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ORIGINAL COMMUNICATION

Cognitive dysfunction in patients with spinocerebellar ataxia type 6

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Abstract The aim of this study was to assess the cognitive functions of patients with spinocerebellar ataxia type 6 (SCA6). We examined 13 patients with genetically confirmed SCA6 and 13 healthy control subjects matched for age, years of education, global cognitive status, and intellectual ability. We administered verbal memory (word recall and word recognition), executive function (digit span, category and letter fluency, Frontal Assessment Battery, and Trail Making Test-A and B), and visuospatial construction (figure copying) tests. We found that the patients with SCA6 had significantly lower scores on the demanding word recall and letter fluency tests compared to the control subjects, while word recognition was well preserved in the patients with SCA6. The other executive functions tested, as well as visuospatial construction, were preserved in the SCA6 group. However, although memory encoding and storage processes were preserved, the retrieval of memorized information concerning frontal function might be selectively affected in patients with SCA6 compared to in control subjects. The impaired word recall and letter fluency noted in patients with SCA6 were interpreted as being related to a word-retrieval disability. Such dysfunctions may be attributed to damage in the frontal-cerebellum circuit owing to SCA6.

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Introduction

Recently, research has shown that the cerebellum plays a role in cognitive processes [1]. Spinocerebellar ataxia type 6 (SCA6) is a type of autosomal-dominant cerebellar atrophy caused by a CAG trinucleotide repeated expansion in the α1A voltage-dependent calcium channel submit gene (*CACNA1A* gene) on chromosome 19p13 [2]. Neuropathologically, SCA6 is associated with Purkinje cell-dominant cortical cerebellar degeneration, and no other abnormalities in the central nervous system have been noted except for cerebellar atrophy [3]. Thus, patients with SCA6 serve as an adequate model for researching the cognitive functions of the cerebellum [4].

To date, because of the low prevalence of SCA6, only a few studies have examined the cognitive impairments associated with SCA6. These studies found that general intellect and attention [5–8], verbal working memory [5, 7, 8], and recognition memory [6] were preserved in patients with SCA6. In contrast, patients with SCA 6 demonstrated impairments in immediate verbal memory [6, 8] and immediate visual memory [7, 8] when compared to control subjects. Patients with SCA 6 also demonstrated impairments on various tests of executive function [6–9]. However, while one study found that patients' scores on category and letter fluency tests were significantly lower than the control participants' scores [7], other studies found that letter fluency was intact [6] or that both category and letter fluency were preserved in patients with SCA6 [9]. Moreover, to the best of our knowledge, no previous

studies have administered visuospatial construction (figure copying) tests to patients with SCA6.

Clearly, the cognitive disturbances in patients with SCA6 require further research. Accordingly, the aim of the present study was to examine the cognitive functions of patients with SCA6 using verbal memory (word recall and recognition memory), word fluency, executive function, and visuospatial construction tests. In the present study, we administered three word recall tests of varying difficulty to clarify the immediate word recall impairments in patients with SCA6. In addition, a recognition memory test was employed to compare the word recall results.

Methods

Subjects

Thirteen patients with genetically confirmed SCA6 and 13 healthy control (HC) subjects participated in this study (Table 1). All of the subjects were Japanese. The ataxia severity was rated using the Scale for the Assessment and Rating of Ataxia (SARA). None of the HC subjects had a history of neurologic or psychiatric disease that might affect cognition. The groups were not significantly different in terms of age, years of education, global cognitive status, as assessed by the Mini Mental State Examination, or intellectual ability, as assessed by Raven's Colored Progressive Matrices. All patients were in a stable clinical state throughout the testing period. No visible signs of depression were noted in the patients with SCA6.

