Neuropsychological Features of Patients with Spinocerebellar Ataxia (SCA) Types 1, 2, 3, and 6

Ina Klinke · Martina Minnerop · Tanja Schmitz-Hübsch · Marc Hendriks · Thomas Klockgether · Ullrich Wüllner · Christoph Helmstaedter

Abstract A subtype-specific impairment of cognitive functions in spinocerebellar ataxia (SCA) patients is still debated. Thirty-two SCA patients (SCA1, 6; SC2, 3; SCA3, 15; SCA6, 8) and 14 matched healthy controls underwent neuropsychological evaluation testing attention, executive functions, episodic and semantic memory, and motor coordination. Severity of ataxia was assessed with the Scale for the Assessment and Rating of Ataxia (SARA), nonataxia symptoms with the Inventory of Non-Ataxia Symptoms. Depressive symptoms were evaluated with the Beck Depression Inventory. The SARA scores of our SCA patients (range 1–19.5) indicated an overall moderate ataxia, most pronounced in SCA6 and SCA1. Mean number of nonataxia symptoms (range 0–2.2) were most distinct in SCA1 and nearly absent in SCA6. SCA1 performed poorer than controls in 33% of all cognitive test parameters, followed by SCA2, SCA3, and SCA6 patients (17%). SCA 1–3 patients presented mainly attentional and executive dysfunctions while semantic and episodic memory functions were preserved. Attentional and executive functions were partly correlated with ataxia severity and fine motor coordination. All patients exhibited mildly depressed mood. Motor and dominant hand functions were more predictive for depressed mood than cognitive measures or overall ataxia. Besides motor impairments in all patients, SCA patients with extracerebellar pathology (SCA 1–3) were characterized by poor frontal attentional and executive dysfunction while mild cognitive impairments in predominantly cerebellar SCA6 patients appeared to reflect mainly cerebellar dysfunction. Regarding the everyday relevance of symptoms, (dominant) motor hand functioning emerged as a marker for the patient's mood.

Keywords Spinocerebellar Ataxia (SCA) · Cerebellum · Cognition · Attention · Executive functions

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Introduction

The spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of autosomal-dominantly inherited neurodegenerative disorders, characterized by prominent ataxia and cerebellar atrophy. Up to now, almost 30 different gene loci have been identified. In six SCAs (SCA 1, 2 3, 6, 7, 17) the mutation is a translated CAG repeat expansion coding for an elongated polyglutamine tract within

the respective protein. The consecutive degenerative process can either be rather limited to the cerebellum (e.g., in SCA6) or may involve further extracerebellar structures, as in SCA 1–3, the most common forms of SCA [1].

A possible subtype-specific impairment of cognitive functions in SCA patients is still debated [2, 3]. SCA1, 2, and 3 are associated with deficits in executive functions and verbal memory [4], and additional impairments in visual memory, visuoconstruction, and visual attention have been described in SCA3 [5–7]. Burk et al. documented dementia in 25% of one SCA2 sample and impairments in verbal memory and phonemic word fluency in a non-demented SCA2 group [8]. Recently, cognitive impairments were also reported in SCA6 patients [9, 10].

The sole function of the cerebellum as a motor control structure has been questioned in several studies, and cognitive functions have been ascribed to it in addition [11–14]. Anatomical studies described connections between the cerebellum and prefrontal lobe via cerebello-ponto-thalamico-cortical pathways [15]. PET and fMRI studies showed evidence of cerebellar activation during pure cognitive tasks [16–18]. Clinical studies further suggested participation of the cerebellum in executive functions, like selective attention, strategic planning, decision making, and working memory. Even behavior associated with frontal lobe functioning like control of affect is related to functioning of the cerebellum [19]. Other studies emphasized normal cognitive functions in patients with cerebellar disorders or attributed cognitive deficits to additional extracerebellar involvement [20, 21]. The major difficulty in comparing cognitive properties of cerebellar disease patients is the heterogeneity of extracerebellar involvement. Therefore, Timmann and Daum proposed a comparison of patients with purely cerebellar disorders in order to determine the specific cerebellar contribution to cognition [22]. We tried to execute this proposal by comparing cognitive profiles of predominantly cerebellar disease patients (SCA6) with patients that show additional extracerebellar involvement (SCA 1–3).

