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The Cerebellar Cognitive Affective/Schmahmann Syndrome Scale in Spinocerebellar Ataxias

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Declarations

Ethics Approval Approval was obtained for study procedures at all sites via the local IRB at each institution, and all participants gave informed consent. The central sites (UCLA for CRC-SCA and Houston Methodist for READISCA) prepared the original IRB documents that were used by all participating sites during their local reviews.

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Abstract

The Cerebellar Cognitive Affective/Schmahmann Syndrome (CCAS) manifests as impaired executive control, linguistic processing, visual spatial function, and affect regulation. The CCAS has been described in the spinocerebellar ataxias (SCAs), but its prevalence is unknown. We analyzed results of the CCAS/Schmahmann Scale (CCAS-S), developed to detect and quantify CCAS, in two natural history studies of 309 individuals Symptomatic for SCA1, SCA2, SCA3, SCA6, SCA7, or SCA8, 26 individuals Pre-symptomatic for SCA1 or SCA3, and 37 Controls. We compared total raw scores, domain scores, and total fail scores between Symptomatic, Pre-symptomatic, and Control cohorts, and between SCA types. We calculated scale sensitivity and selectivity based on CCAS category designation among Symptomatic individuals and Controls, and correlated CCAS-S performance against age and education, and in Symptomatic patients, against genetic repeat length, onset age, disease duration, motor ataxia, depression, and fatigue. Definite CCAS was identified in 46% of the Symptomatic group. False positive rate among Controls was 5.4%. Symptomatic individuals had poorer global CCAS-S performance than Controls, accounting for age and education. The domains of semantic fluency, phonemic fluency, and category switching that tap executive function and linguistic processing consistently separated Symptomatic individuals from Controls. CCAS-S scores correlated most closely with motor ataxia. Controls were similar to Pre-symptomatic individuals whose nearness to symptom onset was unknown. The use of the CCAS-S identifies a high CCAS prevalence in a large cohort of SCA patients, underscoring the utility of the scale and the notion that the CCAS is the third cornerstone of clinical ataxiology.

Keywords

Cerebellar cognitive affective syndrome; Scale; Spinocerebellar ataxia; Cognition

Introduction

The Cerebellar Cognitive Affective/Schmahmann Syndrome (CCAS) [1] describes the cognitive and neuropsychiatric profile associated with cerebellar disease and injury. Conceptualized as the third cornerstone of clinical ataxiology alongside the cerebellar motor syndrome and the vestibulocerebellar syndrome [2], the CCAS is characterized by deficits in executive function, visuospatial function, linguistic processing, and affect regulation [1–4]. The CCAS has been described in both adult and pediatric populations and in both acute and chronic cerebellar conditions [1, 4–12] including the autosomal dominant spinocerebellar ataxias (SCAs). It has been conceptualized as a manifestation of dysmetria of thought and disruption of the cerebellar contribution to the distributed neural circuits subserving cognition and emotion [13–16].

The polyglutamine SCAs are autosomal dominant neurodegenerative disorders characterized by cerebellar ataxia and caused by expanded genetic repeat sequences [17]. The nature of the resulting cellular dysfunction, neuropathology, and phenotypic profile varies across different SCA types [17]. Cognitive deficits have been observed in SCA patients with overt cerebellar motor dysfunction [18–20] and may have an important impact on individuals' daily functioning and relationships. It is therefore important to test for and identify the CCAS in the clinical setting.

The Cerebellar Cognitive Affective/Schmahmann Syndrome Scale (CCAS-S) is a 10-domain scale developed as a screening measure for the presence of the CCAS in individuals with known cerebellar disease or injury [21]. Since its publication in 2018, the CCAS-S has been applied to several cerebellar disease and injury cohorts. In SCA2, SCA3, and SCA6, 36–91% of individuals met criteria for Definite CCAS based on failure of 3 or more domains [22–24], with performance on the CCAS-S showing moderate-to-large associations with disease duration and motor ataxia rating scale scores [22–24]. False positives in matched control groups ranged from 13 to 36% in a mixed cerebellar degeneration cohort and were more prevalent in older individuals and in those with lower educational level [25]. These findings motivate further investigation into the presence of the CCAS in the SCAs and an exploration of factors potentially underlying inter-individual variability on the scale. It remains unknown whether the CCAS-S is sensitive to cognitive changes that may precede the onset of motor symptoms in SCAs (see [26]).

Our aims in this study were to evaluate the prevalence of CCAS in a large, mixed cohort of patients with SCA; investigate the ability of the CCAS-S to discriminate between people with Symptomatic SCA, Pre-symptomatic SCA, and Controls; and to explore the influence of demographic and other factors on interindividual variability in CCAS-S performance.

Methods

We analyzed data in two natural history studies of patients with SCA: the Clinical Research Consortium for the Study of Cerebellar Ataxia (CRC-SCA; 2009-) and Clinical Trial Readiness for SCA1 and SCA3 (READISCA; 2018-) [27]. CRC-SCA included individuals symptomatic for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, or SCA10. READISCA

included individuals who were symptomatic for SCA1 or SCA3, and individuals who were at-risk for SCA1 or SCA3 due to family history, but who did not have symptoms of SCA and whose confirmed gene status was unknown to investigators.

Participants in the natural history studies conducted in 18 sites across the USA undergo a comprehensive battery of clinical assessments with longitudinal follow-up (Supplementary Materials; Fig. S1). CCAS-S administration commenced in 2016. Both studies had ongoing participant enrolment at the time of this investigation. The earliest assessment used for this analysis was in May 2016, and the latest in November 2021.

Participants

Participants with at least one CCAS-S assessment were extracted from the databases. Cases were retained for analysis if the first recorded CCAS-S was complete, i.e., none of the 10 domains had been omitted.

Individuals with self-reported motor ataxia symptoms from both the CRC-SCA and READISCA studies at the time of the first CCAS-S visit were classified as being Symptomatic. The results of genetic analysis of the SCA1 or SCA3 genes were reviewed for individuals in the READISCA study who did not have self-reported motor ataxia symptoms at the time of the visit but were enrolled due to being at-risk for SCA1 or 3. Individuals without motor ataxia who were subsequently found to be gene-positive were classified as Pre-symptomatic, and those who were determined to be gene-negative were classified as Controls. Cases with inconsistent or missing information regarding SCA type or the onset of ataxia symptoms were excluded from analysis ($n = 28$).

