Resting-State Functional Connectivity and Cognitive Dysfunction Correlations in Spinocerebellar Ataxia Type 6 (SCA6)

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Abstract: *Objective:* The aim of this study is to evaluate the correlation between resting state functional MRI (RS-fMRI) activity and motor and cognitive impairment in spinocerebellar ataxia type 6 (SCA6). *Methods:* Twelve patients with genetically confirmed SCA6 and 14 age matched healthy controls were imaged with RS-fMRI. Whole brain gray matter was automatically parcellated into 1000 regions of interest (ROIs). For each ROI, the first eigenvariate of voxel time courses was extracted. For each patient, Pearson correlation coefficients between each pair of ROI time courses were calculated across the 1000 ROIs. The set of average control correlation coefficients were fed as an undirected weighted adjacency matrix into the Rubinov and Sporns (2010) modularity algorithm. The intranetwork global efficiency of the thresholded adjacency sub-matrix was calculated and correlated with ataxia scores and cognitive performance. *Results:* SCA6 patients showed mild cognitive impairments in executive function and visual-motor processing compared to control subjects. These neuropsychological impairments were correlated with decreased RS functional connectivity (FC) in the attention network. *Conclusions:* Mild cognitive executive functions and visual-motor coordination impairments seen in SCA6 patients correlate with decreased resting-state connectivity in the attention network, suggesting a possible metric for the study of cognitive dysfunction in cerebellar disease. *Hum Brain Mapp* 38:3001–3010, 2017. © 2017 Wiley Periodicals, Inc.

Key words: spinocerebellar ataxia type 6; SCA6; resting state; fMRI; functional connectivity

INTRODUCTION

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Spinocerebellar ataxia type 6 (SCA6) is a rare autosomal dominant disorder characterized by cerebellar atrophy. It is associated with an unstable CAG trinucleotide repeat expansion on chromosome 19 that encodes for a subunit of the voltage-dependent calcium channel CACNA1A, which is highly expressed in cerebellar Purkinje cells [Globas et al., 2003]. Pathologically, there is a loss of Purkinje cells [Zhuchenko et al., 1997], leading to progressive cerebellar dysfunction. Although SCA6 is characterized by isolated cerebellar degeneration with sparing of cortical structures and basal ganglia [Seidel et al., 2012], SCA6 patients may exhibit mild cognitive impairment, especially in fronto-executive tasks [Globas et al., 2003].

TABLE I. Demographics of sample

	Controls (<i>n</i> = 14)	SCA6 (<i>n</i> = 12)	<i>P</i> value ^a
Gender (male:female)	5:9	1:11	NS
Ethnicity (Caucasian:African-American:Asian)	8:1:5	11:0:1	NS
Disease duration (years)	-	6 ± 4 (0.5–13)	-
	Mean ± SD (range)	Mean ± SD (range)	
Age	54 ± 12 (40–83)	61 ± 8 (45–69)	NS
Education (years)	18 ± 4 (13–24)	16 ± 4 (4–21)	NS
Mean head motion (mm/s)	0.11 ± 0.08 (0.003–0.27)	0.07 ± 0.03 (0.0002–0.16)	NS

^aChi-squared test was used for gender and ethnicity comparisons; 1-way ANOVA with post hoc *t* tests were used for the remaining variables. NS, not significant (*P* > 0.05).

Conventional structural MRI studies have failed to show an anatomical substrate for the cognitive impairment associated with cerebellar lesions, other than morphometric studies of the cerebellum itself [Berquin et al., 1998; Mostofsky et al., 1998]. Alternatively, functional MRI may be a valuable tool for the understanding of cerebellocortical circuits. Several studies in the past decade have shown cerebellar activation in a variety of cognitive tasks in healthy subjects, especially in the posterior lobe of the cerebellum, as described in a meta-analysis of neuroimaging studies by Stoodley and Schmahmann [2009]. Recent task-based fMRI studies in SCA6 have shown functional abnormalities of cerebellar cortex and nuclei, during visual [Falcon et al., 2016] and hand-motor paradigms [Stefanescu et al., 2015].