The aim of the present study was to clarify (1) whether patients with SCA 1, 2, 3, and 6 have cognitive impairments regarding attention, executive functions, episodic, and semantic memory; (2) whether these impairments are independent from motor control problems; and (3) to evaluate a possible SCA subtype-specific pattern of cognitive deficits.

Materials and Methods

Participants

The study comprised two asymptomatic SCA1 carriers and 32 SCA patients, selected from the SCA outpatient clinic of the Department of Neurology, University Hospital of Bonn. All patients were examined neurologically and rated according to the Scale for the Assessment and Rating of Ataxia (SARA) and the Inventory of Non-Ataxia Symptoms (INAS) [23, 24]. Two female asymptomatic SCA1 carriers, six patients with SCA1, three with SCA2, 15 with SCA3, and eight with SCA6 were investigated. Fourteen healthy matched controls for age, sex, and IQ—mostly spouses of the patients—served as controls. Further patient characteristics are given in Table 1.

All subjects were tested with an extensive neuropsychological test battery comprising tests of attention, executive functions, episodic and semantic memory, and motor control. All subjects signed informed consent. The study was approved by the Ethics Committee of the University of Bonn.

Neuropsychological Battery

Attention

Processing speed was examined with a symbol-counting task (subtest 1 of the *c.I. Test*) [25] and psychomotor speed by a simple and a choice reaction time task which are part of the computerized neuropsychological screening test battery *NeuroCogFX* [26].

Executive Functions

– Phonemic verbal word fluency was assessed via a German oral word-fluency test (subtest 6 of the *Leistungsprüfsystem*) [27]. Subjects had to generate as many words as possible starting with a given letters within 1 min. This was done three times with different letters. The total sum of words was the variable of interest.
– The subtest response inhibition of the *c.I. Test* requires inverse reading of a string of the letters A and B (e.g., AABAB as BBABA) [25]. The time needed to read the two rows including the time needed for corrections represent the score.
– Inverse choice reaction with a reversal of the target and non-target stimuli was tested with the *NeuroCogFX* computer test [26]. Besides reaction time, the number of errors was assessed.
– Planning was assessed via the *Tower of Hanoi* [28]. This task requires shifting of a tower consisting of four disks with increasing size from one peg (out of three) to another peg under the condition that no larger disk is placed on top of a smaller one. The number of trials needed to complete the test was the dependent measure.

Table 1 Means and standard deviations (SD) of neuropsychological test performance in SCA 1, 2, 3, 6 patients and controls

NP Test	Controls (N=14) (Mean±SD)	SCA1 (N=6) (Mean±SD)	SCA2 (N=3) (Mean±SD)	SCA3 (N=15) (Mean±SD)	SCA6 (N=8) (Mean±SD)
Clinical data					
Sex (m/f)	7/7	3/3	0/3	9/6	6/2
Age [years]	48.1±11.8	45.7±9.9[b]	53.0±4.6[b]	42.2±9.6[b]	60.0±8.9[b,c]
Age of onset [years]	–	36.3±7.6[b]	44.7±3.2[b]	37.2±11.0[b]	51.0±6.8[b]
Disease duration [years]	–	9.3±6.4	8.3±1.5	5.7±3.5	9.0±5.4
Repeat length of exp. Allele	–	47.2±3.5	36.0±0.0	71.7±3.9	21.7±0.8
SARA	–	12.5±4.7	3.8±1.4	8.2±6.4	12.6±4.8
INAS	0.0±0.0	2.2±0.8	1.0±1.0	1.1±1.3	0.1±0.4
BDI	4.71±5.88	11±4.24[b,c]	7±4.36	5.29±3.94[b]	11.38±2.33[b,c]
Handedness (right/left/both)	13/1/0	5/0/1	2/0/1	12/3/0	8/0/0
Motor functions					
Gross motor coordination[a]	4.79±1.21	8.00±2.10[c]	5.30±1.53	5.86±3.21	8.88±3.72[c]
Fine motor coordination[a]	72±10.98	26.83±13.64[b,c]	45±4.58[c]	48.2±14.57[b,c]	28.29±12.55[b,c]
Attention					
Processing speed					
Symbol counting test[a][s]	16.64±2.74	29.00±10.18[b,c]	21.00±1.00	21.73±5.96[b,c]	25.75±8.60[c]
Psychomotor speed					
Simple+choice reaction [s]	336.31±62.27	463.00±69.82[c]	508.33±170.01[c]	395.61±137.15	408.71±114.12
Executive functions					
Tower of Hanoi	29.43±6.91	29.08±9.33	24.50±5.29	29.00±8.64	27.94±9.51
Phonemic Word Fluency	13.17±4.44	9.22±2.21[c]	11.44±4.86	8.73±2.86[c]	10.17±4.34
Response Inhibition[a] [s]	19.79±4.44	26.00±6.16	21.67±2.52	25.13±7.88	29.25±10.46
Inverse choice reaction [s]	385.23±77.27	565.60±137.60[c]	652.67±213.38[c]	456.07±132.54	507.57±146.88
Inverse choice errors[a]	0.23±0.6	0.83±2.04[b]	0±0[b]	0.43±0.94[b]	2.57±1.81[b,c]
Episodic memory					
Verbal memory	13±2.42	12±1.55	12.33±2.52	12.13±3.02	10.88±3.27
Figural learning	7.71±2.13	6.40±1.52	7±2	8±1.57	4.88±3
Semantic memory					
Vocabulary: MWT-B-IQ	110.79±13.55	111.83±11.27	130.00±6.00	116.46±13.22	114.25±18.78
Boston naming test	57.67±2.53	54.5±2.67	58.33±2.73	56.36±2.73	55.29±4.19
Semantic word fluency test	21.29±5.62	15.50±4.18	17.67±4.16	17.33±5.77	18.00±5.29

