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ORIGINAL PAPER

Selective Procedural Memory Impairment but Preserved Declarative Memory in Spinocerebellar Ataxia Type 3

Zohar Elyoseph[1] · Matti Mintz[1,2] · Eli Vakil[3,4] · Roy Zaltzman[5,6] · Carlos R. Gordon[2,5,6]

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Abstract

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is an autosomal dominant neurodegenerative disorder that affects mainly the cerebellum and less other brain areas. While the ataxic/motor features of the disease have been well described, the cognitive consequences of the degeneration require additional testing. The aim of this study was to evaluate learning abilities in SCA3. We tested 13 SCA3 patients and 14 age-matched healthy controls, all of Yemenite origin, on a neuropsychological battery of procedural and declarative memory tests. SCA3 patients demonstrated impaired sequence learning on the procedural Serial Reaction Time test (SRTt) but normal learning on the procedural Weather Prediction Probabilistic Classification test (WPPCt). SCA3 patients showed normal learning on the declarative Rey Auditory Verbal Learning test (Rey-AVLt). The correlations between the learning measures of the SRTt, WPPCt, and Rey-AVLt tests in SCA3 and controls separately were not significant. These results imply that the cerebellar degeneration in SCA3 causes selective impairment in procedural sequence learning while the procedural probabilistic learning and declarative memory were mostly preserved. These findings support the assumption that procedural learning is not a homogeneous function and could be dissociated in cerebellar neurodegenerative disease.

Keywords Cerebellum · SCA3 · Machado-Joseph disease · Procedural tests · Declarative tests

Introduction

Spinocerebellar ataxia (SCA) is a family of genetic disorders with motor signs such as incoordination of gait and movement of extremities and eyes [1]. The search for cognitive and affective symptoms in SCA is expanding following the establishment of the "Cerebellar Cognitive Affective Syndrome" (CCAS) in cerebellar patients [2,3].

The most common type of SCA worldwide is SCA3, also known as Machado-Joseph disease, which has been described in Israel exclusively in families of Jewish Yemenite descent [4,5]. SCA3 is caused by an autosomal dominant mutation with an expansion of CAG (cytosine-adenine-guanine) trinucleotide repeats in the *ATXN3* gene [6]. Initial and subsequently main brain deficit includes the cerebellar cortex, its brainstem input pontine nucleus, and its output dentate nucleus [7,8]. Widespread and heterogeneous atrophy was observed in the cerebral cortex, mainly the pre- and para-central cortex and the hippocampi [9], caudate nucleus, and putamen of the basal ganglia and some cranial nerve nuclei [10–12]. Together, the cerebellar and frontal cerebral damage is consistent with the claim of a cerebro-cerebellar-cerebral disconnection [13,14]. Despite such a seemingly widespread progressive degenerative process, early studies reported minimal cognitive impairments [14–18] and concluded that there is "no clinical evidence of dementia or global cognitive impairment" in SCA3 [19]. For example, the SCA3 patients showed significant deficiency only in immediate recall of randomized verbal categories [20]. In contrast, recent studies recognized an extensive and progressive, although highly variable, profile of cognitive impairments

✉ Carlos R. Gordon
cgordon@post.tau.ac.il

1 School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel

2 Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

3 Department of Psychology, Bar Ilan University, Ramat Gan, Israel

4 Gonda Multidisciplinary Brain Research Center, Bar Ilan University, Ramat Gan, Israel

5 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

6 Department of Neurology, Meir Medical Center, Kfar Saba, Israel

in SCA3, including executive, visuospatial, memory, and verbal functions [21–23]. Deficits could be of mild severity but nevertheless were demonstrated on multiple neuropsychological tests [24]. Here we tested SCA3 patients with the intention to verify whether their supposedly extensive brain damage affects both procedural and declarative learning.

Procedural learning is about acquisition of "knowledge of how" to execute skills [25]. It may require a long period of repeated training but may proceed without conscious intention [26]. Acquisition enables automatic fast performance and therefore reduction in reaction time is an accepted index of learning [27]. Procedural learning typically engages the cerebellum, basal ganglia, and the prefrontal cortex in combinations that may vary with the task under investigation [28]. Damage to the cerebellum impairs the procedural learning on the Serial Reaction Time test (SRTt) [29–32], Tower of Hanoi test [33], and eyeblink conditioning [34], although learning on the Weather Prediction Probabilistic Classification test (WPPCt) is preserved [35]. Damage to the basal ganglia, i.e., Parkinson's disease, also results in impairment in procedural learning documented with SRTt [36], Tower of Hanoi [37] ,and WPPCt [35,38]. Considering the evident cerebellar damage but possibly less affected basal ganglia, we anticipate selective deficiency in the procedural SRTt but not the WPPCt in SCA3 patients.