Resting-state functional MRI (RS-fMRI), a rapidly growing subfield of functional brain mapping, is a task-free functional imaging technique that may be useful for understanding the complexity of cognitive impairments underlying neurodegenerative disorders. RS-fMRI facilitates investigations of the intrinsic functional organization of the brain, as compared with indirect examination using local blood-flow changes during task-based fMRI. This intrinsic functional organization is called “functional connectivity,” which is defined by temporal correlation of neural activity-induced fMRI signal changes in anatomically dispersed brain regions within particular networks [Habas et al., 2009; Krienen and Buckner, 2009; O’Reilly et al., 2010]. An RS-fMRI study conducted in SCA type 7, which is characterized by progressive ataxia and retinal dystrophy, demonstrated abnormal functional connectivity patterns, including both hypo- and hyperconnectivity between cerebellum and cortical regions [Hernandez-Castillo et al., 2013].

Despite the vast literature in neuroimaging, there is no consensus regarding the overall cerebellar contribution to cognition. A recent review of RS-fMRI data on the functional organization of the cerebellum [Stoodley, 2012] showed that, consistent with the anatomical studies cited above, the cerebellum is part of “cognitive” networks that include the prefrontal and parietal association cortices, in addition to the motor control networks. Most of these studies, however, were focused on demonstrating the topographical organization of cerebrocerebellar circuits in healthy subjects.

These studies have not correlated such intrinsic functional changes with cerebellar diseases and the cognitive performance of the patients, rendering it difficult to create a reliable profile of cerebellar cognitive impairment.

Thus, our aim here was to explore the resting-state functional abnormalities associated with SCA6, in which pathological changes are mostly restricted to the cerebellum and have been associated with mild cognitive deficits [Globas et al., 2003; Seidel et al., 2012]. Based on this, we hypothesized that clinical impairments would be correlated with dysfunction in higher brain regions, indicating a role for the cerebellum in cognition.

METHODS

Subjects

Neuroimaging of 12 participants with molecular diagnosis of SCA6 and 14 healthy controls was acquired (See Table I for subject demographics including age, gender, ethnicity, education, and duration of disease). All patients and 7 controls underwent a complete neurological evaluation (Table II). SCA6 patients were part of a larger prospective neuropsychological and neuroimaging study on spinocerebellar ataxias conducted at our Institution. Informed consent was obtained for each subject and the study was IRB approved. Controls were obtained as a part of the study from the spouses of study participants (ensuring they had no known neurological disorder). Healthy volunteers were also recruited through a telephone database available at our institution for subjects interested in participation in a research study. Genetic testing for CAG repeat expansions was performed. The control group consisted of unaffected family members (typically spouses) or healthy volunteers, and none had a history of neurological disease and/or psychiatric symptoms or was taking medication at the time of testing. The age at first signs of unambiguous motor impairment reported by knowledgeable family members was considered the age of disease onset. All patients and controls were self-reported right hand dominant.

TABLE II. Neuropsychological features in patients with SCA6 and controls^a

	Controls (<i>n</i> = 7)	SCA6 (<i>n</i> = 12)	<i>P</i> value ^b
<i>Cognitive profile</i>			
MMSE	27 ± 3 (24–30)	27 ± 2 (24–30)	NS
Digit span index			
Forward	11 ± 3 (8–15)	10 ± 1 (9–13)	NS
Backward	7 ± 2 (4–10)	6 ± 1 (4–9)	NS
RAVLT			
Learning	40 ± 8 (29–52)	44 ± 13 (24–63)	NS
Delayed recall	8 ± 3 (5–12)	9 ± 4 (3–15)	NS
Recognition	12 ± 2 (9–14)	12 ± 3 (3–15)	NS
RCFT			
Copy	34 ± 12 (30.5–36)	34 ± 4 (24.5–36)	NS
Immediate recall	21 ± 9 (10.5–36)	21 ± 6 (12–29)	NS
Delayed recall	21 ± 9 (10–34)	19 ± 6 (11.5–31)	NS
Boston naming test	55 ± 5 (54–60)	56 ± 5 (44–60)	NS
Trail making test ^c			
Part A (s)	34 ± 11 (20.9–49)	46 ± 26 (24–101)	NS
Part B (s) ^c	57 ± 23 (27–101)	111 ± 70 (49–300)	0.028 ^c
Stroop			
Color	106 ± 17 (68–112)	102 ± 25 (26–112)	NS
Color-word	98 ± 15 (68–112)	61 ± 30 (11–108)	0.007 ^c
Grooved pegboard test			
Dominant	80 ± 19 (57–106)	134 ± 74 (77–306)	NS
Nondominant	90 ± 38 (64–116)	165 ± 82 (81–300)	0.009 ^c
COWA			
FAS	48 ± 16 (26–72)	35 ± 15 (14–59)	NS
Nouns	38 ± 13 (23–50)	40 ± 14 (19–68)	NS
Verbs	16 ± 6 (7–23)	14 ± 7 (4–24)	NS
<i>Motor examination</i>			
ICARS	5 ± 3 (2–11)	27 ± 19 (2.5–62)	0.0009 ^c