SARA Scale for the Assessment and Rating of Ataxia, *INAS* Inventory of Non-Ataxia Symptoms

[a] Marks tests that correlate with ataxia severity

[b] Significant differences between the patient groups in post-hoc analyses

[c] Significant differences between a patient group with the control group

Episodic Memory

– Verbal memory was assessed with the VLMT (Verbaler Lern- und Merkfähigkeitstest, [29]) a German version of the *Rey Auditory-Verbal Learning Test*. A list of 15 nouns is to be learned and immediately recalled in five consecutive trials. This is followed by learning and immediate recall of a second word list in one trial, unexpected free recall after distraction, and again after a 30-min delay and a recognition trial in which learned words are to be recognized from a list with distractors. From all possible scores of this test, the total number of words correctly recalled after a delay of 30 min was chosen as the parameter of interest ("verbal memory") since this is the most sensitive and most representative score for the assessment of verbal long-term memory [30].

– Figural memory was assessed by a revised version of the *Diagnosticum für Cerebralschädigung* [31]. This list-learning test requires learning and reproduction of

nine abstract designs composed of five lines in six consecutive learning trials by use of five sticks of equal length. From this test, the number of correctly reproduced designs in the last learning trial (learning capacity) served as the parameter of interest ("figural learning"). Since very poor performers often do not proceed to the 6th trial, this parameter best reflects the performance in this test.

Semantic Memory

– The *Mehrfachwahl Wortschatz Interferenztest* (*MWT-B*) is a vocabulary test which comprised 37 rows composed of four words and required word vs. non-word recognition [32]. Performance on this test is a good indicator for crystallized intelligence and highly correlated with the level of education.
– The *Boston Naming Test* requires confrontation naming and also reflects semantic memory by means of crystallized intelligence [33]. Sixty line drawings are to be named and the number of incorrect answers served as outcome parameter.
– Finally, categorical semantic word fluency for animals in a 60-s interval was assessed.

Motor Functions

– Gross motor coordination was examined with a motor sequencing task adopted from Luria [34]. This task requires rapid alternation of uni- and bimanual motor sequences. The sum of the four subscores was used as the total score with higher scores representing poorer performance (score range 4–16 points). Procedure and scoring of this test have been described elsewhere [35].
– Fine motor coordination was assessed with the *Purdue Pegboard* [36]. The participant had to plug as many pegs as possible into small holes vertically arranged on a Pegboard using either left or right hand and both hands simultaneously. A fourth test required an assembly using both hands. These scores were merged into one total score with higher scores representing better performance.