Declarative learning is about acquisition of episodic and semantic information [25,39]. It involves working memory, proceeds fast, and improves with enhanced intention [40]. It typically engages the medial temporal lobe and particularly the hippocampus [39,41]. Damage to the hippocampus leads to selective impairment in declarative learning on the Rey Auditory Verbal Learning test (Rey-AVLt) [42] and verbal sub-tests of the Wechsler Intelligence scale [43]. In a sample of SCA3 patients, MRI demonstrated that the hippocampus is largely spared, although reduction in gray matter density was observed in the parahippocampal gyri [44]. Subsequently, the same group demonstrated excessive volumetric reduction of the cerebellum, but only a moderate reduction of the hippocampus [9]. Based on these findings, we anticipate that SCA3 patients would have normal or minimally deficient declarative learning.

In summary, we hypothesized that SCA3 patients will present selective deficit on the procedural memory mainly on implicit serial/sequence learning with preserved probabilistic classification learning without declarative memory impairment.

Methods

Participants

The SCA3 group consisted of 13 genetically confirmed patients of Jewish Yemenite descent (six women and seven men, aged 56.4 ± 12.7 years). They were examined at the Machado-Joseph disease Clinic of the Meir Medical Center where they underwent a detailed neurological examination, including the Scale for the Assessment and Rating of Ataxia (SARA) [45,46]. Table 1 details the clinical and genetic data of the SCA3 patients. Their education level was 11.7 ± 2.6 years without cognitive impairment in clinical testing and without moderate or severe depression on the BDI-II scale [47,48]. The control group was recruited from townships populated by individuals of Jewish Yemenite descent. One control participant showed moderate depression level on the BDI-II scale (score = 23) and was removed from the analysis. The final control group was composed of 14 participants with *f*/*m* ratio of 7/7, age 52.43 ± 12.13 years, and education level of 12.8 ± 2.4 years. Control participants received a basic payment equivalent of 25 USD in compensation for their time spent during their participation in the study. The protocol of the study was approved by the Ethics Committee (Institutional Review Board) of the Meir Medical Center, Kfar Saba, Israel, and followed the tenets of the Declaration of Helsinki. All participants signed an informed consent form after receiving an explanation regarding the research procedures.

Cognitive Battery

Rey Auditory Verbal Learning Test

A Hebrew version [49] of the original test [50] examines declarative auditory verbal short-term memory, learning rate, proactive and retroactive interference to long-term memory, delayed retrieval, retrieval efficiency, and memory for temporal order [51–52]. The test starts with a list of 15 common nouns (list A), which were read to the participants at the rate of one word per second along consecutive trials 1 to 5; each reading was followed by a free recall of list A. In trial 6, a second list (list B) of 15 new common nouns was read; it served as interference and was followed by free recall of list B. In trial 7, without any reading, participants were asked to recall list A. Twenty minutes later, in trial 8 again without any reading, participants were asked to recall list A. Next, in trial 9, a list of 50 words was read (15 of list A, 15 of list B, and 20 new common nouns), and participants were asked to retrieve the 15 words of list A. Performance scores were calculated as the number of correct words reported per trial [53]. Last, in trial 10, participants received list A written in a scrambled order and were asked to reorganize the list into its original order. Performance scores were calculated by running two-tailed Spearman correlations between the correct order of words in the first list and the order rearranged by participants in trial 10.

Learning was assessed as a progress of scores along trials 1 to 5. Proactive interference was assessed as a decline in scores on trial 6 vs 1. Retroactive interference was assessed as a

decline in scores on trial 7 vs 5. Delayed recall was assessed as a decline in scores on trial 8 vs 5. Retrieval efficiency was assessed by comparing scores on trial 9 vs 8. Memory for temporal order was assessed in trial 10.

