. Reorganization of verbal and nonverbal memory in temporal lobe epilepsy due to unilateral hippocampal sclerosis. Epilepsia 2007;48:1512-1525.
54. Thivard L, Hombrouck J, du Montcel ST, et al. Productive and perceptive language reorganization in temporal lobe epilepsy. Neuroimage 2005;24:841-851.
55. Corbetta M, Shulman GL, Miezin FM, Petersen SE. Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. Science 1995;270:802-805.
56. Wolpert DM, Goodbody SJ, Husain M. Maintaining internal representations: the role of the human superior parietal lobe. Nat Neurosci 1998;1:529-533.
57. Cavanna A, Trimble M. The precuneus: A review of its functional anatomy and behavioural correlates. Brain 2006;129:564-583.
58. Kawashima R, Roland PE, O'Sullivan BT. Functional anatomy of reaching and visuomotor learning: a positron emission tomography study. Cereb Cortex 1995;5:111-122.
59. Wenderoth N, Debaere F, Sunaert S, Swinnen SP. The role of anterior cingulate cortex and precuneus in the coordination of motor behaviour. Eur J Neurosci 2005;22:235-246.
60. Witiuk K, Fernandez-Ruiz J, McKee R, et al. Cognitive deterioration and functional compensation in ALS measured with fMRI using an inhibitory task. J Neurosci 2014;34:14260-14271.
61. Zuo X-N, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP. Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. Neuroimage 2010;49:2163-2177.
62. Laird AR, Fox PM, Eickhoff SB, et al. Behavioral interpretations of intrinsic connectivity networks. J Cogn Neurosci 2011;23:4022-4037.
63. Sharp DJ, Beckmann CF, Greenwood R, et al. Default mode network functional and structural connectivity after traumatic brain injury. Brain 2011;134:2233-2247.
64. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 2009;33:279-296.

Supporting Data

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