Three-hundred and nine Symptomatic, 26 Pre-symptomatic, and 37 Control individuals with valid data were identified. Baseline characteristics of these three groups are summarized in Table 1. The Symptomatic group included individuals with SCA1 ($n = 58$), SCA2 ($n = 52$), SCA3 ($n = 132$), SCA6 ($n = 47$), SCA7 ($n = 11$), and SCA8 ($n = 9$). The Pre-symptomatic group included 11 individuals who were gene-positive for SCA1 and 15 gene-positive for SCA3.

One Control participant failed 5 CCAS-S domains (case not included in Table 1). This is inconsistent with performance in a cognitively healthy individual, and the subject was excluded.

Demographic and clinical information within each SCA type, among the Symptomatic and Pre-symptomatic groups, is presented in Supplementary Table S1.

Analysis Variables

Data from a single time point corresponding to the first CCAS-S assessment were included in the analyses. We evaluated the following clinical assessments for each subject.

The CCAS-S has 10 domains which probe semantic fluency, phonemic fluency, category switching, forward digit span, reverse digit span, cube draw and copy if needed, verbal recall, abstraction, go/no-go performance, and an evaluation of the presence of

neuropsychiatric symptoms. The sum of the raw score for each domain produces a total raw score, range = 0–120, a granular measure of cognitive and affective performance. A unique feature of the scale is that each domain has a pass/fail cut-off score (Supplementary Table S2). Based on the number of failed tests observed in patients and controls during scale development (the fail score), failure of one of the ten domains is considered to represent Possible CCAS, two domains failed to represent Probable CCAS, and three or more domains failed to represent Definite CCAS [21].

The Scale for the Assessment and Rating of Ataxia (SARA) [28] is an 8-item neurological examination used as a measure of motor ataxia severity. The total scale score ranges from 0 to 40, with higher scores indicating greater motor impairment. The scale comprises examiner ratings of performance for gait, stance, sitting, speech, finger chase, nose-finger, fast alternating hand movements, and heel-shin slide.

The Brief Ataxia Rating Scale (BARS) [29] is a 5-item neurological examination evaluating gait, heel-to-shin, finger-to-nose, speech, and oculomotor performance, also used as a measure of motor ataxia severity. The total scale score ranges from 0 to 30, with higher scores indicating greater motor impairment.

The Functional Staging of Ataxia Scale is a 1-item scale included in the Friedreich Ataxia Rating Scale [30] which indicates an individual's overall functional ability based on motor symptoms. Scores range from 0 (normal) to 6 (total disability).

Fatigue was measured with the Fatigue Severity Scale (FSS), a nine-item self-report rating scale which uses a 7-point rating scale from 1 = strongly disagree to 7 = strongly agree. A higher total score indicates higher impact of fatigue on functioning [31].

Depressive symptoms were measured with the Patient Health Questionnaire-9 (PHQ-9), a nine-item self-report which uses a 4-point rating scale from 0 = not at all to 3 = nearly every day. A higher total score indicates greater depression severity [32].

Participants' educational attainment was obtained as either the highest level of education (e.g., High School, Master's Degree) or total number of years of education. Highest level of education was converted to number of years of education as follows: Less than High School, < 12 years; High School/GED, 12 years; Some College, 13 years; Associate Degree, 14 years; Bachelor's Degree, 16 years; Master's Degree, 18 years; Doctorate, > 18 years. All values less than 12 were converted to 11, and values greater than 18 were converted to 19, for the purposes of rank-based statistics.

Age of onset (AO) data was available across multiple ataxia symptoms for 241 of the Symptomatic participants and was defined as the AO of walking problems where relevant, which was the case for 232/241 participants. In other cases, AO of walking problems was not reported, and AO of ataxia was instead defined by AO of speech problems ($n = 2$), balance problems ($n = 5$), falling ($n = 1$), or hand problems ($n = 1$). In the remaining 68 Symptomatic cases, AO was missing, unknown, or was reported but not linked to a specific symptom.

Statistical analyses

Statistical analyses and graphical outputs were generated using RStudio Server Pro (R Version 4.1.2).

Discriminative Ability of the CCAS-S

To evaluate the discriminative ability of the scale, CCAS-S total raw scores and fail scores were compared between the three cohorts (Symptomatic, Pre-Symptomatic, and Control). Welch's ANOVA was performed due to non-equal variance in raw and fail scores between groups. Welch's ANOVA was also used to compare the performance of different SCA types within the Symptomatic group. Games-Howell tests with correction for multiple comparisons were used for post-hoc analyses following all significant ANOVAs.

To evaluate group differences in CCAS-S performance while controlling for the influence of age and education, both parametric ANCOVAs and robust ANCOVAs with no parametric assumptions were employed due to violation of statistical assumptions.

Individual CCAS-S domain performance was assessed, with individual domain scores compared between the Symptomatic, Pre-Symptomatic, and Control groups and between the different SCA types within the Symptomatic group. The proportion of individuals failing each domain (based on the cut-off scores presented in Table S2) was compared between the Symptomatic and Control groups using Fisher's exact test.

Sensitivity and Selectivity

CCAS-S performance in the Symptomatic and Control groups was used to evaluate the sensitivity and selectivity of the scale (1-false positive rate) in differentiating between individuals with and without a cerebellar condition. The term selectivity relates to the ability of the scale to distinguish between individuals with a known cerebellar disorder and healthy controls. The term *specificity* is avoided because the current data do not include patients with non-cerebellar disorders, and therefore, it cannot be claimed that these findings are specific to patients with cerebellar disease. Sensitivity and selectivity were obtained for each of the Possible (1 failed domain), Probable (2 failed domains), and Definite (≥3 failed domains) CCAS categories. Sensitivity was calculated as the percentage of Symptomatic individuals who failed ≥3 domains, out of all Symptomatic individuals. Selectivity, i.e., the ability of the scale to select between individuals with a known cerebellar disorder and healthy controls, was calculated as the percentage of Control individuals who did *not* fail ≥3 domains, out of all Control individuals.

Areas under the receiver operating characteristic curve were also calculated to evaluate the ability of the total raw score and fail score to discriminate between the Symptomatic and Control groups.

Factors Influencing CCAS-S Performance

We evaluated the effect of age and educational attainment on CCAS-S performance by correlating CCAS-S total raw score and fail score against age at assessment and years of education in the Symptomatic and Control groups.

Within the Symptomatic group, CCAS-S total raw score and fail score were correlated against the number of genetic repeats on the expanded allele, AO, and disease duration, and against total scores on the SARA, BARS, Functional Staging of Ataxia, PHQ-9, and FSS, and our newly-developed S-Factor for the polyQ SCAs which incorporates CAG repeat length and disease duration into a single metric of disease severity as follows [33]:

$$S-factor=\frac{Q_e-Q_{max}}{Q_{max}}\times(Current\ \ age-AO)\times 10$$

where Q_e = number of repeats in the CAG repeat expansion,

Q_{max} = maximum number of repeats in the normal / non−expanded allele, and

AO = age at disease onset.