^aData are given as mean ± SD (range).^b*P* values were calculated by Wilcoxon rank sum test.^cSignificantly different, *P* < 0.05.

Abbreviations: MMSE, Mini-Mental State Examination; RAVLT, Rey's Auditory Verbal Learning test; RCFT, Rey–Osterrieth complex figure; COWA, Controlled Oral Word Association Test; FAS, words starting with letters f, a, and s; FSFA, Functional Staging score For Ataxia; ICARS, International Cooperative Ataxia Rating Scale.

Neuropsychological Assessment

All patients and seven control subjects were evaluated neurologically and neuropsychologically on the same day as their MRIs. The neurological motor evaluation included the International Cooperative Ataxia Rating Scale (ICARS) [Trouillas et al., 1997], considered one of the most reliable semiquantitative ataxia scales used in clinical practice [Saute et al., 2012]. For neuropsychological evaluation, the following tests were administered: the Mini-Mental State Examination (MMSE) for a global measure of cognitive function [Folstein et al., 1975], the Digit Span test [Blackburn and Benton, 1957] for verbal working memory, the Rey Auditory Verbal Learning test (RAVLT) [Savage and Gouvier, 1992] for verbal learning, the Rey–Osterrieth Complex Figure test (RCFT) [Loring et al., 1990] for visuospatial abilities and executive functions, the Boston naming test [Nicholas et al., 1989] for measure of aphasia, the Trail making test (TMT) [Bowie and Harvey, 2006] and the

Stroop test [MacLeod, 1991] for attention, the Grooved Pegboard Test (GPT) [Ruff and Parker, 1993] for visual-motor processing, the Controlled Oral Word Association Test (COWA) [Sumerall et al., 1997] for measure of verbal fluency, and the Stroop Color and Word test to examine the effects of interference on reading ability and attention and assess cognitive functions related to the frontal cortex [Espe-Pfeifer and Wachsler-Felder, 2000].

Imaging Data Acquisition

A 7-min resting-state single-shot gradient echo T2* echo-planar imaging (EPI) scan (47 slices, matrix = 96 × 96, 2.6 × 2.6 mm in plane resolution, slice thickness 3.0 mm, 168 volumes, flip angle = 75°, TR/TE = 2,500/30 ms) and a high-resolution T1-weighted turbo field echo (TFE) structural scan (140 axial slices, matrix = 256 × 256, 1.0 mm isotropic resolution, TR/TE = 10.0/6.0 ms) were acquired on

each subject using a 3 T Philips scanner (head 8-channel coil). Patients were instructed to relax, stay still as possible and fixate on a center cross.

