Journal of Neurology (2018) 265:1563–1572
https://doi.org/10.1007/s00415-018-8883-y

ORIGINAL COMMUNICATION

Executive dysfunction in patients with spinocerebellar ataxia type 3

Itaru Tamura[1] · Asako Takei[2] · Shinsuke Hamada[2] · Hiroyuki Soma[2] · Michio Nonaka[2] · Sanae Homma[2] · Fumio Moriwaka[2]

Received: 1 February 2018 / Revised: 23 April 2018 / Accepted: 24 April 2018 / Published online: 3 May 2018

Abstract
The aim of this study was to assess the cognitive functions of patients with spinocerebellar ataxia type 3(SCA3). We examined 15 patients with genetically confirmed SCA3 and 15 healthy control subjects matched for age, years of education, and intellectual ability. We administered verbal memory (word recall and word recognition) and executive function tasks (word fluency test, forward and backward digit and visual span tests, Kana Pick-out Test, Trail Making Test, and conflicting instructions and a Go/NoGo task from the Frontal Assessment Battery). We found that patients with SCA3 had significantly lower scores than the healthy control subjects on the word recall, semantic, and letter fluency, and backward digit span tests, while word recognition was well preserved. The other executive function tests showed preserved functions in the SCA3 group, indicating that visual working memory, and attention and inhibition control were not affected. The patients with SCA3 showed impaired word recall and intact word recognition, and accordingly, episodic memory encoding and storage processes in short-term memory were preserved. In category and letter-fluency tests, impairment was attributable to word-retrieval from semantic memory. Impaired verbal working memory may be involved in the retrieval of verbal information from phonological storage by means of continuous subvocal rehearsal, rather than a deficit in initial phonological encoding. Essential executive dysfunction in patients with SCA3 may be due to damage in the cerebellar cortex–ventral dentate nucleus–thalamus–prefrontal cortex circuits, which are involved in strategic retrieval of verbal information from different modes of memory storage.

Keywords Spinocerebellar ataxia type 3 · Word fluency · Verbal working memory · Retrieval process · Cerebellum

Introduction

In recent decades, studies have shown that the cerebellum plays a role in cognitive processes [1]. Spinocerebellar ataxia type 3 (SCA3) is the most common type of SCA in Japan, and is caused by an abnormal expansion of CAG trinucleotide repeats in a gene on chromosome 14q32.1 [2]. The neuropathological findings of SCA 3 consist of degeneration in the dentate nucleus, spinocerebellar tracts, extrapyramidal system (the substantia nigra, red nucleus, globus pallidus, and subthalamic nucleus), and cerebellar and cerebral cortices [3–6]. A broad range of clinical manifestations characterize SCA3, including cerebellar ataxia, spasticity, parkinsonism, dystonia, hyperreflexia, and ophthalmoplegia, however, a clinical report notes that dementia is less frequent in SCA3 than in SCA1 or SCA2 [5].

To date, several studies have examined the cognitive impairments associated with SCA3, and have reported dysfunctions of verbal memory [7–13] as well as visual memory [8]. Moreover, patients with SCA3 have shown various impaired executive functions, such as dysfunction of letter fluency [8, 11, 14–17] or category fluency [8, 10, 11, 16]; impairment of verbal working memory (backward digit span test) [11, 12], or performance in visual span test [10, 16, 17]; lower scores on the Trail Making Test (TMT)-A [16, 17], TMT-B [11, 16, 17], or TMA-(B-A) [11]; and deficits in inhibition control estimated by the Stroop Colour-Word Test (SCWT) [11, 16, 17].

✉ Itaru Tamura
tamurait@hoku-iryo-u.ac.jp

[1] Department of Communication Disorders, School of Rehabilitation Sciences, Health Sciences University of Hokkaido, 1757 Kanazawa, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

[2] Hokuyukai Neurology Hospital, 2-2-4-30, Nizyuyonken, Nishiku, Sapporo, Hokkaido 063-0802, Japan

Previous studies have demonstrated memory and/or executive dysfunctions in patients with SCA3; however, there is no consensus regarding the cognitive impairments following cerebellar degeneration, and further studies are needed. With regard to verbal memory disturbance, our previous study [18] on cognitive dysfunction in patients with SCA6, who displayed atrophy of the cerebellar cortex, suggested impaired word-retrieval, in term of deficits in verbal memory (word recall and paired associate word learning) and word fluency when compared to healthy control (HC) subjects, while recognition memory was intact. Therefore, retrieval of memorized information regulated by frontal function is selectively affected in SCA 6, while encoding and storage remain intact. In neuropsychological studies on cerebellar lesions, impairment of working memory [19–23], and performance in the word fluency test [19, 20, 22, 24], TMT [19, 20], SCWT [19], and Wisconsin Card Sorting Test (WCST) [23] were observed. Neuroimaging studies have demonstrated activation in the cerebellum and frontal cortex during word recall [25, 26] or word fluency task [27–29]. Bellebaum and Daum [30] suggest that the most frequently observed cognitive impairments following cerebellar dysfunction are in working memory and verbal fluency. Based on these studies, we formulated the hypothesis that the essential cognitive impairment in patients with SCA3 involves executive dysfunction. To examine this hypothesis, some issues must be considered. First, to establish the mechanism of impaired verbal memory, word recall must be compared with recognition memory. Several studies have revealed verbal memory deficits in patients with SCA3, but recognition memory has not been sufficiently studied. Zawacki et al. [14] and Garrard et al. [9] reported preserved recognition memory in patients with SCA3; however, their sample populations were small (each, $n=6$). Roeske et al. [13] disclosed that recognition memory in patients with SCA3 ($n=11$) was not affected and did not deteriorate in their follow-up study. Lopes et al. [10] examined recognition memory in a larger group of patients with SCA3 ($n=32$), and found a slight impairment. Second, while deficits in attention control of patients with SCA3 have previously been reported using tasks such as TMT or SCWT. However, Mak et al. [23] reported that SCWT (time 3–1or 2) and TMT (B-A) or (B-A)/A did not show lower scores in patients with cerebellar lesion when compared to control subjects. There is the possibility that ataxia, parkinsonism, dystonia, hyperreflexia, and ophthalmoplegia influences performance in neuropsychological tests that rely on motor output. Third, although some reports have described impairment of verbal working memory [11, 12] in patients with SCA3, others have suggested that verbal working memory is not affected in these patients [7, 8, 10, 16]. According to Baddeley's model [31], working memory represents a process of temporary storage and manipulation of visual and verbal information, and is divided into three subcomponents: the central executive, which controls two slave systems as described below, the visuospatial sketch pad, which stores images, and the phonological loop, which stores verbal information. Further, the phonological loop consists of two components: (1) a passive storage process for verbal information and (2) an active articulatory control process, which is also divided into two stages: (a) a phonological storage in which phonological representation is maintained and (b) an articulatory rehearsal (subvocal repetition) in which memory traces can be refreshed by being retrieved and re-articulated. Based on this model, Chen and Desmond [32] revealed a cerebro-cerebellar network related to phonological storage and articulatory rehearsal in phonological loop using functional magnetic resonance imaging (fMRI). Ravizza et al. [21] suggested that working memory dysfunction in patients with cerebellar lesions resulted from impaired initial phonological encoding and/or strengthening memory trace. The cerebellar involvement in verbal working memory has been disputable.