Results

See Supplementary Materials for additional descriptive statistics related to these results.

Ability of the CCAS-S to Differentiate Symptomatic, Pre-Symptomatic, and Control Groups

Global Performance—Total CCAS-S raw and fail scores by diagnostic group are illustrated in Fig. 1 (see also Tables S3 and S4).

Welch's ANOVA revealed that total raw score differed by symptom status (Symptomatic, Pre-symptomatic, Control), Welch's $F(2, 56.09) = 69.57$, $p < .001$. Effect size was calculated as an adjusted omega-squared, est.$\omega^2 = 0.27$; that is, 27% of the variance in total raw score was accounted for by symptom status. A Games-Howell post-hoc test indicated a significantly lower mean total raw score in the Symptomatic group ($M = 88.53$, $SD = 15.04$) compared to both the Control group ($M = 105.51$, $SD = 7.28$) ($p < .001$) and Pre-symptomatic group ($M = 101.04$, $SD = 12.04$) ($p < .001$), with no significant difference between the Pre-symptomatic and Control groups ($p = .22$).

Fail score also differed by symptom status (Symptomatic, Pre-symptomatic, Control), $F(2, 61.74) = 60.60$, $p < .001$, est.$\omega^2 = 0.25$. A Games-Howell post-hoc test indicated a higher mean fail score in the Symptomatic group ($M = 2.60$, $SD = 2.07$) compared to both the Control group ($M = 0.70$, $SD = 0.81$) ($p < .001$) and Pre-symptomatic group ($M = 0.92$, $SD = 1.32$) ($p < .001$), with no difference between the Pre-symptomatic and Control groups ($p = .70$).

Within the Symptomatic group, Welch's ANOVA showed no significant effect of SCA type on total raw score ($F(5, 46.16)=1.65$, $p = .166$) or fail score ($F(5, 46.10)=1.80$, $p = .133$).

Given the influence of education on CCAS-S performance, and the small effect of age combined with the older age of the Symptomatic group compared to the Control and Pre-symptomatic group, we conducted supplementary analyses to investigate whether the group effects remained when education and age were statistically controlled for, in the subset of individuals with valid education and age data (183 Symptomatic, 15 Pre-symptomatic, and 24 Control participants).

We conducted parametric ANCOVA analyses investigating the effects of Symptom status on CCAS-S total raw and fail score, with education and age entered as covariates (Table S5). The data violated parametric test assumptions such as homogeneity of variance, raising concern about the interpretation of the results. We therefore conducted additional robust ANCOVA analyses that had no parametric assumptions, which allowed for comparison of two groups with one covariate [34]; the Symptomatic and Control groups were contrasted across two ANOVAs, one covarying for age and one for education (Tables S6a and S6b). In the robust ANCOVA analyses, total raw and fail scores were compared between the Symptomatic and Control groups at each of a set of automatically generated design points. The design point for the age analysis (years of age) were as follows: 21.75, 37.74, 43.91, 50.11, and 55. The design points for the education analysis (years of education) were 15, 16, and 17.

Both ANCOVA approaches indicated that total raw and fail scores differed significantly between the Symptomatic and Control groups even when controlling for age and education.

Performance on Individual CCAS-S Domains

The raw scores obtained on each of the 10 CCAS-S domains, by diagnostic group, are shown in Table 2 and Fig. 2. Detailed results regarding the effect of Symptom status (Symptomatic, Pre-symptomatic, Control) and SCA type on raw score and proportion of failures are presented in Supplementary Tables S7 and S8. Semantic fluency, Phonemic fluency, and Category switching which tap executive function and language processing were the most sensitive to group differences and most consistently differentiated Symptomatic from Control individuals after controlling for age and education. With regard to the effect of SCA type, significant differences were observed for the go / no-go domain: SCA1 patients scored lower than the SCA3 and SCA6 groups, but there were no SCA type-specific differences for any other CCAS-S domain (Table 3).

Sensitivity and Selectivity of the CCAS-S

Across the whole sample, sensitivity to the detection of Possible, Probable, and Definite CCAS in patients with SCA was 83.2%, 63.1%, and 46.0%, respectively, and selectivity for the demonstration that Controls did not have Possible, Probable, or Definite CCAS was 45.9%, 89.2%, and 94.6%, respectively. Sensitivity within each SCA type is presented in Table S9a. The proportions of individuals within each diagnostic group meeting criteria for the CCAS categories are presented in Tables S3 and S4, and Fig. S3.

Given the concern about false positives for CCAS designation with older age, the sensitivity calculations were repeated among participants aged under 65 [35], see Table S9b. Sensitivity among all Symptomatic individual aged under 65 was 81.5%, 62.6%, and 45.4% for Possible, Probable, and Definite CCAS, respectively. Selectivity remained unchanged as all Controls were aged under 65 years.

The receiver operating characteristic curve showing the ability of the CCAS-S to differentiate between Symptomatic and Control individuals had an Area Under the Curve of 0.84 for total raw score and 0.79 for fail score (Fig. S4).

Influence of Demographics, Disease, and Clinical Variables on CCAS-S Performance

Age—In the group of 291 Symptomatic individuals with valid age data, there was a small but significant correlation between age and CCAS-S total raw score, $r(289) = -0.14$, $p = .015$, age accounting for 2% of the variance, and between age and fail score, $r(289) = 0.13$, $p = .024$, age accounting for 1.8% of the variance (see Fig. 3a,b).

For comparison, we conducted correlations between age and CCAS-S performance in the Control group and found that age was not associated with either total raw score ($r(35) = 0.01$, $p = 0.965$) or fail score ($r(35) = -0.05$, $p = 0.790$) (Fig. 3a,b).

The age range in the Control group was restricted relative to that in the Symptomatic group. To aid comparison of the within-group correlations, the age vs. CCAS-S correlation was repeated among Symptomatic participants within the same age range as controls (26.66–59.99 years). The correlations remained small but significant for total raw score, $r(204) = -0.18$, $p = .011$, and fail score, $r(204) = 0.15$, $p = .036$ (Fig. S2).

Education—In the 184 Symptomatic individuals with valid education data, years of education (rank data) had a significant, moderate, positive association with total raw score, $r_S(182) = 0.36$, $p < .001$, and a significant, moderate, negative association with fail score, $r_S(182) = -0.36$, $p < .001$. Years of education accounted for 12.6% of the variance in total raw score and 12.9% in fail score (Fig. 3c,d).

