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Distinct Cerebellar Regions Related to Motor and Cognitive Performance in SCA6 Patients

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Abstract

Objective—To demonstrate a correlation between anatomic regional changes in Spinocerebellar Ataxia type 6 (SCA6) patients and measures of cognitive performance on neuropsychological tests.

Methods—Neurocognitive testing was conducted on 24 SCA6 and 28 control subjects. For each cognitive test, SCA6 patients were compared against the controls using Student's *t*-test. For the cerebellar patients, using voxel based morphometry, correlations between cerebellar gray matter

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volume at each voxel and performance on the neuropsychological exams were calculated using the Pearson correlation coefficient implemented in SPM8.

Results—Compared to controls, SCA6 patients exhibited significantly impaired performance on the following cognitive tests: Rey-Auditory Verbal Learning Test Trial V, Controlled Oral Word Association phonemic test and semantic-verb test, Rey-Osterrieth Complex Figure copy test as well as immediate and delayed visuo-spatial memory recall test, Trail Making Test (TMT) Part A and Part B, Stroop Color Task completion time, Stroop Color-Word Task score, and Grooved Pegboard Test (GPT) Dominant and Non-Dominant Hand time. Correlations of gray matter density with cognitive test performance were determined for all SCA6 subjects. Using a p-value threshold of 0.001 and family-wise small volume error correction, significant correlations were found for GPT Non-Dominant, GPT Dominant, TMT Part A, and TMT Part B.

Conclusion—Different regional patterns of cerebellar involvement were found for the motoric GPT task and the executive version of the TMT. The results for the GPT strongly indicated that the integrity of medial superior hemispheric regions was associated with motor task performance, whereas executive cognitive function was localized in distinctly different inferior regions. This is the first VBM study to differentiate cognitive and motor contributions of the cerebellum.

Search Terms

Clinical neurology examination [16]; All Cognitive Disorders/Dementia [25]; Spinocerebellar ataxia [298]; MRI [120]; Cerebellum [312]

1. Introduction

Recent research has suggested that, in addition to its involvement in motor control, the cerebellum is involved in higher-order cognitive tasks (1–5). This additional role is likely due to closed loop patterns of connectivity between neocortical associative cortices and the cerebellum (6,7). Cerebellar diseases that disrupt computations normally provided to these association areas could lead to impairment in cognitive function.

The current study investigated the correlation between gray matter density and cognitive performance in a group of patients with pure cerebellar ataxia known as spinocerebellar ataxia type 6 (SCA6). This is an autosomal dominant neurodegenerative condition characterized by loss of cerebellar Purkinje cells but preservation of other brain structures. Magnetic resonance imaging scans of SCA6 patients show pure cerebellar atrophy, resulting in slowly progressive ataxia and dysarthria (8). Due to the confinement of damage at the cerebellar cortex and deep nuclei, SCA6 patients are well suited for examining the relationship between regional cerebellar damage and cognitive function.

The present study used voxel based morphometry (VBM) to analyze the extent to which regional gray matter density in the cerebellum correlates with behavioral performance. VBM has been used in prior studies to confirm prominent gray matter atrophy in the cerebellar hemispheres and vermis of SCA6 patients, and has been considered a useful tool for diagnosing spinocerebellar degradation (9). We hypothesized that VBM will demonstrate correlations between gray matter density in the cerebellum of SCA6 patients and

neuropsychological performance measures, and that regions implicated in motor performance will differ from those involved in cognitive function.