Neuropsychological examinations

Verbal memory tests

Two word recall tests were used: the Miyake Paired Associate Word Learning Test (MPLT) [10] and the Alzheimer's disease Assessment Scale (ADAS) [11]. The MPLT consisted of two lists of words; each list contained 10 semantically related word pairs (for example, house–garden) or ten semantically unrelated word pairs (for example, swimming–bank). This test is similar to the verbal paired associates test on the Wechsler Memory Scale-Revised (WMS-R). Here, each subject was verbally presented with a list of ten word pairs and was asked to recall one of the words from each pair. Each list of words was presented three times. For the ADAS, 10 items of word recall and 12 items of word recognition were presented three times to the subjects. Scoring was conducted using the MPLT or ADAS procedure, which counted a successfully recalled item as one point, and the mean scores were calculated.

Executive function tests

Various executive function tests were used in the present study. Memory span tests, namely the digit forward and backward span tests from the WMS-R, were administered

Table 1 Clinical characteristics of the patients with spinocerebellar ataxia type 6 (SCA6) and healthy control (HC) subjects

	SCA6 $n = 13$ Mean (SD)	HC $n = 13$ Mean (SD)	Mann–Whitney U test z score and p values
Age (range)	65.30 (9.92) (48–80)	62.54 (7.0) (51–74)	$z = -0.69$, $p = 0.49$
Sex (female/male)	4/9	7/6	
Handedness	Right (13)	Right (13)	
Years of education (range)	11.46 (1.85) (8–14)	12.39 (1.61) (9–16)	$z = -1.29$, $p = 0.20$
MMSE (range)	27.39 (1.98) (25–30)	28.69 (1.03) (27–30)	$z = -1.79$, $p = 0.07$
RCPM (range)	30.15 (4.24) (21–36)	33.00 (2.12) (29–36)	$z = -1.71$, $p = 0.09$
Age at onset (range)	52.39 (10.30) (37–70)		
Disease duration (years) (range)	14.25 (5.96) (4–24)		
CAG repeat length (range)	22.1 (0.6) (21–23)		
SARA total (range)	16.5 (8.2) (2–33)		
Speech disturbance (SARA) (range)	1.5 (1.0) (0–3)		
Finger chase (SARA) (range)	1.3 (0.6) (0–2)		
Nose–finger test (SARA) (range)	1.3 (0.6) (0–2)		

SD standard deviation, *MMSE* Mini Mental State Examination, *RCPM* Raven's Colored Progressive Matrices, *SARA* Scale for the Assessment and Rating of Ataxia

to all of the participants. Scoring was conducted using the WMS-R procedure, which counted a successfully recalled item as one point.

We utilized verbal fluency tests. The subjects were asked to name as many items as possible from a semantic category (animal) and from a phonemic (letter) category [Japanese nouns starting with the Japanese Kana character (a) (sa), excluding proper nouns] within 1 min. In the letter fluency test, we summed the scores for the nouns starting with (a) and (sa). Additionally, the Frontal Assessment Battery (FAB) [12] was administered. The FAB is a cognitive screening test consisting of six subtests that evaluate the following six executive domains: similarities (conceptualization), letter fluency (mental flexibility), motor series (programming), conflicting instructions (sensitivity to interference), Go-NoGo (inhibitory control), and prehension behavior (environmental autonomy). Scoring was conducted using the FAB procedure.

Finally, the Trail Making Test (TMT)-A and TMT-B were administered. For the TMT-A, the numbers 1–25 were distributed pseudo-randomly on a sheet of paper and had to be connected in successive order by a continuous pencil line as quickly as possible. For the TMT-B, the numbers 1–13 and 12 characters [kana letters from (a) to (shi)] were distributed pseudo-randomly and had to be connected in an ordered, alternating number–letter sequence as quickly as possible. The reaction time was measured for each part.

Visuospatial construction test

We employed a visuospatial construction test. Participants were asked to copy four figures from the ADAS. Scoring was conducted using the ADAS procedure, as follows: when the subjects failed copy a figure, then they were assigned one point, and the maximum error scale was four points.