In the 24 Control individuals with valid education data, years of education showed a trend towards correlation with total raw score ($r_S(22) = 0.39$, $p = 0.059$) and no correlation with fail score ($r_S(22) = -0.14$, $p = 0.531$). This analysis was underpowered relative to the correlations in the Symptomatic group, and the correlation coefficients indicate a moderate relationship with total raw score (15.3% variance accounted for) and a small correlation with fail score (1.81% variance accounted for) (Fig. 3c,d).

Correlations with Disease and Clinical Variables

The correlations of CCAS-S total raw score and fail score against disease parameters and clinical assessments for each SCA type within the Symptomatic group are presented in Table 4. Sample sizes were too small to conduct meaningful correlations within the SCA7 and SCA8 groups. The SCA3 group was more than double the size of all other SCA groups, and therefore, correlations for SCA3 were better powered than correlations in other SCA types. For this reason, correlations were conducted across the combination of individuals with SCA1, 2, 6, 7, and 8 to investigate whether disease and clinical variables were associated with CCAS-S performance in non-SCA3 individuals.

The variables that showed the most consistent association with CCAS-S total raw score and fail score across SCA types were the motor ataxia rating scales, namely, the SARA, BARS, and Functional Staging of Ataxia. Greater motor impairment was associated with lower CCAS-S performance (Fig. 4).

The CCAS-S total raw and fail scores correlated with the following disease and clinical variables in SCA3: AO, disease duration, SARA, BARS, Functional Staging of Ataxia,

Patient Health Questionnaire-9 total, Fatigue Severity Scale (FSS) total score, and the S-Factor. CAG repeat length on the expanded allele correlated with total raw score but not fail score in SCA3. In the other SCA types, and in the combined SCA1, 2, 6, 7, and 8 group, CCAS-S performance showed associations with the same disease and clinical parameters, although not as uniformly as in SCA3.

Small to moderate correlations were observed between better CCAS-S performance and lower self-reported fatigue and depression symptoms.

Discussion

We evaluated performance on the CCAS-S in the largest-to-date cognitive study of individuals with SCA. We confirmed the ability of the CCAS-S to differentiate between healthy controls and individuals with SCA. There was variability in CCAS-S performance among individuals with SCAs but minimal differences between different SCA types. We identified clinical measures that were associated with performance, and we add to converging evidence that education and age influence scale performance, with a stronger effect of education compared to age.

The CCAS Is Present Almost Half the Individuals in a Mixed SCA Cohort

We found that 46% of patients in our mixed SCA cohort met criteria for Definite CCAS. This replicates the sensitivity of 46% observed in the original validation cohort of individuals with a variety of cerebellar disorders [21]. Sensitivity across each CCAS category remained essentially stable after excluding individuals aged over 65, indicating that sensitivity was not driven by the presence in our cohorts of this older age group in which there may be a higher incidence of undiagnosed cerebral pathology [35].

The Profile of CCAS-S Performance in the SCAs

A key finding with respect to CCAS-S performance among individuals with SCAs was inter-individual variability; some performed within the range of controls, whereas others performed below this level. This is consistent with the understanding that only a subset of those diagnosed with SCA experience cognitive impairments. This range of performance was most clearly seen with respect to total raw and fail scores but can also be observed in individual CCAS-S domains.

In terms of the pattern of cognitive performance, individuals with symptomatic SCA as a group performed below the average of the Controls in eight of the ten CCAS-S domains when age and education were not considered. The largest effect sizes were observed for the verbal fluency tasks (Semantic fluency, Phonemic fluency, Category switching), which also most consistently showed group differences after covarying for age and education. These findings are in agreement with prior studies showing that patients with cerebellar disorders are impaired on phonemic and semantic fluency tasks [1, 4, 36, 37] even when slower naming speed of the cerebellar patients was taken into consideration [38].

We also evaluated potential differences in CCAS-S performance between SCA types. The autosomal dominant SCAs each involve a different pathological process and a different

pattern of neuropathology [39, 40]. Therefore, we may expect differences between SCA types in the pattern of performance across cognitive tasks, as has been reported in neuropsychological studies [41–43]. However, the CCAS-S and its individual domains did not differentiate the six SCA types in our cohort. In particular, and consistent with the findings of Hoche et al. [21], in our cohort, the CCAS-S did not show differences in performance between individuals with SCA6, considered to involve relatively pure cerebellar pathology, and SCA types with more complex cerebro-cerebellar pathology such as SCA2. Similarity in performance across SCA types may indicate that CCAS-S domain performance is mainly reflective of cerebellar dysfunction as opposed to pathology in other brain regions like the cerebrum. Correlating brain imaging measures such as cerebellar volume against CCAS-S performance across different SCA types may be useful to test this hypothesis. It is also possible that the screening nature of the CCAS-S may lessen its ability to differentiate between SCA types compared to in-depth neuropsychological testing.

For the first time, our study describes cognitive performance in individuals with Pre-symptomatic SCA1 and SCA3. As a group, these Pre-symptomatic individuals did not differ from Controls in either CCAS-S total scores or on any of the individual CCAS-S domains. The Pre-symptomatic cohort size was limited, however, and we were not able to differentiate between individuals who may be closer to motor onset than others, and whether time to motor onset is related to cognitive performance. In other words, are individuals closer to motor onset more similar on the CCAS-S to Symptomatic individuals, compared to those who are further from onset? We were also restricted to Pre-symptomatic SCA1 and SCA3, and it will be important to evaluate other genetic SCAs such as SCA2 in which cognitive changes have been reported before the onset of motor symptoms [26].

False Positive Rates on the CCAS-S

As a measure of scale *selectivity*, we found the false positive rate for Definite CCAS in the Control group to be 5.4%, higher than 0% in the original validation control group [21] but similar to the 5% reported in controls matched to individuals with Friedreich's Ataxia [22]. The mean ages of the control groups in these three studies (present study, Hoche et al [21], Thieme et al [22]) were similar, at 39.8, 40.4, and 40.4 years, respectively. In contrast, false positive rates were higher in the control groups of other studies, in which subjects had higher mean ages [22–25, 44]. This is consistent with Thieme et al.'s [25] finding of higher false positives in an older control sub-cohort (60–90 years) compared to a younger sub-cohort (21–50 years). Given the limited age range of our Control group (all aged < 60), we cannot directly comment on the potential for reduced selectivity among older individuals, but this is an important area for further investigation. Our findings have relevance for future versions of the CCAS-S to improve scale selectivity. The receiver operating curve results (Fig. S4) suggest that it would be preferable to reduce the number of fail scores among Controls rather than, for example, increasing the threshold for CCAS designation. Specifically, the curve showed that changing the criteria of Definite CCAS to failure of 4 domains would produce 100% selectivity in our cohort, at the expense of severely reduced sensitivity (30%).