2. Methods

a. Subjects

A group of 24 SCA6 patients participated in this study: 7 males, 17 females, age range 41–74, with a mean disease duration of 10.86 years (Table 1). Patients were referred to the ataxia clinic by their treating physician, patient support group, or by word of mouth. Patients with acute cerebellar damage or other confounding neurological factors were excluded on the basis of clinical history, physical examination, and MRI findings. The study also included 28 normal healthy control subjects, group matched for age, gender, educational level, and handedness. Written informed consent was obtained from all participants according to a protocol approved by Institutional Review Board of The Johns Hopkins University, School of Medicine.

b. Neuropsychological assessment

All subjects participated in a comprehensive neuropsychological assessment, which included Mini Mental Status Examination (MMSE), Wechsler Adult Intelligence Scale – Forward and Backward Digit Span Test, Rey-Auditory Verbal Learning Test (RAVLT), Controlled Oral Word Association (COWA) Test, Rey-Osterrieth Complex Figure Test (ROCF), Trail Making Test (TMT), Stroop Color and Word Task, Grooved Pegboard Test (GPT), Hooper Visual Orientation Test (VOT), and Boston Naming Test (BNT). The tests were administered according to the protocols described in the manual. Additionally, SCA6 patients underwent MRI scanning either at the time of neuropsychological assessment or within one month of assessment.

c. MRI acquisition

Scans were acquired from all subjects using a 3T Philips NT Intera scanner and a 5 channel phased array head coil. For each subject, a head brace was used to prevent movement. High resolution anatomical scans were acquired from each subject using a 3D magnetization-prepared rapid acquisition with a gradient echo (MP-RAGE) sequence with the following parameters: TR = 10.3 ms, TE = 6 ms, FA = 8°, FOV = 212×212×143 mm acquired in a 192×192×130 matrix to yield 1.1 mm isotropic voxels. This was reconstructed into 256×256×130 volumes, providing a reconstructed resolution of 0.828×0.828×1.1 mm.

i. Image pre-processing and analysis—Image analysis was completed using the Statistical Parametric Mapping software SPM8 running on Matlab R2013a. All image pre-processing steps were completed via a diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) approach. First, segmentation of volumes into gray matter, white matter, and CSF was accomplished using the procedure of Ashburner and Friston (2005) implemented in the New Segment toolbox of SPM8 (10). The output of this step was used to produce more accurate inter-subject alignment using the DARTEL toolbox, which models the shape of the brain using three parameters per voxel, and aligns gray and white matter among the images using an iterative process. The gray matter volumes were

then normalized to MNI space and “modulated” so that the total amount of gray matter signal in the normalized volumes was preserved. Finally, the volumes were spatially smoothed with a Gaussian kernel of FWHM=6.0 mm.

d. Statistical analysis

All statistical analyses were completed using Matlab R2013a. For each cognitive test, SCA6 patients were compared against the controls using Student’s *t*-test. Given the 29 neuropsychological tests that were compared, the nominal $p < .05$ statistical threshold was Bonferroni-corrected to a value of 0.0017, and group differences exceeding this value are indicated in Table 2. For the cerebellar patients, correlations between cerebellar gray matter volume at each voxel and performance on the neuropsychological exams were calculated using the Pearson correlation coefficient implemented in SPM8. To control for the possibility that total brain volume could affect cerebellar regional gray matter volume, total intracranial volume was calculated for each subject by adding the volume of gray matter, white matter, and CSF. These intracranial volume values were then used to normalize the gray matter volumes using the spm8 proportional scaling function. The resulting statistical parametric map was thresholded at $p < .001$. A small volume family-wise error correction on the observed clusters ($p < .05$) was then performed using a cerebellar mask. Only neuropsychological tests that survived this correction are depicted in Figure 1. As an additional correctional measure given that 29 statistical parametric maps were assessed, Table 3 indicates clusters that exceeded a Bonferroni correction on the family-wise $p < .05$ value (ie, a family-wise error of $p < 0.0017$). Cerebellar MNI coordinates were anatomically labelled using the SUIT probabilistic atlas (11), and are described using the nomenclature of the Schmahmann et al cerebellar atlas (12).