Ataxia Severity

The SARA is based on a semiquantitative assessment of cerebellar ataxia and includes eight items (gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, heel-shin slide). It yields a total score from 0 (no ataxia) to 40 (very severe ataxia). Scale validation studies in the past demonstrated a good correlation with disease stages [23, 37, 38].

Nonataxia Symptoms

Nonataxia symptoms were assessed with the INAS. The INAS is a clinical description counting presence or absence of 16 binary variables up to a simple sum score of nonataxia symptoms in each patient [24].

Depression

The *Beck Depressive Inventar* (BDI) measures emotional distress rather than major depression and, therefore, serves as an indicator of depressed mood [39]. This test consists of 21 questions reflecting the most frequent symptoms of depression. Eleven points and above are defined as a mild depressed mood while 18 points and more correspond to a more severe form of depressed mood.

Statistical Analysis

Statistical comparisons were conducted by separate one-way ANOVAs and ANCOVAs specifying group as independent variable and the respective test scores of the cognitive domains as dependent variables. Post hoc paired group comparisons were measured with the Fisher's least significant difference (LSD) test.

The groups differed significantly in age and age at disease onset. To differentiate disease related from normal age related cognitive decline, age correction was included as a covariate in all ANCOVA. Differences with $p<0.05$ were considered as significant. The scores for "gross motor coordination" and "errors" in the inverse choice reaction task were not normally distributed. For these measures, nonparametric Mann–Whitney U tests were calculated additionally. The χ^2 test was used to compare nonparametric ataxia scores and the distribution of sexes. Correlation analyses were conducted using linear regression analysis between the SARA score and each test result of the patients, BDI score, disease duration, age at onset of disease, sex of the patient, and repeat length of the expanded allele. Moreover, we also calculated correlations between fine motor coordination and all test scores of the patients.

For an overall comparison of the cognitive impairment between the different patient subgroups, a summary score was calculated by summing up all cognitive tests exhibiting significant differences between the patient subgroup and controls in the analyses described above. Twelve test scores were taken into account (see Table 1). Finally, taking published normative data as reference, patient scores were rated as impaired versus unimpaired when standardized test scores were below or within the range of the mean±1.5 standard deviation of the norm.

Results

Chi-square testing showed equal sex distribution in all groups. ANOVA revealed significant differences in age ($p=0.005$) and age at disease onset ($p=0.009$) but no difference regarding disease duration (see Table 1). SCA6 patients were significantly older and had a later disease onset compared to all other groups (see Table 1).

Summing up all cognitive test scores in which patients deviated significantly from controls, we found only mild cognitive impairment. SCA1 patients had deficits in four out of 12 cognitive test scores (33%), SCA2, SCA3, and SCA6 in two out of 12 tests parameters (17%), respectively. Both asymptomatic SCA1 gene carriers had normal results in all cognitive, emotional, and motor tests (data not shown).

Deviations of patients from healthy controls in different neuropsychological domains (expressed by Z scores) are illustrated in Fig. 1.

Attention and Reaction Times

Groups (patient groups and controls) differed significantly in processing speed as assessed by *symbol counting* ($F(4,40)=4.880$, $p=0.003$). LSD post hoc comparison revealed that SCA1 ($p<0.0001$), SCA6 ($p=0.013$), and SCA3 ($p=0.022$) patients performed significantly slower than controls. Moreover, SCA1 performed significantly worse than SCA3 ($p=0.03$).
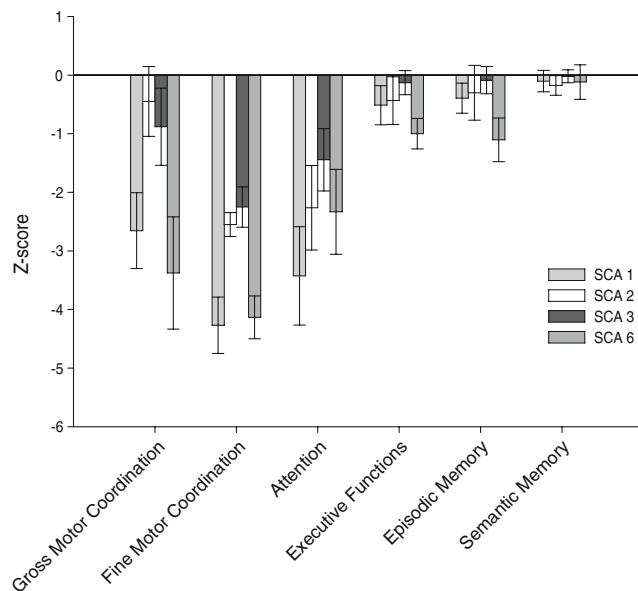
All SCA1 patients (100%), 67% of SCA2 patients, 80% of SCA3 patients, and 75% of our SCA6 patients performed below test norms.