Statistical analyses

The results were subjected to statistical analysis using Statview 5.0 for Windows. The performances of the patients with SCA6 and HC subjects on the neuropsychological tasks were compared using Mann–Whitney *U* tests. Bonferroni correction was employed to adjust for multiple comparisons. Further, we statistically analyzed the relationships among the results of the neuropsychological tests and the subject characteristics of age at onset; disease duration; years of education; the speech disturbance, finger chase, and nose-finger test scores on the SARA; the SARA total scores; the CAG repeat length using Spearman's rank correlation coefficient. Regarding the statistical analyses between the groups and the correlation study, we have to state that because of the small sample size, the statistical power was not sufficient; thus, the type 2 errors may have occurred.

Results

The results of the neuropsychological assessments are listed in Table 2.

Verbal memory (word recall and recognition) tests

In the MPLT (unrelated word pairs), the performances of the patients with SCA6 were significantly lower ($p = 0.008$) than were those of the HC subjects. In the MPLT (related word pairs) and ADAS word recall tests, the patients with SCA6 had lower scores than did the HC group, but the differences were not significant ($p = 0.08$ and $p = 0.16$, respectively). In contrast, for the ADAS word recognition test, patients with SCA6 performed as well as the HC subjects did, and no significant differences were observed between the groups.

Executive function tests

Regarding the letter fluency tests, the scores of the patients with SCA6 were significantly lower ($p = 0.048$) than were those of the HC subjects. According to the results of the category fluency test, patients with SCA6 had lower scores than did HC subjects, although no significant differences were noted between the groups ($p = 0.08$). In contrast, patients' performances on the digit forward and backward span test, TMT-A and -B, and the FAB were not significantly different from the performances of the HC subjects.

Visuospatial construction test (copying ADAS figures)

No significant differences were observed between the groups.

Correlation analysis

According to the correlation analysis for the patients with SCA6, none of the neuropsychological tests that we administered was related to the CAG repeat length, or age at onset. Significant correlations were found between the disease duration and digit forward span ($r = -0.62$, $p = 0.03$) and digit backward span ($r = -0.76$, $p = 0.008$) tests. No significant correlations were found between the patients' impaired neuropsychological tests scores (MPLT unrelated word pairs and letter fluency) and the SARA scores. Additionally, the speech disturbance

Table 2 Results of the neuropsychological assessments for patients with spinocerebellar ataxia type 6 (SCA6) and healthy control (HC) subjects

	SCA6 $n = 13$ Mean (SD)	HC $n = 13$ Mean (SD)	Mann–Whitney U test z score and p values
Word recall test	6.81 (1.83)	9.09 (0.88)	$z = -2.71$, $p = 0.08$
MPLT: related word pairs (mean)			
Word recall test	0.59 (0.64)	3.84 (2.26)	$z = -3.39$, $p = 0.008$**
MPLT: unrelated word pairs (mean)	$n = 9$		
ADAS word recall test (ADAS) (mean)	5.72 (1.09)	6.86 (0.82)	$z = -2.48$, $p = 0.16$
	$n = 9$		
ADAS word recognition test (mean)	9.90 (1.45)	9.64 (1.15)	$z = -0.50$, n.s
	$n = 9$		
Digit forward span (points)	9.15 (2.15)	9.69 (2.02)	$z = -0.67$, n.s
Digit backward span (points)	6.69 (2.21)	7.46 (1.27)	$z = -1.37$, n.s
Category fluency (animal)	14.08 (4.33)	19.15 (3.56)	$z = -2.72$, $p = 0.08$
Letter fluency (a + sa)	12.62 (5.78)	19.23 (4.68)	$z = -2.86$, $p = 0.048$*
FAB total (points)	14.85 (1.72)	16.23 (1.83)	$z = -1.99$, n.s
TMT-A (s)	64.46 (45.93)	35.62 (20.89)	$z = -2.29$, $p = 0.24$
TMT-B (s)	134.58 (55.96)	87.54 (52.54)	$z = -2.34$, $p = 0.24$
	$n = 12$		
Visuospatial construction test	0.33 (0.71)	0 (0)	$z = -1.67$, n.s
Copying ADAS figures (points)	$n = 9$		