Accordingly, the aims of the present study were as follows: First, to examine the essential memory impairment of patients with SCA3, we administered tasks on two paired associate word learning tasks with varying difficulty, word recall, and recognition memory. Second, to investigate attention control (divided attention and inhibition control) deficits in patients with SCA3, we compared performances in complex attention control tasks with those in simple reaction tasks (TMT-A, and B; and Kana Pick-out Test, meaningless [A] and story versions [B]). TMT (B-A)/A was calculated to eliminate a possible bias resulting from the motor disturbances [23, 33]. We originally calculated Kana Pick-out Test (A-B) to estimate divided attention more precisely. In addition, we analysed the correlation between ataxia scores and neuropsychological test scores to investigate the influence of motor deficits on performance in neuropsychological tests. Further, to examine inhibitory control, we employed conflicting instructions (sensitivity to interference) and Go/NoGo (inhibitory control) tasks from the Frontal Assessment Battery (FAB), where participants can respond using simple movements (tapping). Third, to test verbal and visual working memory, we selected forward and backward digit and visual span tests to compare verbal and visual working memories, and performances in simple or easy with complex or difficult tasks.

Materials and methods

Subjects

Fifteen patients with genetically confirmed SCA3 and 15 HC subjects participated in this study (Table 1). All subjects were Japanese. Ataxia severity was rated using the Scale

Table 1 Clinical characteristics of patients with spinocerebellar ataxia type 3 (SCA3) and of healthy control (HC) subjects

	SCA3 $n=15$ Av (SD) [range]	NC $n=15$ Av (SD) [range]	Mann–Whitney U test
Age	53.80 (11.79) [35–72]	54.1 (9.1) [29–66]	$P=0.90$ ns
Sex	Female, 6; male, 9	Female, 6; male, 9	
Handedness	Right, 15	Right, 15	
Years of education	12.27 (2.49) [9–19]	13.2 (2.0) [9–16]	$P=0.20$ ns
MMSE	27.00 (2.24) [24–30]	28.8 (1.37) [27–30]	$P=0.02$
RCPM	31.6 (4.0) [25–36]	33.20 (1.61) [31–36]	$P=0.37$ ns
Age at onset	42.3 (12.2) [26–61]		
Disease duration	11.5 (7.8) [2–31]		
CAG repeat length	70.1 (4.20) [62–76]		
SARA total score	17.4 (8.0) [5–30]		
Gait	4.7 (2.5) [0–7]		
Stance	3.4 (1.8) [1–6]		
Sitting	1.4 (0.8) [0–3]		
Speech disturbances	1.5 (0.9) [0–3]		
Finger chase	1.3 (1.0) [0–4]		
Nose–finger test	1.3 (1.0) [0–4]		
Fast-alternating hand movement	2.0 (1.0) [1–4]		
Heel–shin slide	1.8 (0.9) [1–3]		

SD standard deviation, *MMSE* mini mental state examination, *RCPM* Raven's coloured progressive matrices, *SARA* scale for the assessment and rating of ataxia

ns not significant ($P>0.05$)

for the Assessment and Rating of Ataxia (SARA). None of the HC subjects had a history of neurologic or psychiatric disease. The global cognitive status was assessed using the Mini Mental State Examination. The groups were not significantly different in terms of age, years of education, or intellectual ability, as assessed by Raven's Coloured Progressive Matrices. All patients were in a stable clinical state throughout the testing period.

Neuropsychological examinations

Verbal memory tests

Two-word recall tests were administered: the Miyake Paired-Associate Word Learning Test (MPLT) [34] and the Alzheimer's Disease Assessment Scale (ADAS) [35, 36]. The MPLT consisted of two lists of words; each list contained ten semantically related word pairs (for example, sky—star) or 10 semantically unrelated word pairs (for example, bud—tiger). These two versions are the same in nature, but the difficulty of the tasks is extremely different. This test resembles the verbal paired-associates test that is part of 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. In the word recall task in ADAS, the participants read and memorized the words for ten items presented using cards, and recalled as many words as possible from a presented list. In the word recognition task in ADAS, the participants read and memorized the words for 12 items presented using cards, and were asked to discriminate between the words for the items that they saw earlier and new items, among 24 items (12 new items were added to the 12 memorized items). The MPLT, word recall, and word recognition tasks contained three trial each. Scoring was conducted using the MPLT or ADAS procedure, which counted a successfully recalled item as one point. We did not impose a time limit for the participants to respond in the word recall and recognition tests.

Executive function tests

Verbal fluency tests: The subjects were asked to name as many items as possible from a semantic category (animal) and a phonemic (letter) category (Japanese nouns starting with the Japanese Kana character [a] or [sa], excluding proper nouns) within 1 min. In the letter-fluency test, we calculated scores as the sum of [a] and [sa] words.