3. Results

a. Neuropsychological performance

Summary of participant demographics and statistics of the group performance on each cognitive test are presented in Tables 1 and 2, respectively. GPT Dominant and GPT Non-Dominant times were available for 22 of the 24 SCA6 patients. For all other tests, a score was available for all 24 SCA6 patients. Compared to controls, SCA6 patients exhibited significantly impaired performance on the following cognitive tests using the nominal $p < .05$ threshold: RAVLT Trial V, COWA phonemic and COWA semantic-verb, ROCF copy as well as ROCF immediate and delayed visuo-spatial memory recall, TMT Part A and Part B, Stroop Color Task completion time, Stroop Color-Word Task score, and GPT Dominant and Non-Dominant Hand time. However, with the Bonferroni correction, only the TMT Part B and GPT Dominant and Non-Dominant Hand tests were significant, while the COWA phonemic, TMT Part A, and Stroop Color Word Task approached significance. SCA6 patients did not show significant impairments compared to the controls on the remaining cognitive tests.

b. Correlation of cerebellar gray matter density with cognitive tests

Correlations of gray matter density to cognitive test performance were determined for all SCA6 subjects. Using a p-value threshold of 0.001 and family-wise small volume error

correction described above, significant correlations were only found for GPT Non-Dominant, GPT Dominant, TMT Part A, and TMT Part B. Even using a more stringent Bonferroni family wise error threshold of 0.0017, significant clusters were identified in the GPT Dominant, GPT-Non-Dominant, and TMT Part B tests (indicated by asterisks in Table 3). Using an index score of less than 80 as the benchmark for impairment, 18 SCA6 patients had scores in the impaired range for GPT Non-Dominant, 17 for GPT Dominant, 6 for TMT Part A, and 9 for TMT Part B. The patterns of correlated cerebellar regions was quite different depending on whether the test pertained to motor or cognitive function. Superior cerebellar regions in lobules VI and Crus I were observed for the motor-related tests (GPT Dominant, GPT Non-Dominant, and TMT Part A) while inferior cerebellar regions in lobules VIIb and VIIIa were observed for the more executive TMT Part B. Summary of anatomical locations of correlation clusters for these tests are provided in Table 3.

Voxels exhibiting correlations between gray matter and neuropsychological performance were observed in other tests at a $P < 0.001$ threshold, but none of the clusters were large enough to be significant at $P < 0.05$ for the family-wise correction, and the number of clusters found were not significantly above chance. These tests include RAVLT Trial II, RAVLT Trial III, RAVLT Total: Trial I–V, Stroop Color Task completion time, Stroop Color-Word Task score, and Forward Digit Span.

Given that the cerebellum is both functionally and structurally connected to specific regions of the neocortex, it is possible that degeneration of cerebellar tissue could have resulted in loss of neocortical tissue through a diaschisis-like mechanism. If that was the case, motor neocortical regions might exhibit significant correlations between pegboard performance and gray matter density. Similarly, executive prefrontal neocortical regions might exhibit significant correlations between Trails B performance and gray matter density. To examine these possibilities, we investigated if neocortical clusters could be found in either the left or right precentral gyrus for the pegboard task, or in the left or right middle frontal gyrus for the Trails B task. Regions of interest for the bilateral precentral gyrus and bilateral middle frontal gyrus were created using the probabilistic atlas of Hammers et al. (13). These ROIs were used for small volume correction of p values that were found within these ROIs. Again using a voxel-wise p threshold of .001 and a family-wise error of 0.05 for clusters, no significant clusters were observed for the pegboard task. However, for the Trails B task, one cluster achieved significance with a family wise error of $p = 0.03$. This cluster was observed in the left middle frontal gyrus at MNI coordinate $-32, 14, 33$. Additional middle frontal gyrus clusters on both the left and right sides were observed at the voxel-wise p threshold of .001, but they did not meet the family-wise error criterion.

4. Discussion

In the past 20 years since the proliferation of MRI and functional MRI methods, it has become clear that cerebellar activation is present in a variety of tasks, including verbal fluency (14,15) semantic judgments (16,17) conceptual and syllogistic reasoning (18,19), and planning (20). Investigations of patients has indicated that cerebellar damage produces deficits in such tasks (21–28).

Voxel based Morphometry (VBM) is a tool that is complementary to other methods such as fMRI, and is particularly well suited for investigating populations with varying degrees of gray matter degeneration, such as ataxia patients. VBM has also been used to compare structural gray matter differences between first-episode schizophrenic subjects and normal control subjects (29), to examine the effects of regular meditative exercises on the age-related decline in gray matter volume in healthy subjects (30), and to assess differences in regional gray and white matter volume between heavy cannabis users and controls (31).