There were some patients who refused to perform the examinations for the unrelated word pairs in the MPLT, word recall and recognition test in the ADAS, TMT-B, and figure copying, thus separate n values are listed for these tests

SD standard deviation, *MPLT* Miyake Paired-Associate Word Learning Test, *ADAS* Alzheimer's Disease Assessment Scale, *FAB* Frontal Assessment Battery, *TMT* Trail Making Test

* $p < 0.05$, ** $p < 0.01$, *n.s* not significant. p values <0.25 are listed, and all p values were corrected for multiple comparisons with the Bonferroni correction

scores from the SARA and the MPLT (unrelated word pairs) scores were not significantly correlated ($r = -0.63$, $p = 0.07$). In contrast, patients' scores on the category fluency test, which demonstrated mild disability, displayed a significant correlation with the SARA speech disturbance scores ($r = -0.82$, $p = 0.005$). However, no significant correlations were found between the SARA speech disturbance scores and patients' impaired scores on the letter fluency test ($r = -0.18$, $p = 0.54$) or their mildly impaired scores on the MPLT (related word pairs) ($r = -0.31$, $p = 0.30$). The graphs for the correlations between the SARA speech disturbance scores and the word recall or word fluency scores are shown in Fig. 1.

In addition, to examine the influence of motor disability on the tracking tasks, we performed correlation analyses between the SARA finger chase or nose–finger test scores and the TMT-A or -B performances, which, while not significantly impaired, were slower in the patients with SCA6 than they were in the control subjects. No significant correlations were found between the TMT-A or -B and the SARA finger chase or nose–finger test scores (TMT-A and the SARA finger chase test, $r = 0.17$, $p = 0.55$; TMT-A and SARA nose–finger test: $r = 0.13$, $p = 0.65$; TMT-B and the SARA finger chase test: $r = 0.26$, $p = 0.38$; TMT-B and nose–finger test: $r = -0.01$, $p = 0.97$). The graphs for the correlations between the SARA finger chase or nose–finger test scores and the TMT-A or -B performances are shown in Fig. 2.

Discussion

In the present study, impaired word recall and letter fluency were observed in patients with SCA6 when compared to HC subjects. In the word recall tasks, significant impairment was revealed for the demanding MPLT (unrelated word pairs), but not for the less demanding MPLT (related word pairs) or ADAS recall test. Similar to the findings of Garrard et al. [6], we also found that verbal memory recognition was intact in patients with SCA6. With regard to the three memory processes of encoding, storage, and retrieval, we interpreted the preserved recognition in patients with SCA6 as indicating that their encoding and storage processes for verbal information are intact.