Working memory tests: The forward and backward digit and visual span test from the WMS-R were administered to all the participants. For all tests, testing ended when the participant failed in both trials of a given length. To measure span length, we counted successfully recalled number of digits or span, and the instances when the subjects succeeded in one of the two trials, were scored as 0.5 digit or span.

Divided attention tests: (1) TMT-A and TMT-B: 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 with 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. In addition, TMT (B-A)/A was calculated. (2) Kana Pick-out Test [37]: This test is a popular Japanese attention test, which consists of two versions, one with a meaningless list of Kana (meaningless: A) and another with a Japanese folktale written in Kana (story: B). For the meaningless version, the patients were asked to pick out (by encircling characters) all the five Kana that represent the five vowels in Japanese, as quickly as possible, from randomly listed Kana letters. For the story version, the patients were asked not only to pick out all the five Kana but also to remember the story written in Kana letters. The meaningless version requires selective attention, whereas, the story version requires divided attention. A 2-min time limit was imposed. The number of picked-out Kana was counted, and we subtracted the number of pick-out Kana letters in the story version from the number in the meaningless version (A-B).

Inhibition control: The FAB [38, 39] is a cognitive screening test consisting of six subtests. In this study, we selected conflicting instructions (sensitivity to interference) and Go/NoGo (inhibitory control) tasks to investigate inhibitory functions using simple tapping reactions without visual search. In conflicting instructions, the participants were asked to tap twice when the examiner tapped once, and to tap once when examiner tapped twice. In Go/NoGo task, which was administered immediately after providing the conflicting instructions, the participants were asked to tap once when examiner tapped once, but not to tap when the examiner tapped twice. Scoring was conducted using the FAB procedure.

Statistical analyses

The results were statistically analysed using SPSS version 24 for Windows. The performance of the patients with SCA3 and the HC subjects on the neuropsychological tasks was compared using Mann–Whitney *U* tests. Differences were considered significant at $P < 0.05$. The *P* values were corrected for multiple comparisons using the Bonferroni procedure. Furthermore, we statistically analysed the relationships between the results of the neuropsychological tests and the subject characteristics: age at onset, disease duration, years of education, and CAG repeat length, using Spearman's rank correlation coefficient. Furthermore, to investigate the influence of movement deficits, we statistically analysed the relationships between the results of the neuropsychological tests with motor output and gait, stance, sitting, speech disturbances, finger chase, nose–finger test, fast-alternating hand movement, and heel–shin slide scores in SARA. Regarding the statistical analyses between the groups and the correlation study, because of the small sample size, the statistical power was not sufficient and type 2 errors may have occurred.

Results

Neuropsychological assessments

The results of the neuropsychological assessments are listed in Table 2 and Fig. 1.

Verbal memory tests

In the MPLT (related and unrelated word pairs) and ADAS word recall tests, the performance of the patients with SCA3 was significantly lower ($P = 0.04$, $P < 0.001$, and $P = 0.04$, respectively, corrected *P* values, the same applies hereinafter) than that of the HC subjects. In contrast, for the ADAS word recognition test, the patients with SCA3 performed as well as the HC subjects did, and no significant differences were observed between the groups. The results of each trial showed significantly lower scores in patients with SCA3 compared to HC subjects in both MPLT (Fig. 1a, b), related word pairs (trial 1, $P = 0.027$; trial 2, $P = 0.0006$; trial 3, $P = 0.009$) and unrelated word pairs (all trials, $P < 0.0003$). The HC group attained a perfect score in the third trial of MPLT-related word pairs. In the ADAS word recall task (Fig. 1c), there was no significant difference between the groups in the first trial ($P = 0.24$); however, with the progression of trials, significant differences were observed between the groups (trial 2, $P = 0.002$; trial 3, $P < 0.0003$). Conversely, there was no difference in recognition memory between the groups (Fig. 1d).

Executive function tests

Verbal fluency tests: In the category fluency and letter-fluency tests, the scores of the patients with SCA3 were significantly lower (both, $P < 0.001$) than those of the HC subjects.

Working memory tests: In the forward digit and forward and backward visual span tests, no significant differences were observed between the groups. In the backward digit span test, the scores of the patients with SCA3 were significantly lower ($P = 0.002$) than those of the HC subjects.

Divided attention tests: (1) TMT: In the TMT-A, the patients with SCA3 had significant slower scores than the HC group ($P = 0.04$). In the TMT-B, the patients with

Table 2 Neuropsychological assessments results for patients with spinocerebellar ataxia type 3 (SCA3) and healthy control (HC) subjects

	SCA3 ($n=15$) Av (SD)	NC ($n=15$) Av (SD)	Mann–Whitney U test	
			Uncorrected	Corrected
MPLT: related word pairs (mean)	6.76 (2.19)	8.97 (0.80)	$P=0.002$	$P=0.04$
MPLT:unrelated word pairs (mean)	0.49 (0.66)	4.58 (2.12)	$P<0.0001$	$P<0.001$
ADAS word recall test (mean)	5.79 (1.24)	7.47 (1.13)	$P=0.002$	$P=0.04$
ADAS word recognition test (mean)	9.20 (1.63)	9.63 (1.25)	$P=0.61$ ns	ns
Forward digit span (digit)	6.63 (1.12)	6.87 (0.88)	$P=0.65$ ns	ns
Backward digit span (digit)	4.00 (0.76)	5.10 (0.51)	$P=0.0001$	$P=0.002$
Visual span (forward) (span)	5.03 (1.08)	5.60 (0.71)	$P=0.14$ ns	ns
Visual span (backward)(span)	4.53 (0.77)	4.93 (0.82)	$P=0.19$ ns	ns
Category fluency (animal)	12.73 (4.13)	19.93 (3.73)	$P<0.0001$	$P<0.001$
Letter fluency (a + sa)	11.00 (4.38)	20.80 (4.75)	$P<0.0001$	$P<0.001$
TMT-A (s)	62.53 (27.64)	34.00 (15.09)	$P=0.002$	$P=0.04$*
TMT-B (s)	154.13 (89.47)	81.27 (30.41)	$P=0.003$	$P=0.054$ ns
TMT (B-A/A) (s)	1.42 (0.71)	1.53 (0.89)	$P=0.90$ ns	ns
Kana Pick-out Test Meaningless version (A) (point)	30.20 (9.14)	45.73 (8.42)	$P<0.0001$	$P<0.001$
Kana Pick-out Test Story version (B) (point)	21.27 (9.38)	38.60 (11.17)	$P<0.0001$	$P<0.001$
Kana Pick -Out Test(A-B) (point)	8.93 (6.67)	7.13 (7.33)	$P=0.39$ ns	ns
FAB (conflicting instructions) (point)	2.73 (0.46)	2.93 (0.26)	$P=0.37$ ns	ns
FAB (Go/NoGo) (point)	2.33 (0.82)	2.67 (0.62)	$P=0.31$ ns	ns