Groups also differed significantly in psychomotor speed ($F(4, 36)=2.667$, $p=0.048$). According to post hoc analysis, SCA1 ($p=0.013$) and SCA2 ($p=0.031$) patients showed slower reaction times than controls (Table 1). Evaluating simple and choice reaction times separately and comparing them to test norms, SCA1 (60%/60%) and SCA2 (67%/67%) showed longer simple and choice reaction times more frequently than SCA3 (21%/50%) or SCA6 (43%/14%).

Executive Functions

Groups did not differ in their performance on the Tower of Hanoi task, not one patient scored within the impairment range. Groups did, however, significantly differ in phonemic verbal fluency ($F(4, 40)=2.989$, $p=0.03$). Post hoc comparison revealed that SCA1 ($p=0.033$) and more distinctly SCA3 ($p=0.002$) patients produced significantly fewer words than controls. In contrast to the Tower of Hanoi task, all patients were rated as impaired according to the test norms in this task.

No significant differences between groups were detected in response inhibition, ($F(4, 40)=2.419$, $p=0.064$). However, LSD post hoc comparisons showed a trend for mild deficits in SCA3 and SCA6 when compared to controls ($p=0.018$ and $p=0.041$). Categorization of patients into impaired/ unimpaired patients revealed that 50% of SCA1 patients, 47% of SCA3, and 67% of SCA6 showed impaired performances. SCA2 subjects were not impaired when compared to test norms.

Performance was different among groups in the inverse choice reaction task ($F(4, 36)=3.863$, $p=0.01$). SCA1 ($p=0.005$) and SCA2 ($p=0.004$) showed a significantly poorer performance than controls did.

SCA6 patients did not show any prolonged reaction time, but they produced more errors during the inverse choice reaction task than every other patient or control group; main effect: ($F(4, 37)=5.268$, $p=0.002$), post hoc comparisons: (controls ($p<0.0001$), SCA1 ($p=0.014$), SCA2 ($p=0.002$), SCA3 ($p<0.0001$)). Mann–Whitney U testing revealed the same results. When compared to test norms, not only SCA1 (80%) and SCA2 (67%) but also 29% of SCA3 and 43% of SCA6 patients showed impaired performances.

Episodic and Semantic Memory

Group differences were found neither in verbal or visual memory nor in the vocabulary test MWT-B, confrontation naming task, and semantic word fluency test (Table 1).

Fig. 1. Neuropsychological deficits of SCA 1, 2, 3, and 6. Deviations of patients from healthy controls in different neuropsychological domains are expressed by Z scores

When compared to test norms, 13% of SCA3 and SCA6 patients, respectively, scored below the norms in the total number of words recalled after a delay of 30 min (verbal memory). Figural learning was impaired in two SCA6 patients (25%) when compared to test norms. No patient performed below the norm in the vocabulary test MWT-B. Only one SCA6 patient performed below the norms in the confrontation naming task. Patients were more frequently impaired in semantic fluency when compared to test norms: 50% of SCA1, 33% of SCA2, and 27% of SCA3 patients scored at least 1.5 standard deviations below the norm. No SCA6 patients showed deviation from the norm in this test.

Motor Function

All but one control subject (93%) were right-handed as compared to 27 of the 32 patients (84%; Fisher Test $p=0.45$).

The task on gross motor coordination produced significant group differences (F (4, 39)=3.047, $p=0.028$). SCA1 ($p=0.008$) and SCA6 ($p=0.015$) scored worse than controls. Mann–Whitney U testing revealed the same results. When compared to test norms, 83% of SCA1, 33% of SCA2, 14% of SCA3, and 75% of SCA6 patients scored below test norms.