Serial Reaction Time Test

This test examines procedural learning of motor sequence [31]. Participants were seated in front of a 17″ LCD screen presenting four horizontally lined squares. The test consists of eight blocks interspaced by resting periods of 30 s. Each block is composed of 108 trials during which one of the 4 squares is marked by a red color and participants were asked to respond quickly by pressing a pre-associated keyboard key: "z" and "x" keys for the left hand and "," (comma) and "." (dot) for the right hand, with spatial match between the keyboard keys and the squares on the screen. Unknown to participants, the learning blocks 1 to 6 and 8 are composed of 9 repetitions of a fixed sequence of 12 squares (342312143241). Block 7 serves as a "transfer" block and consists of 9 repetitions of a new sequence of 12 squares (341243142132). Performance RT scores were calculated as the mean of median of correct response in the 9 repetitions per block. Performance of error scores were the number of errors per block. Learning is assessed by reduction in reaction time (RT) and committed key errors along the learning blocks and increase in RT on the transfer block.

Weather Prediction Probabilistic Classification Test

A computerized Hebrew version [54] of the original test [55] examines procedural probabilistic category learning. The test consists of four blocks interspaced by periods of 30 s during which the participants are debriefed about their performance on the preceding block. Each block consists of 84 trials d on each trial one of seven different cues in a form of a colorful shape is presented on the screen, each representing a different probability of rainy weather (8, 25, 33, 50, 67, 75, and 92%). Participants are asked to respond to the cue with a prediction of either "rainy" or "sunny" weather by pressing a keyboard key marked with a corresponding icon. The response is scored as correct if it corresponds to the probability associated with the cue above or below 50% chance of rain. However, to ensure probabilistic learning, responses are followed by positive or negative feedback (happy-smiley with high-pitched tone vs sad-smiley with a low-pitched tone, correspondingly) delivered at a relative rate as that coded by the cue. For example, a "rainy" response to a cue representing rain at 75% is considered a correct response, but nevertheless, it could be followed by a negative feedback on 25% of trials. Performance scores were the percentage of correct response per block or per clue probability. Learning is assessed by the rate of correct responses along blocks.

Ataxia Evaluation

Scale for the Assessment and Rating of Ataxia

This clinical test examines cerebellar ataxia grading the impairment in gait, stance, sitting, speech, finger-chase, nose-finger, fast alternating movements, and heel-to toe tests. The neurologist ranks the sub-tests in accordance with accepted norms (ranges 0–40). SARA underwent a rigorous validation in multi-center trials on SCA and non-SCA ataxia patients, as well as on controls [45,46].

Table 1 Clinical and genetic data of spinocerebellar ataxia type 3 patients

Subjects	Gender/age (years)	Age at disease onset (years)	Disease duration (years)	CAG* bases repeats	Ataxia score (SARA**)	BDI-II***
1	M/62	57	5	63	11.5	2
2	M/43	26	17	70	13	15
3	F/68	55	13	72	13	2
4	F/72	64	8	60	8.5	7
5	M/57	53	4	61	9	16
6	M/61	49	12	67	13	18
7	M/47	41	6	65	10	14
8	M/73	58	15	55	17	14
9	M/69	60	9	62	12.5	16
10	F/39	36	3	70	10	1
11	F/36	31	5	66	10.5	9
12	F/58	55	3	68	10	2
13	F/46	42	4	66	8.5	2

**CAG*, cytosine-adenine-guanine

***SARA*, Scale for the Assessment and Rating of Ataxia

****BDI-II*, Beck Depression Inventory-II

Procedure

Following the detailed neurological examination and SARA scoring carried out by a specialized neurologist (RZ), the neuropsychological battery was carried out by a trained research assistant (ZE) in two phases interspaced by a 10-min resting break. The first phase consisted of either SRTt or WPPCt followed by Rey-AVLt. The second phase consisted of the complementary SRTt or WPPCt followed by Beck Depression Inventory-II.

Data Analysis

Analysis of the Rey-AVLt, SRTt, and WPPCt was performed using repeated measures ANOVA with groups (SCA3 vs controls) and test trials/blocks as between and within subjects variables, respectively. In cases where the interaction effect was significant, we performed post hoc analysis for each group independently using one-way repeated measures ANOVA with trials/blocks as within subject variables. "Recalling of temporal order" (sub-test of the Rey-AVLt) was analyzed using independent samples *t* test. Correlations between scores on cognitive tests (block 9 of the Rey-AVLt, block 4 of the WPPCt, and block 7 minus 6 of the mean of median RT of the SRTt) were calculated separately for each group. Clinical parameters (disease duration, ataxia score on SARA scale) and genetic data (number of CAG bases repeats) were calculated only for the SCA3 group. We used two-tailed Pearson correlation coefficient test. The level of significance in all analyses was $p < 0.05$ and Partial Eta Squared test was used for evaluating effect size.