With respect to SCA6 patients, selective degeneration of the Purkinje cells in the cerebellar cortex, and the combined degeneration of Purkinje cells and other neurons, such as the inferior olivary neurons and granule cells, result in a cerebellar syndrome associated with dysarthria and downbeat nystagmus. This neurodegenerative disease results from a small expansion of a CAG repeats in the alpha1A-voltage-dependent calcium channel gene (32). SCA6 patients exhibit a stereotyped, dorsal to ventral pattern of degeneration in the cerebellar cortex (33), with significant gray matter loss in hemispheric lobes bilaterally and in the vermis, but no significant white matter reduction (34). Severe loss of Purkinje cells is reported in the cerebellar vermis and particularly in the cerebellar vermis lobules I–V. Sagittal sections of the cerebellar hemispheres at the dentate nucleus reveal significant loss of Purkinje cells, especially in hemispheric lobules Crus II, VIIIA/VIIIB, and IV–VI. Many of the remaining Purkinje cells also exhibit abnormalities with heterotopic, irregularly shaped nuclei, an unclear cytoplasmic membrane outline, somatic sprouts, and irregular dendritic arborizations (35).

Previous SCA6 patient studies have demonstrated specific cognitive deficits in patients with this largely cerebellar pattern of degeneration, pointing to the role of the cerebellum in intellectual abilities (36,37). Cooper et al. (2012) examined the correlation between cerebellar gray matter density and cognitive performance in a group of 15 SCA6 patients, demonstrating a relationship between verbal working memory and gray matter density in superior and inferior parts of the cerebellum. Cooper et al. reported correlations of cerebellar gray matter density with verbal working memory performance bilaterally in the superior, posterior, and inferior cerebellum. Overall, Cooper et al. suggested that the cerebellum is part of a neural network serving the verbal working memory system with specific areas involved in the phonological loop mechanism, which stores and rehearses speech-based information, and the central executive system (38).

The present study revealed that regional cerebellar gray matter density was significantly correlated with behavioral performance in two tasks, the GPT task and the TMT. The GPT consists of a pegboard with 25 holes with randomly positioned slots. Using only one hand, depending on whether it is the dominant hand or non-dominant hand trial, the patient must rotate pegs, which have a key along one side, so that they fit in the slots correctly. This manipulative dexterity test measures performance speed in a fine motor task and requires more complex visual-motor coordination than most pegboards. The TMT measures attention, processing speed, and visual screening ability by requiring the patient to connect 25 circles on a sheet of paper in the correct order as quickly as possible. In TMT Part A, the patient must draw lines to connect circles numbered 1–25 in ascending order. TMT Part B consists of circles with numbers 1–13 and letters A–L. Again, the patient must draw lines to

connect the circles in ascending order, but with the additional task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The cognitive alteration required by the TMT Part B reflects additional executive function demands, and the use of the TMT Part B as a measure of executive control has been validated in a previous study using a set-switching paradigm (39). We speculate that the combined executive-with-motor requirements of the TMT Part B may be responsible for the stronger correlations observed in the cerebellum relative to other executive tasks such as backward digit span or the Stroop test. Additionally, Tedesco et al (28) argue that deficits in sequencing are particularly profound in patients with focal cerebellar lesions, and the Trails tests have salient sequencing requirements. Tedesco et al further argue that damage to inferior cerebellar lobules, typically occurring from posterior inferior cerebellar artery infarctions, is especially associated with sequencing deficits, an observation that is consistent with the inferior distribution of clusters that we report for Trails B (Table 3). Other studies of focal cerebellar lesions have also reported deficits in the Trails test (40–43) as well as for the Pegboard task (40,43–45).