SD standard deviation, *MPLT* Miyake paired-associate word learning test, *ADAS* Alzheimer's disease assessment scale, *FAB* frontal assessment battery, *TMT* trail making test

ns not significant ($P>0.05$)

P values for multiple comparisons were adjusted using the Bonferroni correction

SCA3 had slower scores than did HC subjects, although no significant differences were noted between the groups ($P=0.054$). In the TMT-(B-A)/A, no significant differences were observed between the groups. (2) Kana Pick-out Test: In the meaningless version (A) as well as in the story version (B), the scores of the patients with SCA3 were significantly lower (both, $P<0.001$) than those of the HC subjects. When the numbers of picked-out Kana letters in the story version were subtracted from the numbers in the meaningless version (A-B), no significant difference was observed between the groups.

Inhibition control: For conflicting instructions and the Go/NoGo task from the FAB, no significant differences were observed between the groups.

Correlation analysis

Based on the correlation analysis for the patients with SCA 3, none of the neuropsychological tests that we administered was related to the CAG repeat length, age at onset, or disease duration. Higher correlations were found between performances in the ADAS word recall tests and the speech disturbances revealed by SARA scores ($\rho=-0.70$, $P=0.001$, uncorrected P values, the same applies hereinafter). However, no correlations were found between impaired the neuropsychological test scores of the patients with SCA assessed by verbal responses (MPLT-related and -unrelated word pairs, letter fluency, and backward digit span tests) and the speech disturbances revealed by SARA scores.

To examine the influence of motor disability on the performance in tracking tasks, we performed correlation analyses between the gait, stance, sitting, finger chase, nose–finger test, fast-alternating hand movement, and heel–shin slide scores in the SARA and the scores for TMT-A and B, and Kana Pick-out tests (meaningless and story version), and the conflicting instructions and Go/NoGo tests from the FAB. Higher correlations were found between performance in the Kana Pick-out Test (story version: B) and sitting, as well as fast-alternating hand movements ($\rho=-0.58$, $P=0.02$; $\rho=-0.54$, $P=0.04$, respectively) and between the Kana Pick-out Test (meaningless version: A) and the sitting, finger chase, and nose–finger test scores ($\rho=-0.57$, $P=0.03$; $\rho=-0.54$, $P=0.04$; $\rho=-0.54$, $P=0.04$, respectively). Higher correlations were not found between performance in the TMT-A, B, (B-A)/A, Kana Pick-out Test (A-B), and conflicting instructions or Go/NoGo test from the FAB and any ataxia score. For all correlation analyses, the P values mentioned above were obtained before applying the Bonferroni