Results

Cognitive Tests

Table 2 summarizes the results of the Rey-AVLt, SRTt, and WPPCt cognitive tests.

Learning on the *Rey Auditory Verbal Learning Test*

Figure 1 shows the number of recalled words along the test trials for SCA3 and controls groups. Both groups demonstrated learning as an increase in the number of recalled words along trials 1–5 (trials effect; $F(4, 100) = 99.4$, $p < 0.001$, $\eta^2 = 0.8$), with no significant groups effect or interaction [$0.23 < p < 0.49$].

Both groups showed no proactive interference expressed as a similar recall of words on trial 6 vs 1, with no significant main effects of groups and trials and interaction [$0.16 < p < 0.94$]. Both groups demonstrated retroactive interference expressed as a decrease in the number of recalled words on trials 7 vs 5 (trials effect; $F(1, 25) = 31.3$, $p < 0.001$, $\eta^2 = 0.56$), with no significant groups effect or interaction [$0.23 < p < 0.35$].

We found a delay effect expressed as a decrease in the number of recalled words on trials 8 vs 5 (trials effect; $F(1, 25) = 34.7$, $p < 0.001$, $\eta^2 = 0.58$), with no significant group effect [$p = 0.11$]. The delay effect was stronger in SCA3 vs controls (groups by trials interaction; $F(1, 25) = 7.1$, $p < 0.05$, $\eta^2 = 0.22$). Only SCA3 group showed significant difference between trials (post hoc; $F(1, 12) = 45.63$, $p < 0.001$, $\eta^2 = 0.79$ for SCA3 and $F(1, 13) = 4.45$, $p = 0.055$, $\eta^2 = 0.25$ for controls).

SCA3 vs controls retrieved less words on trials 8 and 9 (group effect; $F(1, 25) = 5.5$, $p < 0.05$, $\eta^2 = 0.05$), but both groups demonstrated similar retrieval efficiency expressed as an increase in the number of retrieved words on trials 9 vs 8 (trials effect; $F(1, 25) = 34.7$, $p < 0.001$, $\eta^2 = 0.58$), with no significant interaction ($p = 0.26$).

Both groups demonstrated positive correlations confirming good recalling of the temporal order [0.52 ± 0.24 and 0.63 ± 0.22, for SCA3 and controls, respectively], with no significant difference between the groups (groups effect; $t(25) = 1.3$, $p = 0.20$).

In summary, SCA3 showed declarative learning and memory within the normal range on all parameters of the Rey-AVLt, except a mild impairment in delayed recall.

Learning on the Serial Reaction Time Test

Figure 2 a. shows the RTs along the 8 blocks of the task for the two groups. Sequence learning was assessed testing for a decrease in RTs on learning blocks 1–6. SCA3 vs controls showed longer RTs (group effect; $F(1, 25) = 19.1$, $p < 0.001$, $\eta^2 = 0.43$). Progressive decrease in RTs was found along blocks 1–6 (blocks effect; $F(5, 125) = 10.02$, $p < 0.001$, $\eta^2 = 0.29$), but this expression of learning was contributed by controls rather than by SCA3 (groups by blocks interaction; $F(5, 125) = 5.73$, $p < 0.01$, $\eta^2 = 0.18$). Only the control group showed significant difference between blocks (post hoc; $F(5, 60) = 1.25$, $p > 0.05$, $\eta^2 = 0.09$ for SCA3 and $F(5, 65) = 22.9$, $p < 0.001$, $\eta^2 = 0.64$ for controls). Sequence learning was also assessed by testing for an increase in RTs to a new sequence introduced on transfer block 7 vs last learning block 6. SCA3 vs controls showed longer RTs (group effect; $F(1, 25) = 26.46.6$, $p < 0.001$, $\eta^2 = 0.51$). An increase in the RTs was found at the transfer block 7 vs learning block 6 (blocks effect; $F(1, 25) = 7.5$, $p < 0.05$, $\eta^2 = 0.23$), but this expression of learning was contributed by controls rather than by SCA3 (groups by blocks interaction; $F(1, 25) = 5.4$, $p < 0.05$, $\eta^2 = 0.18$) Only the control group showed significant difference between blocks (post hoc; $F(1, 12) = 0.13$, $p > 0.05$, $\eta^2 = 0.01$ for SCA3 and $F(1, 13) = 9.67$, $p < 0.01$, $\eta^2 = 0.43$ for controls). Finally, sequence learning was assessed by