Education had a moderate impact on global CCAS-S performance accounting for more than 12% of variance in performance, but there was a wide range of performance within most

educational levels. This was exemplified by two outliers in our Control cohort who met criteria for Definite CCAS despite 16 years of education. Our limited Control group data precluded us from drawing firm conclusions about how educational attainment affected scale selectivity, i.e., whether individuals were more likely to be incorrectly classified as having CCAS if they had a shorter educational history.

Associations Between CCAS-S Performance and Other Features of SCAs

A key finding with respect to CCAS-S performance in individuals with SCAs is the inter-individual variability; some performed within the range of Controls, whereas others performed below this level. This is consistent with the understanding that not all patients with SCA experience cognitive impairments at every stage of the disorder. While further investigation is warranted into who is most at-risk of the CCAS, our correlational analyses provided some insights into factors underlying interindividual variability.

The most consistent correlate of CCAS-S performance across SCA types was disease severity, as measured by the SARA, BARS, and Functional Staging of Ataxia scale. Associations between the CCAS-S and motor severity measures have been reported previously in individuals with SCAs [23, 24] and other cerebellar conditions [21, 45]. Our finding in this cohort that motor and cognitive dysfunction are correlated could reflect cerebellar degeneration of both motor and cognitive regions of cerebellum, a consequence of the shared underlying pathophysiology. In our cross-sectional cohort, we cannot comment on whether motor and cognitive symptoms evolve together within individuals.

We found small to moderate associations between disease duration and CCAS-S performance in patients with SCA2 and SCA3. Moderate correlations in SCA3 were also reported by Maas et al. [23] and Thieme et al. [22]. This should motivate investigation into the longitudinal trajectory of CCAS-S performance, including in Pre-symptomatic individuals. It will be valuable to determine in future studies whether the covariance of CCAS-S and SARA or BARS performance can be observed in the same subjects over time.

CCAS-S performance did not correlate with CAG repeat length or AO in most SCA types, consistent with previous CCAS-S investigations in genetic ataxias. However, we found, for the first time, significant but small correlations in SCA3, with a greater number of CAG repeats and an earlier AO associated with lower total raw scores and an earlier AO associated with a higher number of failed items. The fact that this finding was not found previously may reflect the statistical power of our large SCA3 cohort. It may therefore be prudent to avoid over-interpreting the absence of significant associations between CCAS-S performance and disease/clinical variables in our SCA1, SCA2, and SCA6 groups, each of which had fewer than half the number of SCA3 participants.

Fatigue and depression symptoms are important and inter-related features of SCAs [46–48]. These correlated with CCAS-S global performance to a small to moderate degree in the expected direction (i.e., poorer performance with worse depression and fatigue), although not consistently among SCA types. In combination with the significant correlates discussed above, these disease features may help explain some of the inter-individual variability in CCAS-S performance among individuals with symptomatic SCAs.

Limitations and Future Research Directions

The Control group consisted of individuals who were at-risk for having SCA1 or SCA3 by virtue of a family history of the diagnosis, in whom subsequent genetic testing indicated that they did not carry the genetic mutation. It is possible that individuals in this group had conditions impacting performance on the CCAS-S that were not screened for in the natural history study. The Control group was also small, not matched to the Symptomatic cohort, and the analyses of the discriminative ability of the CCAS-S when controlling for age and education were limited by incomplete age and education data for some Controls. Further development of the scale might consider ways to accommodate the effects of age and education.

The results of the selectivity analysis and the proportions of Controls failing individual CCAS-S domains provide useful information for further scale refinement. For example, the domains with the highest fail rate in Controls were Digit span forward and Digit span backward. The proportions of individuals failing Digit span forward did not significantly differ between the Control and Symptomatic groups, although other studies have reported Control fail rates for Digit span forward [22, 23]. We are investigating whether digit span false positive rates could be reduced by allowing examinees a second attempt at each digit length.

We were not able to evaluate performance on the CCAS-S over time, as Version 1A was used for serial CCAS-S assessments confounding potential changes in performance with practice effects. It will be important to investigate CCAS-S performance longitudinally using Versions 1B, 1C, and 1D of the CCAS-S, given that progression of cognitive deficits has been reported in SCAs as measured by neuropsychological batteries [8, 49].

The variability in CCAS-S performance among individuals with SCAs provides an opportunity to investigate factors potentially accounting for inter-individual differences. These may include demographics and general health status, as well as the topography of neuropathological changes unique to each patient.

Conclusion

The CCAS-S is a useful tool that identified Definite CCAS in 46% of individuals in a large unselected cohort of patients with spinocerebellar ataxias type 1, 2, 3, 6, 7, or 8. We identify factors associated with CCAS-S performance and confirm that education and age are relevant considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Primary data from the natural history studies (CRC-SCA and READISCA) are housed and curated at the Heath Informatics Institute (HII) at the University of South Florida. Data that serve as the basis for this analysis were downloaded to secure, password-protected Massachusetts General Hospital servers maintained in the Schmahmann Laboratory for Neuroanatomy and Cerebellar Neurobiology. Data are de-identified and available from the senior author upon reasonable request.