Although significant relationships between brain anatomy and task performance were found in the present study, the correlational VBM technique relies on sufficient variability in both neuropsychological performance and gray matter density in regions that are relevant to performance. Thus, failure to find significant correlations for any of the tests in the present study could be due to insufficient variability, either behavioral or in gray matter, in the population under study. This is likely the reason why our correlation results for digit span were not as robust as those reported by Cooper et al. (37).

The results of the present study are striking in that different regional patterns of cerebellar involvement were found for the motoric GPT task and the executive version of the TMT. The results for the GPT strongly indicated that the integrity of medial superior hemispheric regions was associated with motor task performance. The left-sided regions that were indicated for the non-dominant hand test are consistent with the fact that the left hand was non-dominant for the majority of subjects (2 of the 24 SCA6 patients and 4 of the 28 control patients were left-handed). The medial superior localization of involvement for the GPT task is consistent with patterns of finger/hand motor activation seen in fMRI studies. In contrast, the TMT resulted in a different pattern of significant voxels in inferior hemispheric regions. These different regions of cerebellar involvement likely reflect different cerebro-cerebellar loops, as indicated by resting state fMRI studies. Specifically, the superior hemispheric regions of the GPT task are associated with connectivity with motor frontal regions, whereas the significant voxels in Crus I and inferior regions including hemispheric VIIB and VIIIA are associated with connectivity with dorsolateral prefrontal and parietal regions (46,47). Although we examined the possibility that, through specific cerebro-cerebellar loops, correlations between gray matter density and neuropsychiatric test performance observed in the cerebellum would lead to similar correlations in the appropriate neocortical region, only partial support for such a pattern was observed. For the Trails B test, correlations observed in the inferior cerebellum were also associated with correlations in the middle frontal gyrus. However, the correlations found in the superior cerebellum for the pegboard task were not associated with similar correlations in the motor cortex.

The present results are consistent with other studies that indicate that impairments seen in SCA6 patients are not confined to the motor domain. A previous VBM study suggests involvement of the posterolateral cerebellar region in motor and cognitive functions in patients with cerebellar degenerative disease based on correlations between gray matter volume loss in the left Crus II and right lobule VI and increased error rates in performance monitoring (48). Considering the literature is limited in VBM studies that localize function in patients with cerebellar degeneration, specifically SCA6, our study presents a valuable contribution to the current understanding of specific cerebellar regions involved in motor and cognitive performance in this population of patients. Future studies could apply VBM techniques to investigate brain-behavior relationships in other types of cerebellar ataxia, including children, who experience acute cerebellar ataxia as a result of parainfectious, postinfectious, or postvaccination cerebellar inflammation (49). Of additional interest would be the extent to which the regions identified in Figure 1 would correspond to functional activation pattern differences for SCA6 vs. control subjects on the same neuropsychological tests.

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Figure 1.

Cerebellar regions showing significant negative correlation between gray matter density and test performance (time to complete) in SCA6 patients are depicted in red/yellow, using a $p < .001$ voxelwise threshold and familywise correction for multiple comparisons at $p < .05$. Each row depicts the results of a different neuropsychological tests (indicated in yellow font). Numbers at the top of the figure indicate the MNI Y coordinate for the coronal sections.

Table 1

Demographic information of SCA6 patients and controls

	SCA6 (n=24) (7M/17F)			Controls (n=28) (12M/16F)			SCA6 vs. Control p-value
	Mean	SD	Range	Mean	SD	Range	
Age	60	9	41-74	56	10	39-76	0.191
Years of Education	16.52	2.55	12-22	16.68	3.04	12-24	0.842
Duration of Disease	10.86	9.26	0-34	-	-	-	-

Neuropsychological exam scores of SCA6 patients and controls. Group differences that exceeded the Bonferroni corrected p value are indicated with asterisks.