Table 2 Summary of the cognitive tests results

Tests	Compared trials/blocks	Trial/block effect	Group effect (SCA3^ vs controls)	Interaction effect	Post hoc within SCA3	Post hoc within controls
Rey-AVLt*	1–5	$p < 0.001$	ns	ns		
	6 vs 1	ns	ns	ns		
	7 vs 5	$p < 0.001$	ns	ns		
	8 vs 5	$p < 0.001$	ns	$p < 0.05$	$p < 0.001$	$p = 0.055$
	9 vs 8	$p < 0.001$	$p < 0.05$	ns		
	10		ns			
SRTt**	1–6 (RT#)	$p < 0.001$	$p < 0.001$	$p < 0.01$	ns	$p < 0.001$
	7 vs 6 (RT)	$p < 0.05$	$p < 0.05$	$p < 0.05$	ns	$p < 0.01$
	8 vs 7 (RT)	$p < 0.01$	$p < 0.01$	ns		
	1–6 (Er##)	ns	$p < 0.05$	$p < 0.01$	ns	$p < 0.001$
	7 vs 6 (Er)	ns	ns	ns		
	8 vs 7 (Er)	ns	ns	ns		
WPPCt***	1–4	$p < 0.001$	ns	ns		
	67% vs 75% vs 92%	$p < 0.001$	ns	ns		

**Rey-AVLt*, Rey Auditory Verbal Learning test

***SRTt*, Serial Reaction Time test

****WPPCt*, Weather Prediction Probabilistic Classification test

#*RT*, reaction time

##*Er*, errors

^*SCA3*, spinocerebellar ataxia type 3

testing for a decrease in RTs, i.e., recovery of RTs, in learning block 8 vs transfer block 7. Both groups showed decrease in RTs at block 8 vs 7 (blocks effect; $F(1, 25) = 11.8$, $p < 0.01$, $\eta^2 = 0.32$), more so by controls, but the interaction was not significant [groups by blocks interaction; $F(1, 25) = 2.2$, $p = 0.15$).

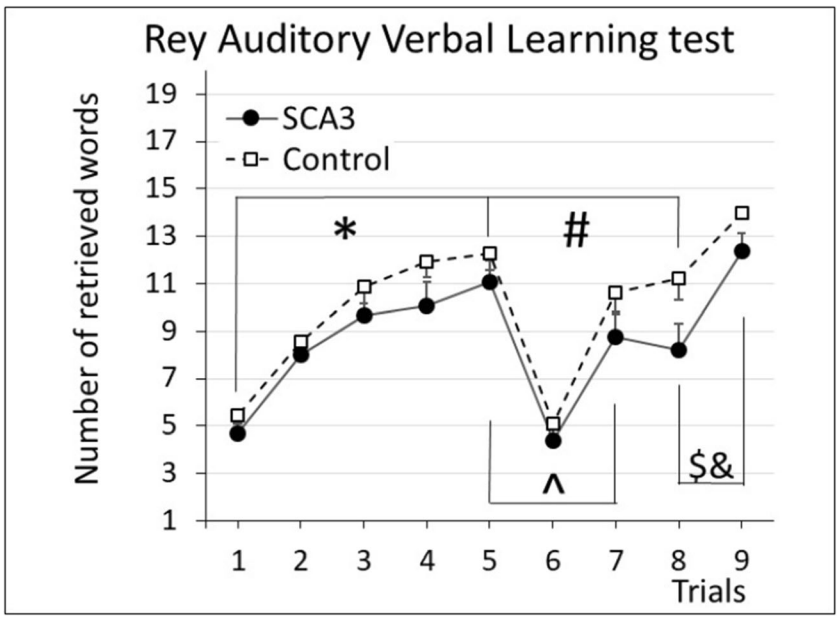

Fig. 1 Learning and memory on the Rey Auditory Verbal Learning test (Rey-AVLt). Number of recalled words (mean ± SEM) along trials of the test for SCA3 and controls. Both groups demonstrated similar learning rate along trials 1–5 (*trials effect; $p < 0.001$), similar lack of proactive interference in trials 6 vs 1, and similar retroactive interference in trials 7 vs 5 (^trials effect; $p < 0.001$). SCA3 vs controls showed impaired delayed recall in trials 8 vs 5 ($^{\#}$groups by blocks interaction; $p < 0.05$). SCA3 vs controls retrieved fewer words in trials 9 and 8 ($^{\$}$groups effect; $p < 0.05$), but both groups retrieved more words on trials 9 vs 8 ($^{\&}$trials effect; $p < 0.001$)