Network Construction

Data preprocessing

The BOLD images were preprocessed using FSL (FMRIB, Oxford, UK), SPM8 (Wellcome Trust, UK), and custom MATLAB (The MathWorksInc., MA) scripts to complete slice-timing correction, rigid-body motion correction, coregistration, segmentation, and normalization to a standard template (MNI152 space, 2 mm). Subsequently, COMPCOR nuisance regression [Behzadi et al., 2007] was used for removal of cerebrospinal fluid and white matter variables. The images were detrended and subsequent bandpass temporal filtering (0.01–0.1 Hz) and spatial smoothing (6-mm FWHM Gaussian kernel) performed. The time courses of head motion were obtained by estimating the translations in each direction and the angular rotations about each axis for each of the 168 consecutive volumes. We evaluated group differences in head motion between patients and normal controls according to the criteria of Van Dijk et al. [2012] and framewise displacement (FD) and DVARS proposed by Power et al. [2011].

Anatomical parcellation, time-series extraction, and connectivity matrix

Whole-brain gray matter was parcellated into 1,000 regions of interest (ROIs), based on a voxel-scale functional connectivity parcellation atlas by Craddock et al. [2012]. The time course of each ROI was expressed as the first eigenvariate of the processed time series of all voxels associated with that region. Pearson's linear correlation coefficients between the ROI timecourses were calculated across the 1,000 ROIs. In this way, for each subject, a $1,000 \times 1,000$ connectivity matrix was generated. Finally, the correlation coefficients were normalized into Z scores for between-subject comparison.

Network Construction and Analysis

The Matlab Toolbox for Functional Connectivity (<http://www.brain-connectivity-toolbox.net/>) [Rubinov and Sporns, 2010] was used to **detect** network modules and calculate global efficiency metrics.

Network construction, defining ROIs, and calculating network global efficiency

For the group-level analysis (controls and patients), the set of average correlation coefficients from all individual correlation matrices was corrected for multiple comparisons using the false discovery rate (FDR) and the undirected weighted adjacency matrix was thresholded to include

Figure 1.

Cerebral ROIs. Control group modules used as ROIs for calculation of network GE in both groups. Cerebellar regions were excluded. DM: default mode network; SM: sensorimotor network. [Color figure can be viewed at wileyonlinelibrary.com]

edges at a significance level of $P < 0.05$. The undirected weighted adjacency matrix was utilized to generate network modules of nonoverlapping nodes by maximizing edges within groups and minimizing edges between groups using default parameters (resolution parameter $\gamma = 1$) in the Connectivity Toolbox, using the classic Newman's modularity algorithm [Newman, 2006]. The clustering and quality Q function through 1,000 runs were considered stable across subjects (mean adjusted mutual information = 0.9992; mean and SD of Q scores across 26 subjects: 0.199 ± 0.049) [Vinh and Epps, 2009; Vinh et al., 2009, 2010]. The ROIs used in this analysis were extracted from the control group (Figure 1; details of these modules are described in Table III) because we were interested in the extent to which connectivity differed from the normal pattern. The connectivity matrix of each patient was made binary by setting all edges with a correlation coefficient > 0.25 to the value of 1. Global efficiency (GE) in

TABLE III. Modules identified in the normal subject group and used as ROIs. Mean global efficiency and standard deviations found in each module in both groups

Module	Location ^a	No of voxels/ROIs ^b	Mean global efficiency (SD)	
			SCA 6	Controls
DM	R/L frontal poles; R/L superior frontal gyrus; R/L precuneus cortex; R/L lateral occipital cortex; cingulate gyrus, posterior division; cerebellum, Crus I and II	35,041/105	0.80 (0.03)	0.82 (0.05)
Attention	R/L middle frontal gyrus; R/L inferior frontal gyrus; R/L supramarginal gyrus; R/L superior parietal lobules; R/L lateral occipital cortex, superior division	24,838/223	0.78 (0.04)	0.79 (0.06)
SM	R/L pre- and postcentral gyri, superior part	16,448/95	0.88 (0.03)	0.87 (0.06)
Saliency	R/L pre- and postcentral gyri, inferior part; cingulate gyrus, R/L inferior frontal gyrus, pars opercularis; central opercular cortex; parietal operculum cortex	27,182/141	0.82 (0.04)	0.80 (0.05)
Visual	R/L lingual gyrus; R/L lateral occipital cortex; occipital poles; R/L cuneal cortex; R/L Superior parietal lobule	27,333/150	0.86 (0.05)	0.83 (0.03)

^aHarvard–Oxford Cortical Structural Atlas and Cerebellar Atlas in MNI152 space after normalization with FLIRT (FSL).