Groups also differed in fine motor coordination (F (4, 45)= 14.305, $p<0.0001$). All patient groups, SCA1 ($p<0.0001$), SCA2 ($p=0.003$), SCA3 ($p<0.0001$), and SCA6 ($p<0.0001$) performed significantly worse than controls. Additionally, SCA1 ($p=0.008$) and SCA6 ($p=0.011$) performed worse than SCA3. When compared to normative data, nearly all patients were impaired. Only three SCA3 patients (20%) showed an average performance in the subtest executed with the dominant hand (two right-handed and one left-handed patient). One of these patients and additionally one SCA6 patient scored normal in the assembly subtest. In all other subtests, all patients scored at least 1.5 SDs below the norm.

Evaluating to which degree the impairment of fine motor coordination affects cognitive functions, significant correlations were mainly found with tests that exhibit speed components like symbol counting ($r=0.71$, $p<0.0001$), simple and choice reaction time ($r=0.48$, $p=0.009$), response inhibition ($r=0.67$, $p<0.0001$), inverse choice reaction time ($r=0.46$, $p=0.013$), and semantic word fluency ($r=0.39$, $p=0.03$).

Ataxia

The mean SARA score was 9.3 (range 3.8–12.6) and most severe in SCA6 (12.6) and SCA1 (12.5) followed by SCA3 (8.2) and SCA2 (3.8). These differences were not significant (F (3, 31)=2.776, $p=0.06$).

Significant correlations were found between ataxia severity (SARA scores), performance on symbol counting ($r=0.57$, $p=0.001$), response inhibition ($r=0.45$, $p=0.01$), and number of errors during the inverse choice reaction task ($r=0.45$, $p=0.002$). The correlation between ataxia severity and gross and fine motor coordination was also significant ($r=0.52$, $p=0.003$ and $r=0.6$, $p<0.0001$, respectively). All other tests did not significantly correlate with the SARA scores. Regarding the patient characteristics, neither disease duration nor age at disease onset, sex, or repeat length showed significant correlations with ataxia severity.

Nonataxia Symptoms

The mean number of nonataxia symptoms ranged between 0 and 2.2 and were more often present in SCA1 (2.2), SCA2 (1.0), and SCA3 (1.1) and nearly absent in SCA6 (0.1). Found nonataxia symptoms included mostly areflexia (legs), sensory symptoms (legs), and brainstem oculomotor signs. In single patients, muscle atrophy (legs), rigidity (in one SCA3 patient), spasticity (legs), dystonia (torticollis in one SCA1 patient), or urinary dysfunction was documented. Since the INAS score merely counts symptoms and is not a true scale, no further correlation analyses were performed.

Depression

The SCA groups differed significantly in degree of depressed mood as assessed with the BDI (F (4, 40)= 3.81, $p=0.01$). Post hoc group comparison revealed that SCA1 and SCA6 showed more pronounced depressed mood than controls and SCA3 (p value ranging between 0.014 and 0.005).

No patient showed scores indicating severely depressed mood (BDI score ≥18). Mildly depressed mood (BDI score 11–18) was indicated in 75% of SCA6 patients, 50% of SCA1 patients, 33% of SCA2 patients, and 13% of SCA3 patients. Interestingly, 14% of controls scored between 11 and 18 points. All other participants scored below 11 points in the BDI questionnaire, which corresponds to no depressive symptoms.

The correlation between patient's SARA and BDI scores was not significant ($r=0.32$, $p=0.073$). However, when taking the test data into account, depressed mood was highly correlated with gross and fine motor coordination ($r=0.52$–0.54, $p<0.03$–0.002). Taking dominant and non-dominant hand motor functions separately into consideration, depressed mood was mostly correlated with dominant hand performance (hand performance in gross and fine motor coordination: dominant: $r=0.5$–0.63, $p< 0.005$–0.0001; non-dominant: $r=0.38$–0.58, $p<0.03$–

0.0001). Apart from figural learning ($r=0.43$, $p=0.01$), response inhibition ($r=0.42$, $p=0.02$), and inverse choice reaction ($r=0.38$, $p=0.04$), none of the remaining test parameters on attention, speed, fluency, naming, planning, vocabulary, or verbal memory were significantly correlated with BDI scores.