Figure 2 B shows the number of errors along the 8 blocks of the task for the two groups. SCA3 showed higher rate of errors on learning blocks 1–6 (groups effect; $F(1, 25) = 6.6$, $p < 0.05$, $\eta^2 = 0.21$), and a progressive decrease in the number of errors along the blocks compared with controls (groups by blocks interaction; $F(5, 125) = 3.32$, $p < 0.01$, $\eta^2 = 0.12$). Only the control group showed significant difference between blocks (post hoc; $F(5, 12) = 1.83$, $p > 0.05$, $\eta^2 = 0.13$ for SCA3 and $F(5, 65) = 6.21$, $p < 0.001$, $\eta^2 = 0.32$ for controls). Groups did not differ in the rate of errors on blocks 7 vs 6 and 8 vs 7, and blocks effect and interactions were not significant, throughout.

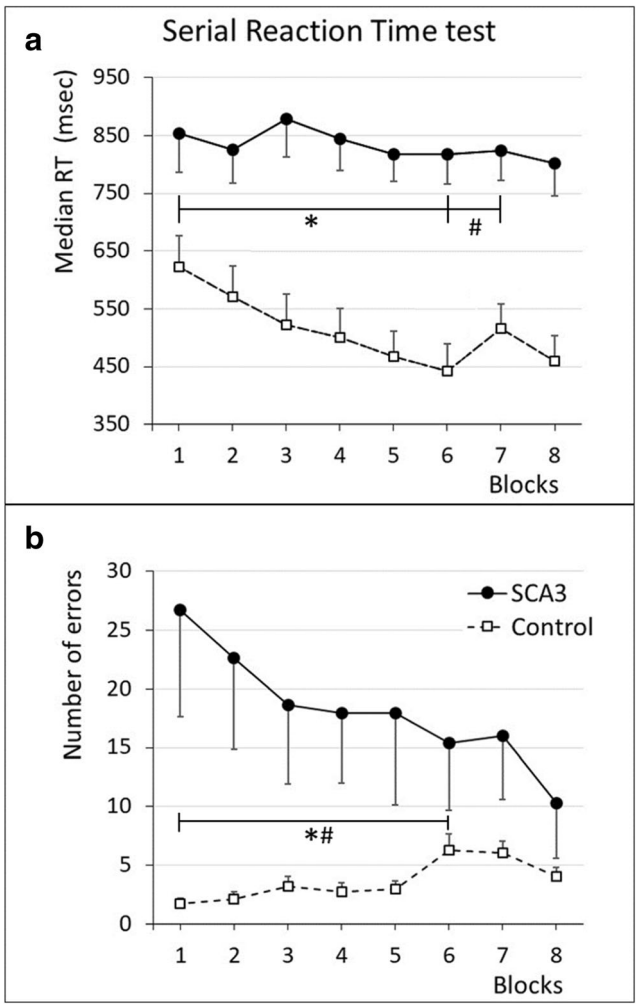

Fig. 2 Learning on the Serial Reaction Time test (SRTt). : a: Reaction time (mean of medians ± SEM) along blocks of the test for SCA3 and controls. Controls but not SCA3 demonstrated a reduction in reaction time along the learning blocks 1 to 6 and an increase in reaction time in the transfer block 7 vs 6 (groups by blocks interaction; $*p < 0.01$ and $^{\#}p < 0.05$, respectively). b: Number of erroneous responses (mean ± SEM) along blocks of the task for SCA3 and controls. SCA3 vs controls showed higher number of errors along learning blocks 1 to 6 (*groups effect; $p < 0.05$), but also a reduction in the number of errors along the blocks ($^{\#}$groups by blocks interaction; $p < 0.01$)

In summary, SCA3 showed deficient procedural sequence learning on the SRTt. SCA3 reduction in the number of errors is likely related to a stimulus-response learning.