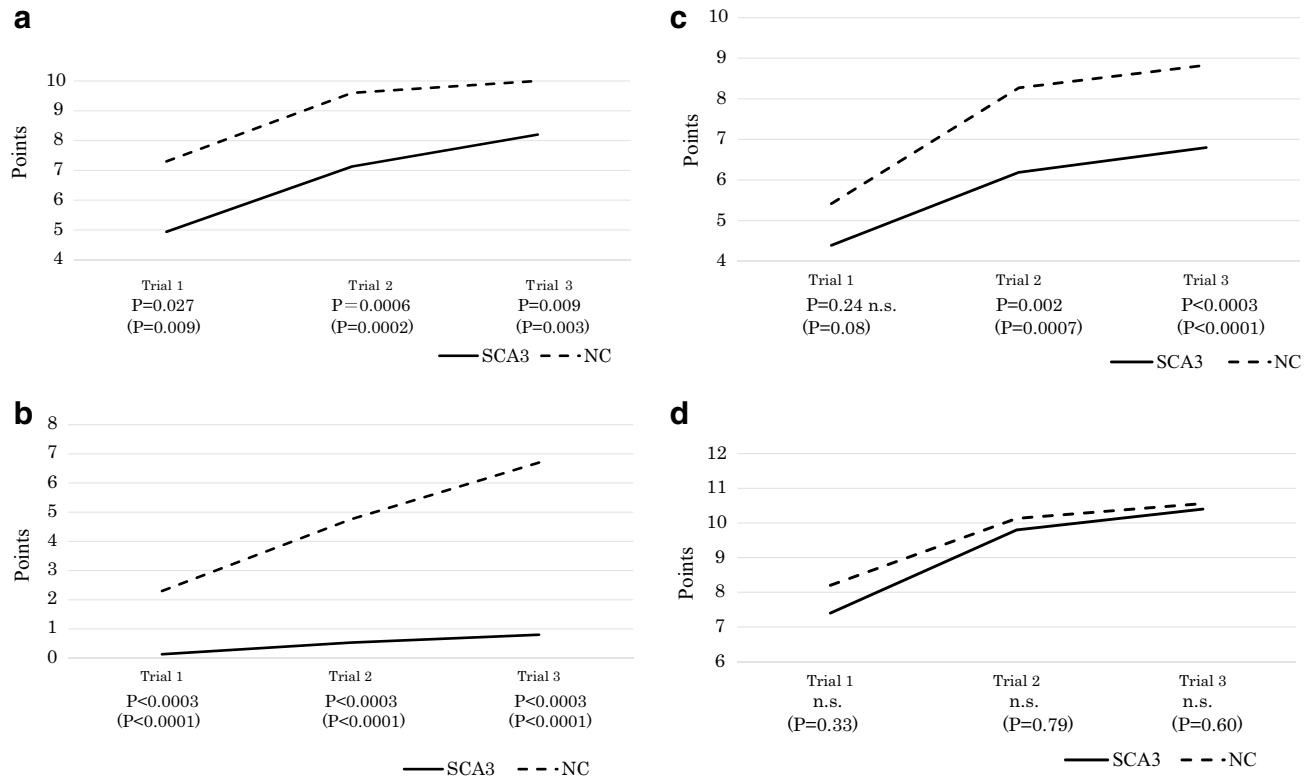

Fig. 1 **a**–**d** Task scores of each three trials for patients with SCA3 and for healthy control subjects are presented. The *P* values calculated using Mann–Whitney *U* test indicated the statistical significance of differences in scores between the two groups. Corrected *P* values were adjusted using the Bonferroni correction. Uncorrected *P* values were presented in parenthesis. *ns* not significant ($P > 0.05$)

procedure, because the correlation was not strong due to the small sample size, and we considered higher ρ-values ($\rho > 0.50$). Additionally, we examined the graphs for the correlations between each SARA score and each neuropsychological test which showed an absence of outliers, suggesting that the results of the correlation analyses are likely to be accurate.

Discussion

In the present study, impairments in word recall, letter and semantic fluency, and verbal working memory were found in patients with SCA3, while recognition memory, attention, and inhibition control were preserved. None of the neuropsychological tests that we administered was related to the CAG repeat length, age at onset, or disease duration. Therefore, these characteristics are not related to cognitive dysfunction in patients with SCA3.

In accordance with previous studies [7–13], impairment of verbal memory in the word recall tasks was observed in patients with SCA3 when compared to HC subjects. With progression of the three trials in MPLT and word recall tasks, learning disability was observed in patients with SCA3 when compared to HC subjects. Furthermore, the performance in both MPLT tasks were significantly different between the two groups for all trials; however, there was no significant difference between the performance of the groups in first trial of ADAS recall, which is more difficult than MPLT-related word pairs. We interpreted that patients with SCA3 were unable to utilize semantic-related word pairs as a cue to retrieve memorized information. In contrast, we found that verbal memory recognition was intact in patients with SCA3. Considering the three memory processes of encoding, storage, and retrieval, we interpreted the preserved recognition in patients with SCA3 as indicating that their encoding and storage processes for verbal information are intact. The recall disturbances that were identified in patients with SCA3 thus seem to be caused by a selective inability to retrieve memorized information from episodic memory storage, which is also observed in SCA6 [18].

In terms of verbal fluency, our patients with SCA3 showed severe impairments in letter and semantic fluency, similar to the findings of previous studies [8, 11, 16]. Letter and semantic fluency tasks require the ability to initiate strategic searches using phonemic or semantic cues and to retrieve words from semantic memory storage. Our interpretation is that a common mechanism underlying the retrieval

from previously stored episodic memory (short-term memory) storage in word recall and from word information in semantic memory (long-term memory) storage in word fluency is impaired in patients with SCA3.

With regard to results of the correlation analyses, in terms of speech disturbances, significant correlations were found between reduced scores on the ADAS word recall tests and the speech disturbances indicated by SARA scores. However, no correlations were found between the poorer test scores of the patients with SCA3 assessed by verbal responses (MPLT-related- and unrelated word pairs, letter fluency, and backward digit span tests) and the speech disturbances revealed by SARA scores. Moreover, there was no time limit for the participants to respond in these word recall tests. While subtle motor disabilities affecting verbal output in the patients with SCA3 may influence their cognitive function test scores to some extent, the influence of motor speech disabilities on neuropsychological examinations requiring verbal output cannot be excluded, but is likely to be minimal in our patients with SCA3.

The results of Kana Pick-out Test and the TMT-A and B showed attention dysfunction in the SCA3 group when compared to HC subjects. However, there were no significant differences between the patients with SCA3 and HC subjects regarding the subtraction (A-B) of numbers of picked-out Kana letters in the story version (B) from the number in the meaningless version (A) and the TMT (B-A) /A. This suggests that divided attention was not impaired in the patients with SCA3, which is consistent with the results of a previous study [16]. Inconsistent with previous studies using SCWT in patients with SCA3 [11, 16, 17], our patients showed preserved inhibitory control, as examined using conflicting instructions and Go/NoGo tests from the FAB. Gottwald et al. [19] reported that inhibitory control tested by a SCWT was impaired, while Go/NoGo performance was preserved, and a neuroimaging study [40] revealed that a NoGo task did not activate the cerebellum.

Regarding the results of the correlation analyses, higher correlations were found between some SARA scores and both Kana Pick-out Tests. The results of the conflicting instruction and the Go/NoGo test from the FAB using simple hand movements without visual search showed preserved inhibitory control in patients with SCA3, and there was no significant correlation with any SARA score. Taken together, the results show that tracking tasks with subtle hand movements or rapid speech output accompanied by visual search are influenced by motor dysfunction in patients with SCA3.

The impaired verbal working memory observed in our patients with SCA3 is in accordance with the findings of previous studies [11, 12], however, several studies have reported preserved verbal working memory in these patients [7, 8, 10, 16]. Our results are consistent with neuropsychological studies where impaired verbal working memory was found in patients with cerebellar lesions [19–23]. It is necessary to note that our patients' scores on backward digit span test were not severely affected and almost within the normal range, which has also been found in previous neuropsychological studies [21, 23]. While the forward and backward visual spans were preserved in our patients with SCA3, suggesting that visual working memory was not affected, the results do not match the previous findings in patients with SCA3 [10, 16, 17]. However, our results were consistent with that of a neuropsychological study [21]. In a fMRI study, Ng et al. [41] demonstrated activations of the bilateral superior and inferior cerebellar areas during visual working memory tasks. Further studies on cerebellar involvement in visual working memory are needed.