Table 2

	SCA6 (n=24) (7M/17F)			Controls (n=28) (12M/16F)			p-value
	Mean	SD	Range	Mean	SD	Range	
Mini-Mental Status Exam	27.08	2.17	21–30	27.96	1.69	24–30	0.1009
Digit Span							
Forward	10.46	1.89	7–13	10.61	2.20	7–15	0.795
Backward	6.75	2.19	3–12	7.21	2.25	3–13	0.453
Rey-Auditory Verbal Learning Test							
Trial I	5.12	1.90	1–8	5.61	2.39	–1–11	0.445
Trial II	7.96	2.24	4–13	7.68	2.59	3–14	0.682
Trial III	9.71	2.24	6–14	9.75	2.85	4–15	0.954
Trial IV	10.63	2.87	6–15	11	2.60	5–15	0.628
Trial V	11.42	2.65	7–15	12.71	1.94	8–15	0.049
Total: Trial I–V	44.83	10.38	26–63	46.75	9.97	28–67	0.509
Trial VI	3.79	1.72	1–8	4.68	2.07	2–9	0.099
Trial VII	9.04	3.42	3–15	10.18	2.80	5–15	0.198
Trial VIII	9.08	4.04	–1–15	10.18	3.37	1–15	0.291
Trial IX	12.25	2.42	7–15	12.79	2.38	5–15	0.422
Controlled Oral Word Association							
Phonemic (FAS)	38.38	12.50	19–62	49.36	12.31	27–72	0.003
Semantic (noun)	39.33	11.04	25–68	43.5	10.51	21–61	0.171
Semantic (verb)	15.13	6.22	4–25	19.18	6.35	8–34	0.024
Rey-Osterrieth Complex Figure Test							
Figure Copy	32.71	5.40	15–36	35.21	1.30	31–36	0.021
Immediate visuo-spatial memory recall	18.04	7.61	3.5–29	22.63	7.60	4–35	0.034
Delayed visuo-spatial memory recall	16.92	6.89	4–29	21.59	7.05	7.5–35	0.019
Trail Making Test							
Part A	44.73	19.78	24–95	30.43	16.59	14–104	0.006
Part B	108.73	41.72	47–195	72.57	35.74	34–200	0.001*

		SCA6 (n=24) (7M/17F)			Controls (n=28) (12M/16F)			SCA6 vs. Control
		Mean	SD	Range	Mean	SD	Range	
Stroop	Score	109.42	7.70	80–112	109	5.54	83–112	0.866
	Time	71.54	22.34	43–120	56.94	15.43	39–120	0.015
Color Task	Score	79.26	23.86	28–112	95.42	18.32	57.80–116.57	0.008
	Time	116	11.44	70–120	115.54	17.74	70–164	0.912
Grooved Pegboard Test								
Dominant Hand Time		148.24	77.34	52–306	76.95	18.32	51–118	<0.001*
	Non-Dominant Hand Time	215.58	201.18	63–1000	85.39	25.14	44–139.81	0.001*
Hooper Visual Organization Test		14.30	0.82	12–15	14.37	0.90	12–15	0.787
	Boston Naming Test	57.33	2.93	48–60	57.14	3.00	48–60	0.839

Anatomical locations of correlation clusters for tests that survived family-wise error correction. Bold values represent a main peak while nonbold values represent a sub peak within cluster. Clusters that were significant using a Bonferroni-corrected family-wise error of 0.0017 are indicated with asterisks.

Table 3

	p(FWE)	N	Z score	x	y	z	Cerebellar region
Grooved Pegboard Test							
Non-Dominant Hand	0.003	343	4.30	-21	-72	-18	Left VI
			3.36	-27	-58	-21	Left VI
Dominant Hand	<0.001*	1443	4.19	30	-49	-30	Right VI
			3.22	30	-63	-36	Right Crus I
	<0.001*	1619	3.88	-14	-63	-15	Left VI
			3.86	-24	-61	-25	Left VI
			3.80	-16	-54	-31	Left Dentate
			3.76	-12	-73	-16	Left VI
			3.41	-10	-61	-30	Left Dentate
Trail Making Test							
Part A	0.029	193	4.01	22	-87	-27	Right Crus I
Part B	0.001*	471	3.98	-20	-70	-46	Left VIIb
			3.75	-12	-73	-42	Left VIIb
	0.009	275	3.88	26	-60	-48	Right VIIa