Learning on the Weather Prediction Probabilistic Classification Test

Figure 3 A and B show the rate of correct responses along the blocks of the task and along cues probability, in the two groups. Both groups demonstrated learning expressed as an increase in the rate of correct responses along blocks 1–4 (blocks effect; $F(3, 75) = 8.3$, $p < 0.001$, $\eta^2 = 0.25$) and along cues probability (cues probability effect; $F(2, 50) = 8.9$, $p < 0.001$, $\eta^2 = 0.26$]. Groups effect and interaction were not significant ($0.29 < p < 0.99$).

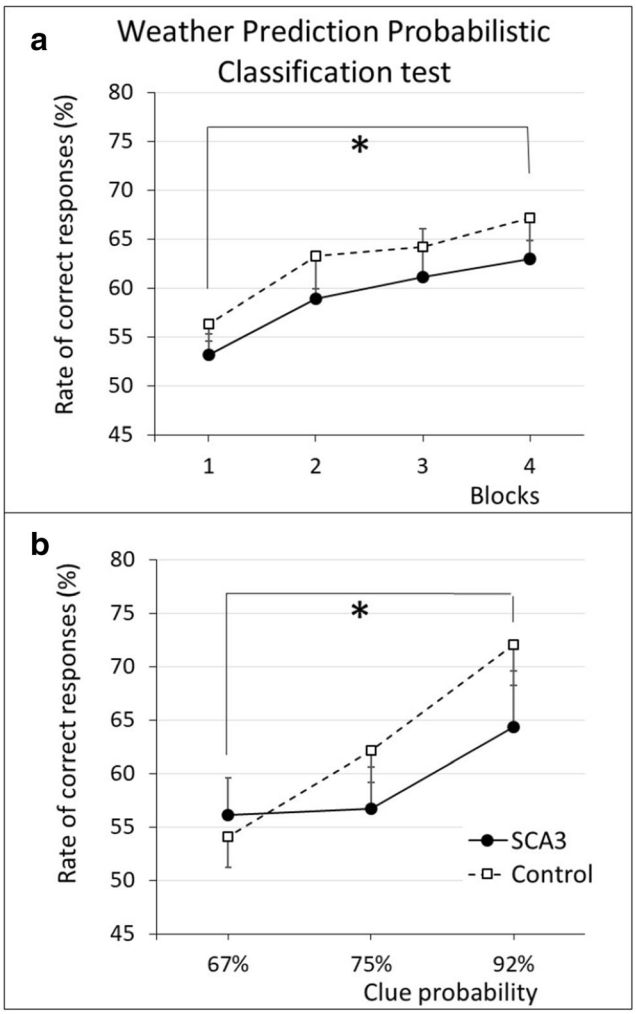

Fig. 3 Learning on the Weather Prediction Probabilistic Classification test. **a** Rate of correct responses (mean ± SEM) along blocks of the task for SCA3 and control participants. Both groups demonstrated similar learning rate (*blocks effect; $p < 0.001$). **b** Rate of correct responses (mean ± SEM) along clues probability. Both groups demonstrated similar rate of learning (*clues probability effect; $p < 0.001$)

In summary, SCA3 showed declarative learning within the normal range on all parameters of the WPPCt.

Correlations Between Cognitive Tests

Two-tailed Pearson correlations between scores on cognitive tests (block 9 of the Rey-AVLt, block 4 of the WPPCt, and block 7 minus 6 of the mean of median RT of the SRTt) were calculated separately for SCA3 and control groups. The above blocks were chosen because they reflect the final level of learning on each of the tasks. In both SCA3 and control, no significant correlations were found between the scores on different cognitive tests.

Correlations Between Performance on Cognitive Tests and Clinical and Genetic Indices

Within the SCA3 group, two-tailed Pearson correlations between cognitive tests (block 9 of the Rey-AVLt, block 4 of the WPPCt, and block 7 minus 6 of the mean of median RT of the SRTt), clinical indices (disease duration, ataxia score on SARA scale), or genetic indices (number of CAG bases repeats) were calculated. No significant correlations were found between the cognitive tests and clinical or genetic indices.