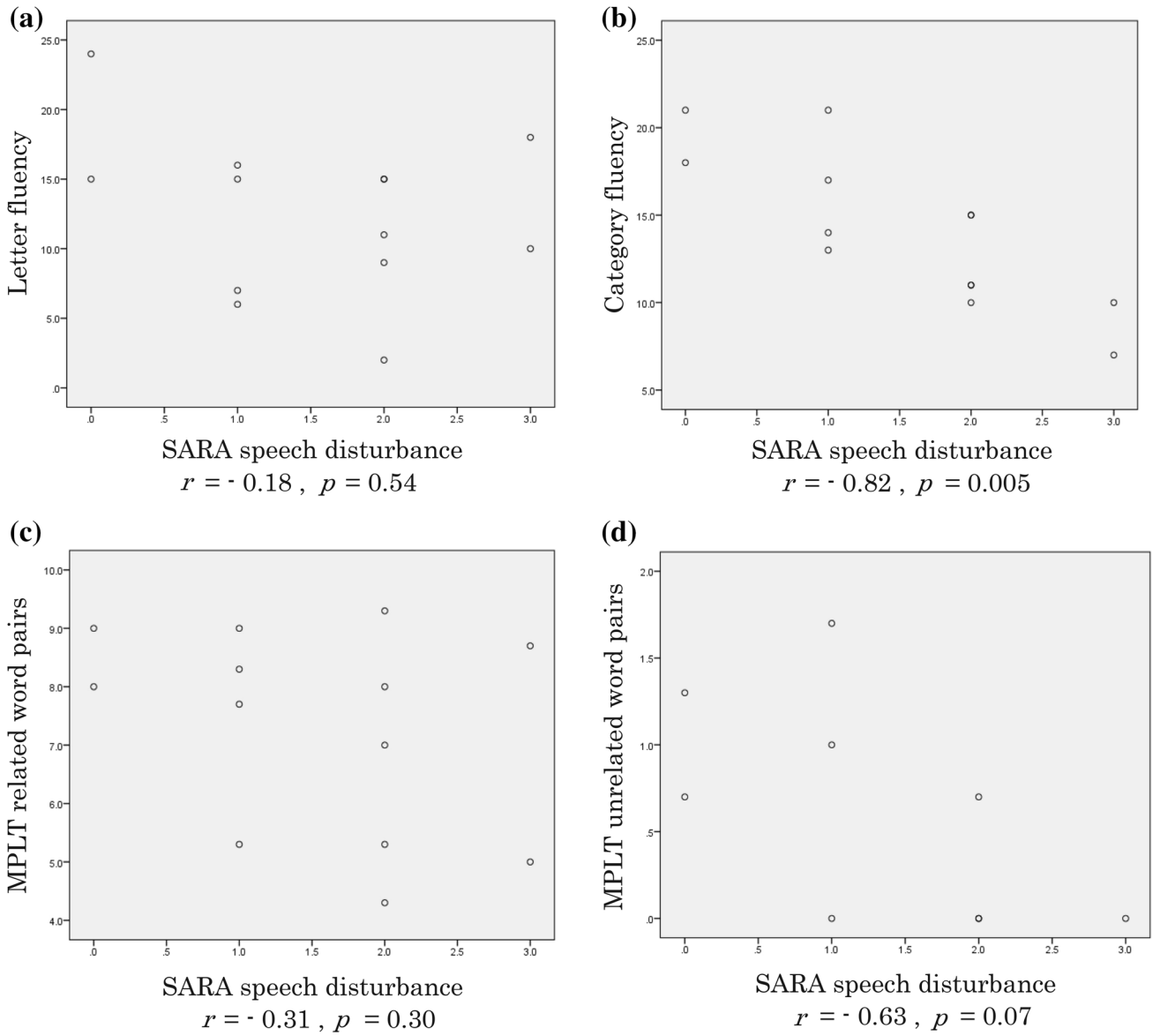

Fig. 1 Graphs demonstrating the correlations between the impaired scores on the neuropsychological tests and the speech disturbance scores from the Scale for the Assessment and Rating of Ataxia (SARA). Some dots overlap in the graphs. **a** Correlation between the letter fluency scores and SARA speech disturbance scores. **b** Correlation between the category fluency scores and SARA speech disturbance scores. **c** Correlation between the Miyake Paired Associate Word Learning Test-related word pairs scores and SARA speech disturbance scores. **d** Correlation between the Miyake Paired Associate Word Learning Test unrelated word pairs scores and SARA speech disturbance scores

Therefore, we believe that the recall disturbances that were identified in the patients with SCA6 were caused by a selective inability to retrieve memorized information.