^bVoxel size = 2 × 2 × 2 mm; ROI, Craddock regions of interest.

Abbreviations: DM, default mode; SM, sensorimotor; R/L, right/left.

each ROI was calculated using Rubinov's Matlab toolbox and compared between groups. Between-group effects in network GE were assessed by a two-sample two-tailed *t* test.

Correlation between Network GE and Cognitive/Motor Performance

Pearson's (linear) correlation coefficients between cognitive/motor performance and network GE were calculated. Benjamini and Hochberg (1995) corrections were then used for multiple comparisons ($P < 0.05$). We performed this analysis for the entire subject population as well as for the patient and control groups separately.

Analysis of Individual Connections

The individual elements of the connectivity matrices were tested for group differences. Differences between two groups were assessed by mass univariate (two-sided) *t* tests.

RESULTS

Patients Versus Controls Demographics and Clinical Data

No significant differences in demographics were observed between SCA6 and control groups. In addition to the expected significant differences in the ataxia scores between SCA6 patients and controls, they presented statistical differences in three cognitive tests: the color-word part of Stroop

(98×61 , $P = 0.008$), the nondominant hand part of Grooved Pegboard test (90×165 , $P = 0.010$), and the part B of the Trail making test (33×111 , $P = 0.012$). Even though significant differences between patients and controls were not observed for the dominant hand part of the Grooved Pegboard test, SCA6 patients had a mean score that was almost 2 standards deviations above that of the control subjects (134 vs 80; normal mean for + 60 yo: 82.70 ± 18.70 , Grooved Pegboard Test Manual, S. I. Instruments). No significant differences between the two groups were found for the other cognitive tests (Table II).

Preprocessing Results

No significant differences in head motion were found between the two groups (one-way analysis of variances [ANOVA] with post hoc *t* test, $P = 0.46$, Table I). One subject was excluded because head movements exceeded 2 mm/s in at least one direction.

Between-Group Analysis of Network's GE

Five distinct modules were found (Figure 1), corresponding to default mode (DM), frontoparietal (or attention), sensorimotor (SM), saliency, and visual networks reported in the literature [Damoiseaux et al., 2006]. All networks were organized in a bilateral manner (See Table III for modular size and involved regions). We found a significantly higher GE in the visual network in patients (0.86×0.83 , $P = 0.04$) compared to controls. No statistically

Figure 2.

Correlations between ataxia scores (ICARS) and cognitive test results in the patient group. Numbers over columns represent statistically significant correlation coefficients ($P < 0.05$). Abbreviations: MMSE, Mini-Mental State Examination; DSI, Digit span index;

RALVT, Rey's Auditory Verbal Learning test; RCFT, Rey–Osterrieth Complex Figure; TMT, trail making test; GPT, Grooved Pegboard Test; COWA, Controlled Oral Word Association Test; FAS, words starting with letters f, a, and s.

significant differences of intranetwork connectivity were found between groups in other modules.

Correlations Between ICARS and Cognitive Tests

Some tests were strongly correlated (correlation coefficients > 0.7 or < -0.7 , $P < 0.05$) with ataxia severity, as showed in Figure 2. The highest positive correlations were observed with the GPT ($r^2 = 0.94$; for the dominant hand part and 0.85 for the nondominant part).

Modular GE Versus Cognitive/motor performance (Fig. 3)

Ataxia severity (ICARS scores)

We found a moderate negative correlation ($r = -0.40$) between ataxia scores and GE in the attention network and a moderate positive correlation ($r = 0.41$) in the visual module.

Cognitive performance

Correlations between cognitive scores and modular GE are shown in Figures 3 and 4. Overall, we found

Figure 3.

Pearson's correlations between motor and cognitive scores and modular global efficiency (GE) in patients. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 4.