Discussion

SCA patients primarily suffered from motor problems of different degrees. The SARA scores of our SCA patients ranged between 1 and 19.5 (SCA1 5.5–17, SCA2 3–5.5, SCA3 1–18, SCA6 4.5–19.5) indicating an overall moderate ataxia. Accordingly, all patients showed problems in distal fine motor coordination. Problems in gross motor coordination (proximal) were evident in group comparison only in SCA1 and SCA6 patients who also exhibited the most severe ataxia. Nonataxia symptoms were only present in SCA1, 2, 3 and one individual SCA6 patient. These symptoms mainly included brainstem oculomotor signs and areflexia/ sensory symptoms of legs—most likely due to SCA-related polyneuropathy.

Regarding the core question of this study, we observed cognitive impairments in our SCA patients, particularly in frontal attentional and executive functions. Three tests (symbol counting, response inhibition, and number of errors in inverse choice reaction) correlated with ataxia severity (SARA score) whereas all other tests appeared largely ataxia-independent. Fine motor coordination, as the most sensitive indicator for motor impairment in SCA, was correlated to tests requiring a speed component but affected only one out of the three measures of executive function which differentiated patients from controls (inverse choice reaction).

Going into more detail, SCA1 patients showed the broadest range of impairments in that they scored poorer than controls in 33% of all cognitive test parameters. Patients with SCA2 and SCA3 in contrast showed impairments in only 17% of test scores. The pattern of impairment with reduced processing speed and prolonged reaction times (attention), reduced phonemic verbal fluency, and reduced cognitive flexibility (executive functions) strongly suggests frontal lobe associated impairment of executive functions in SCA1, 2, and 3. Taking published normative data as the reference, semantic fluency was partly impaired in SCA1, 2, and 3, not in SCA6. Considering the fact that no such difference was seen between patients and controls or within the patient groups, we tend to interpret this result to be due to the test norm selection rather than to true group differences. Since the two asymptomatic SCA1 carriers showed normal

cognitive test scores, cognitive dysfunction does not seem to precede cerebellar ataxia.

In contrast to other reports, our group comparison did not confirm previously documented impaired verbal memory in SCA1, 2, and 3 [4, 8, 40, 41]. Whereas the SCA2 group was too small to allow reliable conclusions from these results, SCA1 and SCA3 patients were clearly found to be unimpaired. Since the performance in the *Rey Auditory Verbal Learning Test* has been demonstrated to be strongly related to temporal lobe function, we would suggest that temporal lobe memory function is rather preserved in SCA.

But why did other groups find distinct verbal memory impairment in SCA? A possible explanation may be seen in the fact that different memory tests had been used in the different studies. This is important, since the *California Verbal Learning Test*, the *Wechsler logical memory*, or *Digit Span* from the *Wechsler Memory Test* have much stronger demands on working memory, language processing, and executive functions (organization of learning) than the Rey Auditory Verbal learning test which was used here [42]. Accordingly, these tests must be assumed to pick up the executive impairments in SCA.

Contradictory results may also arise from the heterogeneity of the SCA phenotypes. The presence of nonataxia symptoms is well known in SCA1, 2, and 3 and although a subtype specific pattern of nonataxia symptoms exists, the individual presence or absence varies [24]. As a consequence, the influence of these symptoms on the individual neuropsychological performance and subgroup result is difficult to judge. We assessed nonataxia symptoms in our patient sample with INAS and found brainstem oculomotor signs and signs of polyneuropathy as the most frequently observed nonataxia symptoms in our SCA1, 2, and 3 samples. Brainstem oculomotor signs may have an impact on task execution and performance, respectively, especially in combination with cerebellar oculomotor dysfunctions, found in most SCA patients. It seems, however, unlikely that the observed signs of polyneuropathy, reflecting neuropathological changes at the level of spinal cord or peripheral nerves, have impact on the neuropsychological performance of our patients. However, nonataxia symptoms only observed in single subjects of our patient groups (especially spasticity, rigidity, or torticollis) reflect a more pronounced supratentorial pathology, eventually associated with reduced cognitive abilities in the affected individuals.