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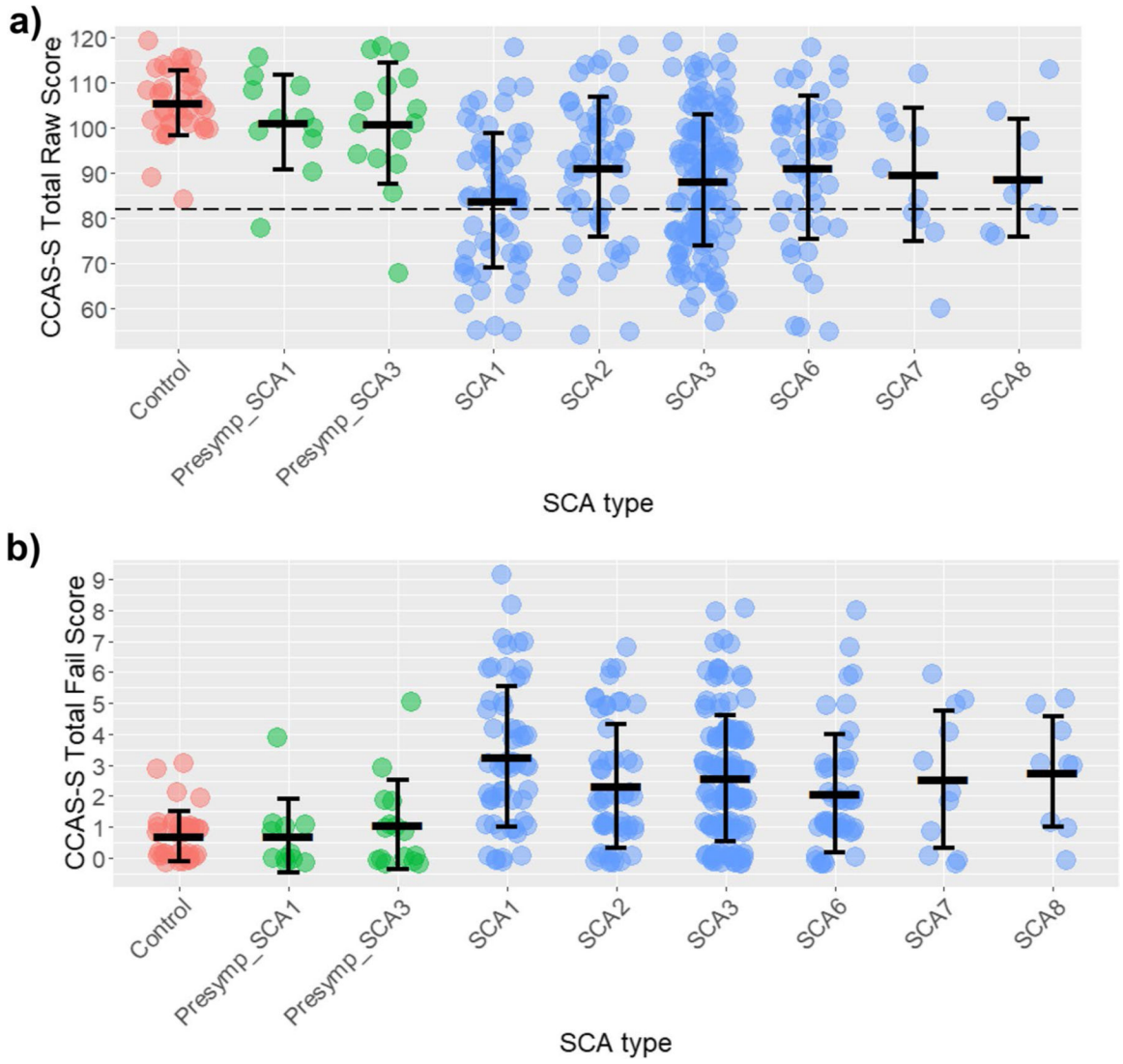

Fig. 1.

Total CCAS-S **a** Raw score and **b** Fail score by diagnostic group. The dashed line at raw score = 82 indicates the score obtained when all CCAS-S items are passed with the minimum score. Error bars indicate Mean +/− 1 standard deviation