Regarding executive function, our patients only showed impairments in letter fluency. In contrast, the patients studied by Suenaga et al. [7] showed impairments in both category and letter fluency. Both letter and semantic fluency tasks require the ability to initiate systematic or strategic searches using phonemic or semantic cues; however, letter fluency tasks are more demanding than category fluency tasks. We speculate that a common mechanism underlies the retrieval of previously stored verbal memory and word information and that this mechanism is impaired in patients with SCA6. Other executive functions, as assessed with the digit forward and backward span tests, TMT-A and -B, and the FAB were not impaired in patients with SCA6. The preserved working memory functions observed in our patients with SCA6 were consistent with the results of previous studies [5, 7, 8].

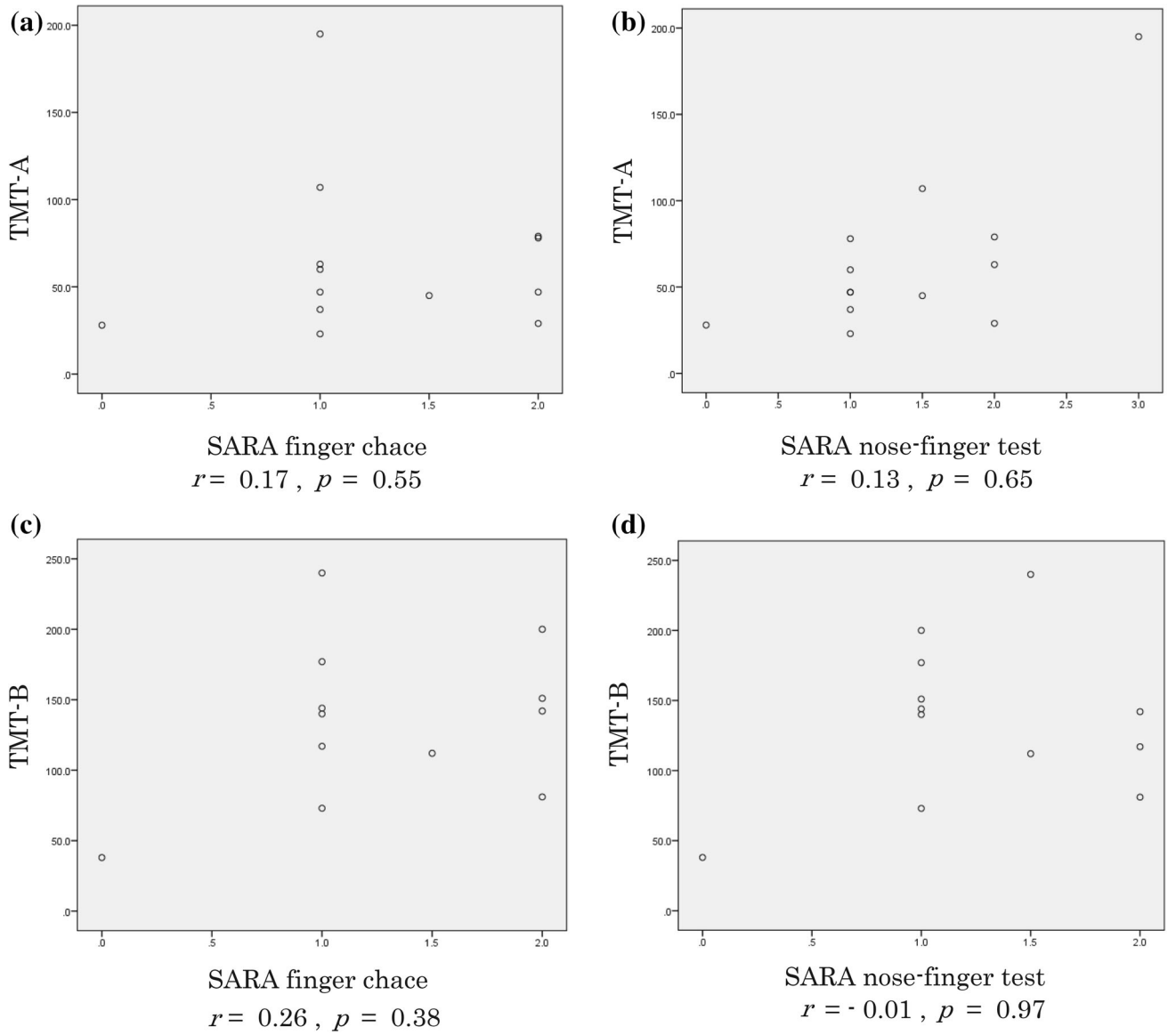

Fig. 2 Graphs demonstrating the correlations between the Trail Making Test (TMT)-A and -B and the finger chase and nose–finger test scores from the Scale for the Assessment and Rating of Ataxia (SARA). Some *dots* overlap in the graphs. **a** Correlation between the TMT-A performances and SARA finger chase scores. **b** Correlation between the TMT-A performances and SARA nose–finger scores. **c** Correlation between the TMT-B performances and SARA finger chase scores. **d** Correlation between the TMT-B performances and SARA nose–finger scores

In this study, no visuospatial construction deficits were noted in patients with SCA6. Thus, their parietal function was preserved.

Here, a significant correlation was found between the SARA speech disturbance scores and the mildly impaired category fluency scores, while the SARA speech disturbance scores and MPLT (unrelated word pairs) scores were not significantly correlated. Moreover, no significant correlations were identified between the SARA speech disturbance scores and the impaired letter fluency and mildly impaired MPLT (related word pairs) scores. Similarly, no significant correlations were found between the TMT-A or -B performances and the SARA finger chase or nose–finger test scores. Thus, motor disabilities such as dysmetria, tremor, and nystagmus did not appear to influence the tracking performances of patients with SCA6. The graphs of the correlations show an absence of outliers; thus, the results of the correlation analysis are likely accurate.

Hence, while subtle motor disabilities in the patients with SCA6 may influence their cognitive function tests scores to some extent, the influence that such disabilities had on the observed impairments in the neuropsychological tests was likely minimal in our patients with SCA6.