All SCA subgroups showed hints of depressed mood. The expression of the indicated mood problem was mild, and not a single patient showed a score indicative for a more severe depression. SCA1 and SCA6 patients who also suffered from the most severe ataxia appeared more affected than the other groups. While no relation between SARA scaling and mood was indicated, highly significant

correlations became evident for gross and fine motor coordination. The highest correlation was found to right, i.e., the dominant hand functioning for our group. Apart from three scores on tests involving visual memory or executive functioning (figural learning, response inhibition, and inverse choice reaction), none of the remaining test parameters were correlated to depression scores. It should be noted that this correlation pattern is not characteristic for patients with major depression who often present nonspecific slowing and diffuse cognitive impairment interrelated with severity of depression. Thus, in line with literature, depression in SCA appears reactive to the perceived motor impairment rather than an organic consequence of the disease [43]. Elevated depression scores in the control group—mostly patient's spouses—may well be discussed as a reflection of being affected by the patient's disease.

Patients with SCA6, neuropathologically regarded as a predominantly cerebellar syndrome, showed significant impairments in only two cognitive scores, symbol counting (attention), and the amount of errors in the inverse choice reaction task (executive function). A nonsignificant trend only pointed towards further executive dysfunction in the test response inhibition, but all three scores are related to motor impairment and/or ataxia severity. Poor performance in these tests can either be explained by motor problems during task execution or by a cerebellar involvement in cognitive operations. Given that one of the three tests requires fast visuomotor search (symbol counting) and deficits were found in all other SCA groups, cerebellar occulomotor problems may explain this finding [44]. The SCA6 sample was older than our control group, and it cannot be ruled out that our findings in SCA6 are attributed to the age difference between both groups. However, the comparison to age-corrected normative data rather supports the idea of impairment. SCA6 patients made more errors in the inverse choice reaction task than the other SCA groups. Prolonged reaction times present in other SCA groups but not in SCA6 may assist in avoiding errors and could be a possible explanation for increased error rates being found only in SCA6 and not in other SCA groups. Whether prolonged reaction times are caused by SCA-type-specific pathology or rather reflect an acquired compensatory mechanism remains to be determined.

The question of a cerebellar contribution to cognitive operations like attention and executive functions is still under discussion [14]. The cerebellum projects via cerebello-ponto-thalamo-cortical pathways to the frontal cortex [15] and loss of cerebellar efferents to the cortex might cause cognitive impairments. This hypothesis is supported by studies in healthy subjects and patients with cerebellar lesions describing severe cognitive and emotional disturbances in patients with isolated cerebellar pathology [11, 45, 46]. However, apart from two studies which documented impairments of visual memory, phonemic, and semantic verbal fluency and cognitive flexibility in parallel to a cerebellar and prefrontal hypoperfusion [9, 10], other publications found normal cognitive functioning or only trends towards mild frontal deficits in SCA6 [47]. Differences regarding the acuity of cerebellar damage or involved cerebellar regions can be considered as possible explanations. Acute cerebellar lesions may have qualitatively different consequences for cognition and emotion as opposed to slow progressive degenerations like in SCA6. Furthermore, ischemic or traumatic lesions may affect more cerebellar tissue—white matter or cerebellar nuclei—than degeneration in SCA6, in which mainly Purkinje cells are involved. The idea of a cerebellar involvement in cognitive functioning is strongly supported by our finding of significant abnormal test results in comparison to published norms in SCA6 that seem to exceed motor impairment. Motor-independent cognitive tests in pure cerebellar patients with either acute or chronic damage are indispensable to further clarify the role of the cerebellum in cognition.

Conclusion

In sum, our results for SCA1, SCA2, and SCA3 patients point towards motor independent neuropsychological impairments of frontally associated functions rather than temporal lobe related functions: although an impact of a subtype-specific pattern of cerebellar pathology, e.g., the involvement or sparing of Purkinje cells or dentate nucleus, cannot be ruled out, we suggest that the more pronounced cognitive motor independent impairments in SCA (1, 2, and 3) patients are mainly attributable to extracerebellar degeneration. As thalamic or basal ganglia pathology has been described in all three subtypes (but not in SCA6), disruption of basal ganglia-thalamocortical loops may well be the morphological substrate for the observed cognitive impairment in these subtypes [3, 48–50]. However, concerning every day relevance for SCA patients, cognitive impairments did—in contrast to (dominant) motor hand functioning—not appear to affect the patient's mood.

Conflict of interest statement The authors declare that they have no competing personal or financial interests.

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