Visualization of the linear correlation between attention network global efficiency and cognitive scores of COWA-FAS (phonemic part of Controlled Oral Word Association Test).

correlations between cognitive tests and GE in all networks: DM (2 tests), attention (9 tests), SM (4 tests), salience (1 test), and visual (6 tests). Of those, we found uncorrected significance in attention (3 tests: TMT, part B; Stroop, color part; and COWA, FAS part; $P = 0.027$, $P = 0.041$, and $P = 0.021$, respectively) and SM modules (1 test, RALVT, delayed recall). Of those, only the attention network showed reduced GE, which correlated with worse cognitive and motor scores. None of the correlations, however, remained significant ($P = 0.27$ for COWA-FAS; Stroop, color part; and TMT, part B) after FDR corrections. With linear correlations, we found that uncorrected statistical significance was reached when including values from two outliers in the STROOP test, color part ($r = 0.59$, $P = 0.04$) and 1 outlier in TMT part B; the uncorrected statistical significance disappeared after removing the outliers ($r = 0.22$, $P = 0.53$ and $r = -0.12$, $P = 0.71$, respectively).

DISCUSSION

We found moderate correlations ($r \geq 0.4$ or -0.4) between most of cognitive executive function test scores and frontoparietal (or attention) network connectivity (worse cognitive scores, lower global connectivity) in SCA6 patients. Although statistically significant correlations were not reached after multiple comparisons testing, this may be due to the rarity of this disease and the low number of participants that were available. The trends observed in our exploratory analysis may be used to narrow the area of investigation in future studies in this disease where subject accrual will be limited.

The uncorrected significance of the first part of COWA (FAS) test supports the relationship of the prefrontal and posterior parietal cortex with executive function such as

phonemic verbal fluency. Indeed, executive dysfunction is a classical manifestation of damage to the dorsolateral prefrontal cortex (PFC) [Ball et al., 2011]. Numerous studies have identified functional networks activated by complex executive processes showing extensive reciprocal connections between PFC, posterior parietal cortex, and various cortical regions [Halgren et al., 2002; Selemon and Goldman-Rakic, 1988]. Dorsal areas of prefrontal cortex are mostly involved in spatial working memory and planning and are major sites of termination of the “dorsal stream” of visual processing [Middleton and Strick, 2001]. Physiological studies have shown that the posterior parietal cortex mediates spatial perception by transforming the retinotopic image into a map of visual space and is involved in relating body position, while the dorsolateral prefrontal cortex plays a role in tasks that require spatial memory, such as the delay response and delayed alternation tasks [Selemon and Goldman-Rakic, 1988]. Accordingly, several functional neuroimaging studies have stated that these regions are richly interconnected, forming the putative frontoparietal dorsal attention network, comprising the dorsal premotor cortex, including the frontal eye field and the cortex along the intraparietal sulcus and the inferior parietal lobe [Beckmann et al., 2005; Damoiseaux et al., 2006; van den Heuvel et al., 2008]. These regions are connected with recurrent fibers passing through the superior longitudinal fasciculus and are primarily involved in the executive control of attention [Ptak, 2012]. Similar to our finding, a previous functional imaging study showed correlations between neuropsychological tests in SCA6 and prefrontal hypoperfusion using single photon emission computed tomography (SPECT) [Kawai et al., 2008].

The SCA6 subjects were impaired in tests of executive functions that required inhibitory control, mental flexibility, and visuospatial abilities (Stroop color/word interference, Trail Making, and Grooved Pegboard tests). Trail Making and Grooved Pegboard test scores were also significantly correlated with ataxia severity. Performance on tests requiring problem solving, planning, verbal, and spatial working memory were not significantly affected in this group. These findings are supported by a number of clinical studies [Gottwald et al., 2004; Kawai et al., 2009; Sue-naga et al., 2008], especially as shown by Cooper et al. [2010] in their assessment of cognitive function in a group of 27 patients with SCA6.

We found significant correlation between ataxia severity and cognitive scores of the first part of Controlled Oral Word Association test (COWA-FAS), demonstrating possible phonemic verbal fluency impairment in these patients. Interestingly, semantic verbal fluency did not show significant correlation. It has been shown that phonemic fluency has greater clinical utility in identifying cognitive impairment in individuals who do not have dementia, whereas impaired semantic fluency is associated with dementia [Steenhuis and Ostbye, 1995]. Significant correlations were also found with the copy part of Rey–Osterrieth Complex Figure test, indicating visuospatial impairments.