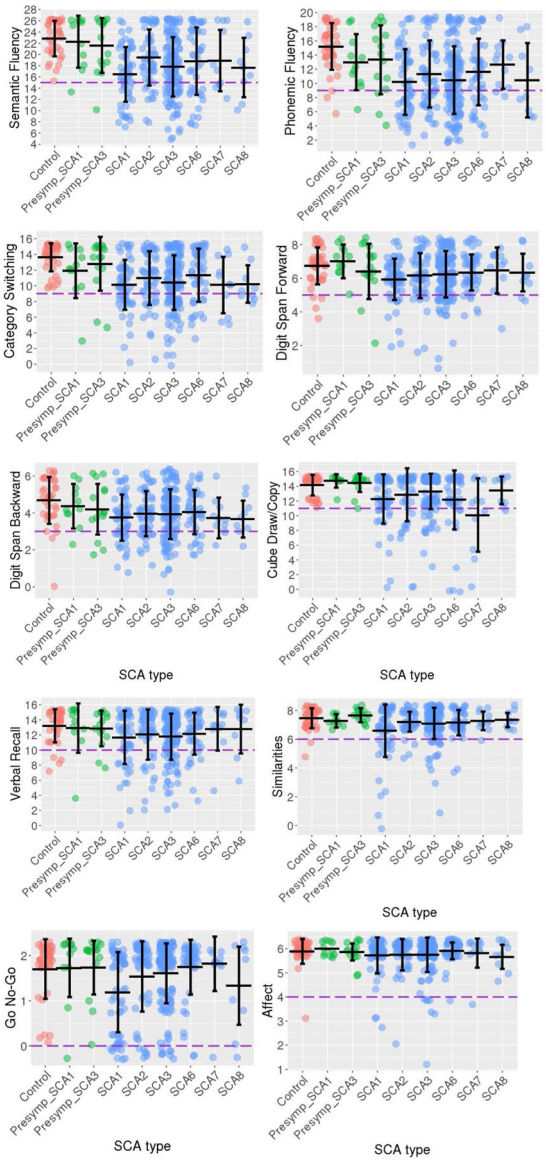

Fig. 2.
Individual CCAS-S item raw scores by diagnostic group

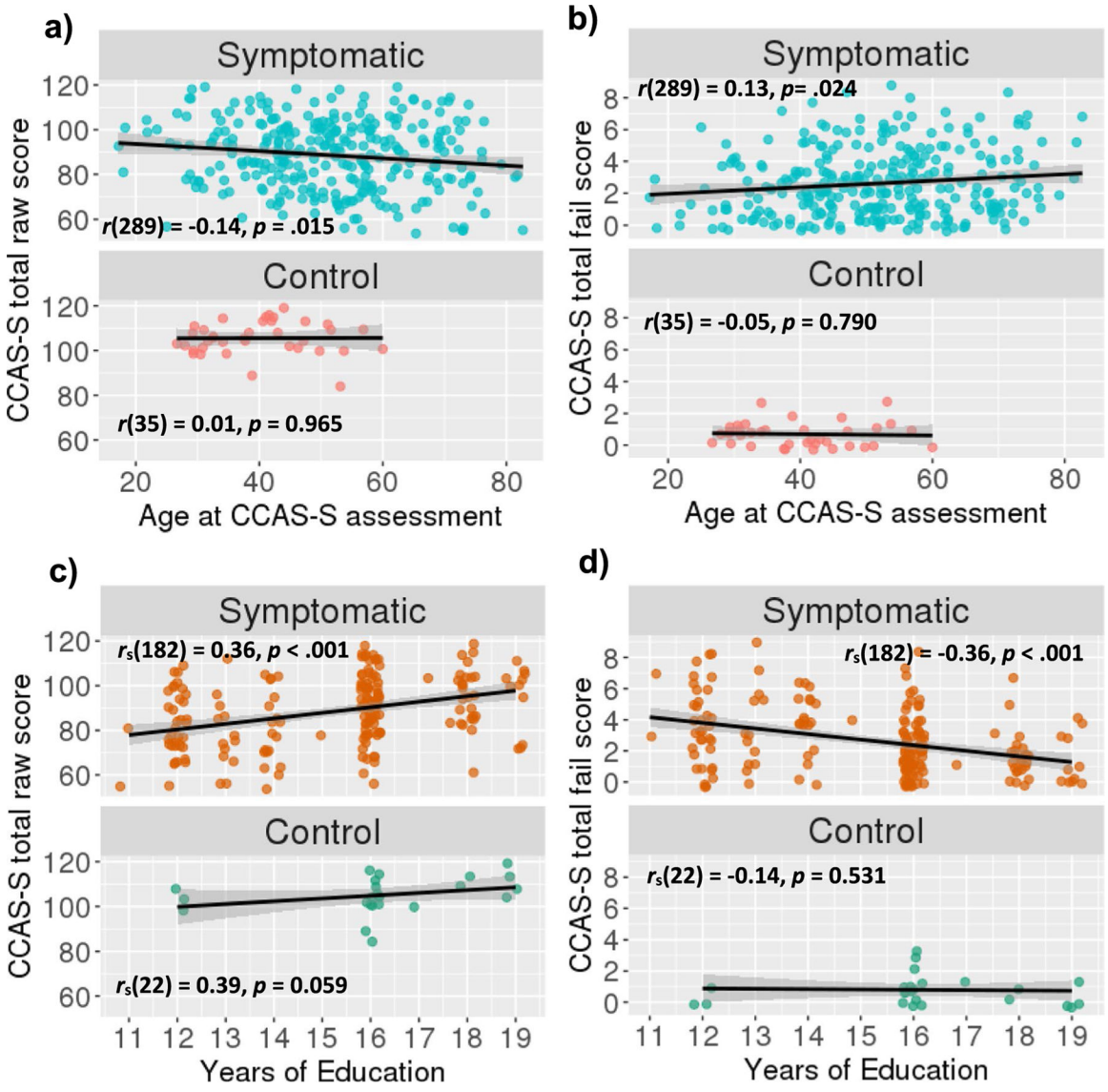

Fig. 3.

Scatterplots of the relationship between Age and **a** CCAS-S total raw score and **b** CCAS-S total fail score, and between Years of Education and **c** CCAS-S total raw score and **d** CCAS-S total fail score, among the Control and Symptomatic groups

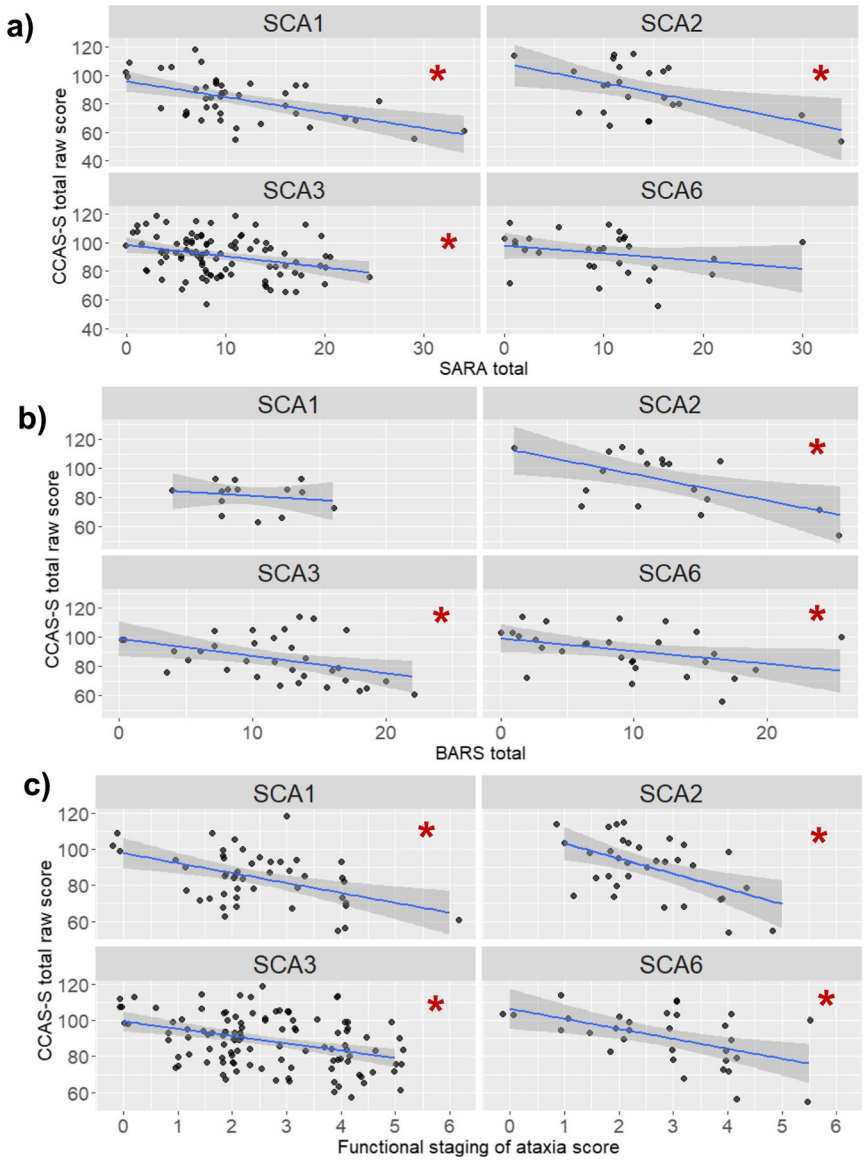

Fig. 4.