Our study is consistent with previous studies on the neuropsychological functions of patients with focal cerebellar lesions, which showed that such patients have word fluency [13, 14], and verbal memory [14] impairments. However, verbal working memory deficits [15] were not found in our patients with SCA6 or in previous studies [5, 7, 8]. There may be differences between patients with focal cerebellar lesions and those with SCA 6, although this topic requires further research.

In neuroimaging studies on healthy subjects, according to the hemispheric encoding retrieval asymmetry model [16], word recall is associated with higher activation in the right prefrontal region, anterior cingulate, globus pallidus, thalamus, and left cerebellum [17]. Moreover, functional brain imaging studies revealed that the left prefrontal and right cerebellar regions are activated during letter fluency tasks [18], while both category and letter fluency tasks commonly activate the left prefrontal lobe, thalamus, and midline cerebellum [19]. A neuroimaging study on patients with SCA6 by Kawai et al. [20] indicated that the patients' impairments in visual memory and word fluency were significantly correlated with a decrease in prefrontal hypoperfusion. The authors speculated that the mechanism underlying the regional cerebral blood flow reduction in the prefrontal cortices of patients with SCA6 is related to the functional deactivation of the cerebello-ponto-thalamo-cerebral pathways. Collectively, the results of these activation studies indicate that the connections between the prefrontal lobe and cerebellum may be related to the cognitive disabilities noted in our patients with SCA6.

In conclusion, our results demonstrated that the disabilities in word recall and letter fluency that were identified in our patients with SCA6 might be attributed to a selective dysfunction in the retrieval of memorized information. These disabilities in patients with SCA6 might be caused by frontal dysfunction following damage to the prefrontal cerebellar pathways.

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Compliance with ethical standards

Conflicts of interest The authors declare that there is no conflict of interest.

Ethical standard statement The study was performed in accordance with the guidelines of the 1964 Declaration of Helsinki. Oral informed consent was obtained from each subject. This study was approved by the local ethics committee.

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