Based on Baddeley's model, Chen and Desmond [32] revealed a cerebro-cerebellar network using fMRI, and suggested that the middle or inferior frontal cortex (Brodmann area: BA44/6) and the superior cerebellar hemisphere (lobule VI, Crus I) are involved in the motoric control system (subvocal repetition) and that the inferior parietal lobule (BA40) and the right inferior cerebellar hemisphere (lobule VIIB) are related to the phonological storage system.

A positron emission tomography study on backward digit span by Gerton et al. [42] revealed the activation sites for verbal working memory: central executive: the prefrontal cortex (BA46/9), subvocal rehearsal system: the frontal cortex (BA44/6) and superior cerebellar cortex; phonological storage: inferior parietal cortex (BA40) and inferior cerebellum. Therefore, all areas involving verbal working memory were activated during the backward digit span test. The authors also found activation of the visual processing areas (BA 17/18/19), and their interpretation was that several participants had used a visualization strategy. In the current study, there was not significant difference in the forward and backward visual spans between the SCA3 and HC groups, and the influence of visual memory could, therefore, be disregarded.

Marvel and Desmond [43], using Sternberg paradigm in fMRI, revealed a distinctive neural network related to verbal working memory, which regulates encoding, maintenance, and retrieval. The authors suggested that the dorsal cerebellar dentate and the supplementary motor area (SMA), which represent the formation of motor trajectories, are involved in the encoding-phase process, while the right ventral cerebellar dentate, middle frontal gyrus (BA 9/46), an pre-SMA are involved in the retrieval process, including maintenance and manipulation of verbal information. The activation of the ventral dentate nucleus was also found during a n-back verbal working memory task [44, 45] and a verb-generation task [46]. Anatomically, communication from the ventral cerebellar dentate to the middle frontal gyrus (central executive) via the thalamus has been reported [47]. SCA 3 is associated with moderate to severe degeneration of the dentate

nucleus, which is involved in receiving the output of the cerebellar cortex [48]. Ravizza et al. [21] suggested that working memory deficit in patients with cerebellar lesions resulted from impaired initial phonological encoding and/or strengthening memory trace. Marvel and Desmond [49] suggested that cerebellar involvement in working memory may be attributable to the encoding process. However, with regard to phonological encoding, the patients of Ravizza et al. [21] showed impairment not only in the backward digit span but also in the forward digit span. However, identical to the current case, an impaired backward digit span and a preserved forward digit span was reported by other studies [11, 12]. Furthermore, recognition memory was intact in our patients with SCA3, suggesting that encoding of verbal information was preserved, and the dorsal cerebellar dentate as well as the SMA circuit were clearly not affected in these patients. In terms of strengthening memory traces, the backward digit span test is related to the maintenance of verbal information (digit sequences presented) in phonological storage (short-term memory) and the manipulation of information (digit sequence reversing operations). The main errors that were observed in the backward digit span test in patients with SCA3 were the decay of digit sequences when the patients were performing reversing operations. Different from verbal recognition memory, which showed intact storage, there was a decay of phonological storage with interference (reversing operations) and the impaired strengthening memory trace may be related to impairment of backward digit span in patients with SCA3. Ravizza et al. [21] reported that patients with a damaged inferior cerebellum showed an impaired backward digit span. The inferior cerebellum is related to phonological storage, and the verbal information in phonological storage needs to be continuously strengthened; therefore, it requires the retrieval of verbal information from phonological storage to perform subvocal repetition. The impairment of strategic retrieval process during manipulation regulated by central executive may be caused by cerebellar dysfunction in SCA3.

In accordance with a suggestion by Garrard et al. [9], we found similarities in cognitive dysfunction in SCA3 in this study and in SCA6 in our previous study [18]: impaired word recall and letter fluency as well as intact recognition memory and attention control were common features in the patients with SCA 3 and those with SCA 6. Neuropathologically, SCA 6 is associated with Purkinje cell-dominant cortical cerebellar degeneration, and no other abnormalities in the central nervous system have been reported, except for cerebellar atrophy. On the other hand, neuropathological findings of SCA 3 consist of degeneration in the dentate nucleus, spinocerebellar tracts, extrapyramidal system, and cerebellar and cerebral cortices [3–6]. However, executive dysfunction in our patients with SCA3 was limited to the retrieval of verbal information and verbal working memory, consistent with a report by Etchebehere et al. [50] suggesting that the functions related to the cerebral cortex in patients with SCA3 are almost intact. The cognitive dysfunctions observed in patients with SCA6 [18] do not involve impairment of verbal working memory, which is observed in patients with SCA3, who exhibit remarkable degeneration of the dentate nucleus. Tedesco et al. [51] revealed that damage of the cerebellar nucleus is related to the severity of cognitive impairment. Accordingly, there is no qualitative difference but a difference in the severity of executive dysfunction between patients with SCA3 and those with SCA6. Moreover, the cerebellar cortex and dentate nucleus may be involved in the observed cognitive dysfunction.

In conclusion, the essential executive dysfunction observed in SCA3 is the impaired strategic retrieval of verbal information. Word recall from short-term memory (episodic memory) storage, word fluency from long-term memory (semantic memory) storage, and verbal working memory from phonological storage (short-term memory storage) are affected in patients with SCA3 following damage of the frontal cortex–thalamus–ventral dentate nucleus–cerebellar cortex circuits. The executive dysfunction revealed in SCA3 is limited to word fluency, and visual working memory, attention and inhibition control are not affected. The cognitive dysfunction observed in SCA3 is similar to that found in SCA6, therefore, the dentate nucleus–cerebellar cortex loop may play a crucial role in cognitive function. Our results also suggest that the retrieval system with cerebellar involvement may be a uniform system working across different modes of memory storage.

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 Declaration of Helsinki. Written informed consent was obtained from each subject, and the study was approved by the local ethics committee.