Discussion

After years of research focusing primarily on the motor symptoms of SCA patients, there has been also an increasing interest in their associated cognitive impairments [20,56,57]. For example, in early publications, mild memory deficiency was reported in only 2 out of 143 SCA3 patients [14]. In contrast, recent studies depict variable and dynamic cognitive profiles, likely affected by the progressive nature of the disorder and expansion of the structural and functional deficits from the cerebellum to the cerebrum [8]. Cerebellar degeneration is a ubiquitous anatomical finding in SCA [58]. In the present study, the SCA3 patients demonstrated ataxia of moderate severity with the highest SARA score of 17, out of a maximum score of 40 [45]. Also, in contrast to previous studies [20,56,57,59–61], patients scored within normal range on the BDI-II depression scale. Given such a relatively benign clinical state of the patients, combined with a generally slow progressive nature of the SCA [62], we could assume a limited spread of degeneration to the cerebrum and could predict modest cognitive impairment on tasks targeting the declarative cerebral systems. Indeed, present SCA3 sample showed normal performance on the Rey-AVLt that tests verbal working memory, learning rate, proactive and retroactive interference, immediate recall, and memory of temporal order. An exception was a mild impairment on a delayed recall, which replicates previous findings [21]. The fact that SCA3 patients performed within the norm range in practically all measures of the Rey-AVLt implies that the cognitive deficits in SCA3 are not a result of general cognitive decline. The absent of significant correlation found between the performance on Rey-AVLt, SRTt, and WPPCt implies that these cognitive components are dissociated.

Based on previous studies, we hypothesized that spinocerebellar degeneration affects procedural sequence learning [63]. Indeed, present SCA3 sample showed impaired procedural learning of the sensory-motor sequence on the SRTt. They showed no improvement in reaction time over the six learning blocks and no increase in reaction time on the seventh transfer block, implying selective sequence learning impairment. The high RT specially on the first block and the lack of improvement throughout the test reflect the expected motor impairment of the patients. Curiously, patients showed a decrease in the number of errors along the eight blocks of the SRTt. This observation does not necessarily imply procedural sequence learning since no increase in the number of errors was observed in the transfer block, actually in both groups. Rather, the decrease in number of errors implies stimulus-response learning. The procedural sequences learning impairment can be ascribed to the diffuse atrophy of the cerebellar cortex, cerebellar output nuclei, or pontine brainstem inputs to the cerebellum [64] that are often found in SCA patients. Indeed, the 1.5-T brain magnetic resonance imaging (MRI) of our patients done as part of their clinical work-up revealed diffuse central nervous system atrophic changes, particularly in the cerebellar hemispheres, vermis, and brainstem. These MRI images did not allow us to identify specific nuclei or areas of the cerebellum and brainstem that have degenerated preferentially, making any association with the learning impairment unfeasible. However, similar learning impairment was associated with damage to basal ganglia in Parkinson disease [29,32,65], Huntington disease [66], and patients with focal basal ganglia infarcts [36]. Obviously, both nodes of the cerebellar-basal ganglia network are essential for sequence learning [32], and therefore, an isolated finding of impairment on SRTt is not indicative of selective damage.

In contrast to the impaired performance of the SCA3 patients on the procedural SRTt, they showed normal performance on the WPPCt that is also considered as a procedural learning test. Patients showed normal learning pattern along blocks and along clues probability. To the best of our knowledge, we are the first to show that the probabilistic classification learning, despite being procedural, is preserved in SCA3 patients. This result reinforces previous assumption that WPPCt-related cognitive probabilistic judgment is not affected by cerebellar degeneration [35]. Our SCA3 sample includes patients with relatively low SARA score and half of them with less than 6-year disease duration. These clinical measures did not correlate with the cognitive impairment, possibly due to the small sample. Further studies including a

larger population with a long-term follow-up are necessary to clarify the relationship between cognitive changes and disease severity and progression.

These findings show that there is dissociation within the procedural memory between impaired sequence learning and normal performance in probabilistic classification learning in SCA3 patients. This reasoning is in line with the assertion that the anatomical basis of procedural learning is not homogenous [28]. The fact that no correlation was found between the SRTt and the WPPCt reinforces the assumption that these are two separate cognitive structures. A possible explanation for this procedural dissociation is the involvement of sequence learning in the SRTt but not in the WPPCt test. This assumption is supported by previous studies that highlighted the importance of cerebellum in sequence learning [67]. Further studies would examine SCA3 patient with other procedural tests that involve sequence learning (i.e., Tower of Hanoi [33]) and that do not involve sequence learning (i.e., Mirror reading test [36]). We predict that the Tower of Hanoi will be impaired, while the Mirror reading will be preserved.

In summary, SCA3 is associated with selective impairment of procedural sensory-motor but not statistical-prediction tasks. SCA3 shows preserved declarative memory except for delayed recall.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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