We found an anticorrelation between cognitive test scores and functional connectivity in sensorimotor, attention, and visual networks (worse cognitive scores, higher network global connectivity). We believe that this could be related to a compensatory reallocation or recruitment of cognitive resources, as previously reported in Alzheimer's disease [Bokde et al., 2006; Pariente et al., 2005; Wang et al., 2007]. Wang et al. [2007] showed that Alzheimer's disease patients had decreased resting-state correlations between prefrontal and parietal regions while having increased correlations either within prefrontal regions or between the prefrontal regions and other brain regions, possibly implying that the increased within-lobe connectivities reflect a compensatory effect for the reduced connectivity between lobes (anterior-posterior disconnection phenomenon). This within-lobe higher connectivity was particularly evident in the occipital region, where the mean global connectivity was significantly higher in SCA6 patients than in controls. This may represent a compensatory effect to dysfunction of the dorsal stream pathway, discussed above.

Recent anatomical studies demonstrate that the output of the cerebellum targets, besides the cortical motor areas, multiple nonmotor areas in the prefrontal and posterior parietal cortex, responsible mostly for executive functioning [Cooper et al., 2012; Strick et al., 2009]. Its modulation is linked to cerebellar lateral posterior hemispheric regions (mostly Crus I and II) [Kelly and Strick, 2003; Middleton and Strick, 2001]. Conversely, terminations from cortical projections are topographically organized in the cerebellum, where the anterior lobe receives afferents from motor and premotor cortices, while the posterior lobe, specifically crus I and II, receives afferents from the prefrontal cortex [Cooper et al., 2010; Schmahmann, 1996]. Our work broadly confirms the role of the cerebellum in cognitive domains not classically attributed to the cerebellum, by examining a disease population whose pathology is limited to the cerebellum however who demonstrate neurocognitive dysfunction typically solely attributed to primary neocortical processes.

In summary, we demonstrated functional connectivity throughout the brain in SCA6 patients by analyzing resting-state data and its correlation with neuropsychological features. We found a trend toward significance between some of the cognitive executive function test scores and attention network connectivity in patients in whom the primary pathology is limited to the cerebellum, indicating cerebellar contribution to cognitive function. Our results are in agreement with published data that degeneration in SCA6 is associated with mild cognitive deficits in executive functions such as phonemic verbal fluency, inhibition control, mental flexibility, and visuospatial abilities. It supports previously described anatomical data that suggests that the cerebellum influences nonmotor regions responsible for executive functions, such as the prefrontal and posterior parietal cortex. Further studies using larger sample data, separating into groups of severity of ataxia, and analyzing

specific cerebral and cerebellar subregions are warranted. As we learn more about the role of the cerebellum in higher cognitive function, global efficiency may be useful as a continuous, quantitative, objective biomarker of cerebellar cognitive dysfunction.

LIMITATIONS

This study has several limitations. The small sample size might have contributed to the lack of statistical significance of mean functional connectivity in the attention network between groups and a lack of statistical significance between GE and cognitive scores after multiple comparison correction. Another limitation is that only seven of our controls had cognitive data, which could affect the statistical analysis of between group cognitive differences.

A common issue with rs-fMRI is the contribution of motion-related artifacts, not limited to gross artifacts but rather minute differences in functional connectivity metrics. Although we ensured no group level differences in motion exist and utilized well-known methods to mitigate the contribution of motion to connectivity estimates, it may be difficult to completely exclude the possibility that connectivity was at least in part influenced by motion.

An additional limitation is inherent in attempting to segregate and label the broad spectrum of network relationships in the brain into well-defined bins of characteristic intrinsic brain networks. Any of the networks examined may further split into smaller networks depending on the granularity of defining networks. In addition, we limited our analysis to examining connectivity as a single metric over time; however, the dynamic nature of intrinsic brain networks has recently begun to gain attention in rs-fMRI and may shed light into additional processes that may not be evident when utilizing analyses that assume the stationarity of networks over time.

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