References

1. Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. Brain 121:561–579. https://doi.org/10.1093/brain/121.4.561
2. Kawaguchi Y, Okamoto T, Taniwaki M, Aizawa M, Inoue M, Katayama S et al (1994) CAG expansions in a novel gene for Machado–Joseph disease at chromosome 14q32.1. Nat Genet 8:221–228. https://doi.org/10.1038/ng1194-221
3. Taniwaki T, Sakai T, Kobayashi T, Kuwabara Y, Otsuka M, Ichiya Y et al (1997) Positron emission tomography (PET) in Machado–Joseph disease. J Neurol Sci 145:63–67. https://doi.org/10.1016/S0022-510X(96)00242-0

4. Iwabuchi K, Tsuchiya K, Uchihara T, Yagishita S (1999) Autosomal dominant spinocerebellar degenerations. Clinical, pathological, and genetic correlations. Rev Neurol (Paris) 155:255–270
5. Schöls L, Bauer P, Schmidt T, Schulte T, Riess O (2004) Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. Lancet Neurol 3:291–304. https://doi.org/10.1016/S1474-4422(04)00737-9
6. D'Abreu A, França MC Jr, Yasuda CL, Campos BA, Lopes-Cendes I, Cendes F (2012) Neocortical atrophy in Machado–Joseph disease: a longitudinal neuroimaging study. J Neuroimaging 22:285–291. https://doi.org/10.1111/j.1552-6569.2011.00614.x
7. Bürk K, Globas C, Bösch S, Klockgether T, Zühlke C, Daum I et al (2003) Cognitive deficits in spinocerebellar ataxia type 1, 2, and 3. J Neurol 250: 207–211. https://doi.org/10.1007/s00415-003-0976-5
8. Kawai Y, Takeda A, Abe Y, Washimi Y, Tanaka F, Sobue G (2004) Cognitive impairments in Machado–Joseph Disease. Arch Neurol 61:1757–1760. https://doi.org/10.1001/archneur.61.11.1757
9. Garrard P, Martin NH, Giunti P, Cipolotti L (2008) Cognitive and social cognitive functioning in spinocerebellar ataxia: a preliminary characterization. J Neurol 255:398–405. https://doi.org/10.1007/s00415-008-0680-6
10. Lopes TM, D'Abreu A, França MC Jr, Yasuda CL, Betting LE, Samara AB,et al (2013) Widespread neuronal damage and cognitive dysfunction in spinocerebellar ataxia type 3. J Neurol 260:2370–2379. https://doi.org/10.1007/s00415-013-6998-8
11. Feng L, Chen DB, Hou L, Huang LH, Lu SY, Liang XL,et al (2014) Cognitive impairment in native Chinese with spinocerebellar ataxia type 3. Eur Neurol 71:262–270. https://doi.org/10.1159/000357404
12. Ma J, Wu C, Lei J, Zhang X (2014) Cognitive impairments in patients with spinocerebellar ataxia types 1, 2 and 3 are positively correlated to the clinical severity of ataxia symptoms. Int J Clin Exp Med 7:5765–5771
13. Roeske S, Filla I, Heim S, Amunts K, Helmstaedter C, Wüllner U et al (2013) Progressive cognitive dysfunction in spinocerebellar ataxia type3. Move Disord 28:1435–1438. https://doi.org/10.1002/mds.25512
14. Zawacki TM, Grace JG, Friedman JH, Sudarsky L (2002) Executive and emotional dysfunction in Machado–Joseph disease. Move Disord 17:1004–1010. https://doi.org/10.1002/mds.10033
15. Klinke I, Minnerop M, Schmitz-Hübsch T, Hendriks M, Klockgether T, Wüllner U et al (2010) Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3, and 6. Cerebellum 9:433–442. https://doi.org/10.1007/s12311-010-0183-8
16. Braga-Neto P, Pedroso JL, Alessi H, Dutra LA, Felício AC, Minett T, et al (2012) Cerebellar cognitive affective syndrome in Machado Joseph disease: core clinical features. Cerebellum 11:549–556. https://doi.org/10.1007/s12311-011-0318-6
17. Braga-Neto P, Dutra LA, Pedroso JL, Felício AC, Alessi H, Santos-Galduroz RF et al (2012) Cognitive deficits in Machado–Joseph disease correlate with hypoperfusion of visual system areas. Cerebellum 11:1037–1044. https://doi.org/10.1007/s12311-012-0354-x
18. Tamura I, Takei A, Hamada S, Nonaka M, Kurosaki Y, Moriwaka F (2017) Cognitive dysfunction in patients with spinocerebellar ataxia type 6. J Neurol 264:260–267. https://doi.org/10.1007/s00415-016-8344-4
19. Gottwald B, Mihajlovic Z, Wilde B, Mehdorn HM (2003) Does the cerebellum contribute to specific aspects of attention? Neuropsychologia 41:1452–1460. https://doi.org/10.1016/S0028-3932(03)00090-3
20. Gottwald B, Wilde B, Mihajlovic Z, Mehdorn HM (2004) Evidence for distinct cognitive deficits after focal cerebellar lesions. J Neurol Neurosurg Psychiatry 75:1524–1531. https://doi.org/10.1136/jnnp.2003.018093
21. Ravizza SM, McCormick CA, Schlerf JE, Justus T, Ivry RB, Fiez JA (2006) Cerebellar damage produces selective deficits in verbal working memory. Brain129:306–320. https://doi.org/10.1093/brain/awh685
22. Peterburs J, Bellebaum C, Koch B, Schwarz M, Daum I (2010) Working memory and verbal fluency deficits following cerebellar lesions: relation to interindividual differences in patients variables. Cerebellum 9:375–383. https://doi.org/10.1007/s12311-010-0171-z
23. Mak M, Tyburski E, Madany Ł, Sokołowski A, Samochowiec A (2016) Executive function deficits in patients after cerebellar neurosurgery. J Int Neuropsychol Soc 22:47–57. https://doi.org/10.1017/S1355617715001174
24. Richter S, Gerwig M, Aslan B, Wilhelm H, Schoch B, Dimitrova A et al (2007) Cognitive functions in patients with MR-defined chronic focal cerebellar lesions. J Neurol 254:1193–1203. https://doi.org/10.1007/s00415-006-0500-9
25. Petrides M, Alivisatos B, Evans AC (1995) Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. Proc Natl Acad Sci 92:5803–5807. https://doi.org/10.1073/pnas.92.13.5803
26. Cabeza R, Kapur S, Craik F, McIntosh AR (1997) Functional neuroanatomiy of recall and recognition: a PET study of episodic memory. J CogNeurosci 9:254–265. https://doi.org/10.1162/jocn.1997.9.2.254
27. Schlösser R, Hutchinson M, Joseffer S, Rusinek H, Rusinek H, Saarimaki A et al (1998) Functional magnetic resonance imaging of human brain activity in a verbal fluency task. J Neurol Neurosurg Psychiatry 64:492–498. https://doi.org/10.1136/jnnp.64.4.492
28. Gourovitch ML, Kirkby BS, Goldberg TE, Weinberger DR, Gold JM, Esposito G et al (2000) A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology 14:353–360. https://doi.org/10.1037/0894-4105.14.3.353
29. Jansen A, Flöel A, Randenborgh JV, Konrad C, Rotte M, Förster AF et al (2005) Crossed cerebro-cerebellar language dominance. Hum Brain Mapp 24:165–172. https://doi.org/10.1002/hbm.20077
30. Bellebaum C, Daum I (2007) Cerebellar involvement in executive control. Cerebellum 6:184–192. https://doi.org/10.1080/14734220601169707
31. Baddeley A (2003) Working memory: looking back and looking forward. Nat Rev Neurosci 4:829–839. https://doi.org/10.1038/nrn1201
32. Chen A, Desmond J (2005) Cereberocerebellar network during articulatory rehearsal and verbal working memory task. Neuroimage 24:332–338. https://doi.org/10.1016/j.neuroimage.2004.08.032
33. Stuss D, Bisschop S, Alexander M, Levine B, Katz D, Izukawa D (2001) The trail making test: a study in focal lesion patients. Psychol Assess 13:230–239. https://doi.org/10.1037//1040-3590.13.2.230
34. Miyake K (1923) The clinical study on memory. Shinkeigakuzassi 24:12–45
35. Mohs RC, Rosen WG, Davis KL (1983) The Alzheimer's disease assessment scale; an instrument for assessing treatment efficacy. Psycho-Pharmacol Bull 19:448–450
36. Homma A, Fukuzawa K, Tsukada Y, Ishii T, Hasegawa K, Mohs RC (1992) Development of a Japanese version of Alzheimer's disease assessment scale (ADAS). Jpn J Geriatr Psychiatry 3:647–655 **(in Japanese)**
37. Imamura Y (1998) Manual on Neuropsychology. Shinkouigaku syuppansya, Tokyo **(in Japanese)**

38. Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: a frontal assessment battery at bedside. Neurology 55:1621–1626. https://doi.org/10.1212/WNL.55.11.1621
39. Takagi R, Kajimoto Y, Kamiyoshi S, Miwa H, Kondo T (2002) The frontal assessment battery at bedside (FAB) in patients with Parkinson's disease. No To Shinkei 54:897–902 **(in Japanese)**
40. Watanabe J, Sugiura M, Sato K, Sato Y, Maeda Y, Matsue Y et al (2002) The human prefrontal and parietal association cortices are involved in NO-GO performances: an event-related fMRI study. Neuroimage 17:1207–1216. https://doi.org/10.1006/nimg.2002.119
41. Ng HB, Kao K-L, Chan YC, Chew E, Chuang KH, Chen SH (2016) Modality specificity in the cerebro-cerebellar neurocircuitry during working memory. Behav Brain Res 305:164–173. https://doi.org/10.1016/j.bbr.2016.02.027
42. Gerton BK, Brown TT, Meter-Lindenberg A, Kohn P, Holt JL, Olsen RK et al (2004) Shared and distinct neuropsychological components of the digits forward and backward tasks as revealed by functional neuroimaging. Neurospychologia 42:1781–1787. https://doi.org/10.1016/j.neuropsychologia
43. Marvel C, Desmond J(2010) The contributions of cerebro-cerebellar circuitry to executive verbal working memory. Cortex 46:880–895. https://doi.org/10.1016/j.cortex.2009.08.017
44. Thüring M, Hautzel H, Küper M, Stefanescu R, Maderwald S, Ladd ME et al (2012) Involvement of the cerebellar cortex and nuclei in verbal and visuospatial working memory: a 7 T fMRI study. Neuroimage 62:1537–1550. https://doi.org/10.1016/j.neuroimage.2012.05.037
45. Küper M, Kaschani P, Thüring M, Stefanescu MR, Burciu RG, Göricke S et al (2016) Cerebellar fMRI activation increases with increasing working memory demands. Cerebellum 15:322–335. https://doi.org/10.1007/s12311-015-0703-7
46. Thüring M, Küper M, Stefanescu R, Maderwald S, Gizewski ER, Ladd ME et al (2011) Activation of the dentate nucleus in a verb generation task: a 7 T MRI study. Neuroimage 57:1184–1191. https://doi.org/10.1016/j.neuroimage.2011.05.045
47. Dum PR, Strick PL (2003) An unfolded map of the cerebellar dentate nucleus and its projections to the cerebral cortex. J Neurophysiol 89:634–639. https://doi.org/10.1152/jn.00626.2002
48. Saab CY, Willis WD (2003) The cerebellum: organization, functions and its role in nociception. Brain Res Rev 42(03):85–95. https://doi.org/10.1016/S0165-017300151-6
49. Mariën P, Ackermann H, Adamaszek M, Barwood CHS, Beaton A, Desmond J et al (2014) Consensus paper: language and the cerebellum: an ongoing enigma. Cerebellum 13:386–410. https://doi.org/10.1007/s12311-013-0540-5
50. Etchebehere EC, Cendes F, Lopes-Cendes I, Pereira JA, Lima MC, Sansana CR et al (2001) Brain single-photon emission computed tomography and magnetic resonance imaging in Machado–Joseph disease. Arch Neurol 58:1257–1263. https://doi.org/10.1001/archneur.58.8.1257
51. Tedesco AM, Chiricozzi FR, Clausi S, Lupo M, Molinari M, Leggio MG (2011) The cerebellar cognitive profile. Brain 134:3672–3686. https://doi.org/10.1093/brain/awr266