Scatterplots of the relationship between CCAS-S total raw score and **a** SARA score, **b** BARS score, and **c** Functional Staging of Ataxia score, by SCA type. *$p < .05$, SARA, Scale for the Assessment and Rating of Ataxia; BARS, Brief Ataxia Rating Scale

Table 1

Demographic and clinical information for study cohort, $N = 372$

Variable	Control	Pre-symptomatic	Symptomatic	Test statistic	*p*-value
Total $n^{\wedge}$	37	26	309		
Age M (SD), [range]	39.81[a] (9.03), [26.66–59.99]	39.02[a] (9.41), [28.59–66.57]	$n = 291$ 51.52[b] (13.52) [17.22–82.67]	Kruskal-Wallis $\chi^2(2) = 45.10$	< .001
Gender, (F:M)	21:16	21:5	$n = 292$ 145:138	Chi-Square test $\chi^2(2) = 7.63$	.022
Years of education, (rank) Median [range]	$n = 24$ 16 [12–19]	$n = 15$ 16 [14–19]	$n = 184$ 16 [11–19]	Kruskal-Wallis $\chi^2(2) = 8.61$	.034
SARA (0–40)	$n = 36$ 0.58[a] (1.09)	$n = 23$ 1.09[a] (1.14)	$n = 205$ 10.55[b] (6.60)	Kruskal-Wallis $\chi^2(2) = 86.96$	.001
Disease duration (years)	N/A	N/A	$n = 240$ 10.23(8.67)		
AO (years)	NA	N/A	$n = 241$ 41.30(12.53)		

Values with different subscript letters (a or b) are significantly different from each other based on Bonferroni-corrected pairwise comparisons using the Wilcoxon rank sum test. AO, age of onset;

$^{\wedge}$,sample size unless otherwise stated in individual cells, showing missing data on some variables

Table 2

Comparison of (a) raw scores and (b) proportion of failures on each CCAS-S domain by symptom status

Item	**Symptomatic (*n* = 309)**	**Pre-symptomatic (*n* = 26)**	**Control (*n* = 37)**			
(a)	**Mean raw score (standard deviation)**			***F***	***p***	**est. ω^2**
Semantic fluency	18.01 (5.34)[a]	21.88 (4.70)[b]	22.84 (3.16)[b]	35.47	< **.001**	0.16
Phonemic fluency	10.81 (4.71)[a]	13.19 (4.42)[b]	15.22 (3.28)[b]	27.75	< **.001**	0.13
Category switching	10.57 (3.38)[a]	12.42 (3.41)[b]	13.62 (1.78)[b]	38.21	< **.001**	0.17
Digit span forward	6.19 (1.29)[a]	6.65 (1.41)[a, b]	6.73 (1.10)[b]	4.68	**.014**	0.02
Digit span backward	3.90 (1.27)[a]	4.27 (1.28)[a, b]	4.68 (1.27)[b]	6.62	**.003**	0.03
Cube draw/copy	12.75 (3.24)[a]	14.58 (1.10)[b]	14.16 (1.40)[b]	23.29	< **.001**	0.11
Verbal recall	11.93 (3.15)[a]	12.88 (2.72)[a, b]	13.22 (2.20)[b]	5.78	**.005**	0.03
Similarities	7.04 (1.18)[a]	7.50 (0.51)[b]	7.46 (0.69)[b]	9.50	< **.001**	0.05
Go no-go	1.54 (0.75)[a]	1.73 (0.60)[a]	1.70 (0.66)[a]	1.93	.156	0.01
Affect	5.77 (0.66)[a]	5.92 (0.27)[a]	5.89 (0.52)[a]	3.04	.055	0.02
(b)	***n* (%) fail**			Fisher exact test (Symptomatic vs. Control); odds ratio		***p***
Semantic fluency	104 (33.7%)	*2 (7.7%)*	1 (2.7%)	18.18		< **.001**
Phonemic fluency	137 (44.3%)	*5 (19.2%)*	3 (8.1%)	8.99		< **.001**
Category switching	109 (35.3%)	*3 (11.5%)*	0 (0%)	Inf		< **.001**
Digit span forward	77 (24.9%)	*3 (11.5%)*	5 (13.5%)	2.12		.153
Digit span backward	112 (36.2%)	*5 (19.2%)*	5 (13.5%)	3.63		**.005**
Cube draw/copy	70 (22.7%)	*1 (3.8%)*	1 (2.7%)	10.51		**.002**
Verbal recall	80 (25.9%)	*3 (11.5%)*	4 (10.8%)	2.88		**.044**
Similarities	51 (16.5%)	*0 (0%)*	2 (5.4%)	3.45		.091
Go no-go	47 (15.2%)	*2 (7.7%)*	4 (10.8%)	1.48		.626
Affect	15 (4.9%)	*0 (0%)*	1 (2.7%)	1.83		1.000

Section (a) results of Welch's ANOVA are reported. In each row, groups that share a superscript letter do not significantly differ from each other based on a Games-Howell post-hoc test with adjusted *p*-values for multiple comparisons. See Supplementary Table S8 for post-hoc test *p*-values for Welch's ANOVA. Effect size is given by est. ω^2 = adjusted omega-squared. Section (a) Fisher's exact test. Significant *p*-values at < .05 are bolded

Table 3

Welch's ANOVA results—effect of SCA type on raw score, for each CCAS-S item

Item	*F*	*p*	Pairwise differences adjusted $p < .05$
Semantic fluency	2.21	.069	N/A
Phonemic fluency	1.30	.282	N/A
Category switching	0.95	.457	N/A
Digit span forward	0.80	.553	N/A
Digit span backward	0.49	.785	N/A
Cube draw/copy	2.15	.077	N/A
Verbal recall	0.51	.768	N/A
Similarities	1.49	.210	N/A
Go no-go	3.30	.012	SCA1 < SCA3, $p = .023$ SCA1 < SCA6, $p = .003$
Affect	1.34	.265	N/A

Pairwise differences assessed using Games-Howell post-hoc test

Table 4

Correlations between CCAS-S total raw score/fail score and disease/clinical variables by SCA type (Symptomatic participants only)

	SCA1			SCA2			SCA3			SCA6			SCA1, 2, 6, 7, 8 combined		
	n	***r***	***p***	***n***	***r***	***p***	***n***	***r***	***p***	***n***	***r***	***p***	***n***	***r***	***p***
CCAS-S total raw score															
CAG repeat expansion	54	−0.059	.669	42	−0.073	.647	120	**−0.216**	**.018**	43	0.051	.745	N/A	N/A	N/A
AO	46	−0.247	.099	36	−0.303	.073	114	**0.192**	**.041**	32	−0.052	.778	127	−0.098	.275
Disease duration	46	−0.012	.939	36	**−0.350**	**.037**	114	**−0.213**	**.023**	32	−0.254	.161	125^	−0.151	0.092
SARA total	44	**−0.528**	**< .001**	23	**−0.517**	**.012**	96	**−0.307**	**.002**	29	−0.262	.170	109	**−0.439**	**< .001**
BARS total	14	−0.183	.531	18	**−0.584**	**.011**	33	**−0.418**	**.016**	28	**−0.377**	**.048**	73	**−0.386**	**< .001**
FSA	48	**−0.456**	**.001**	33	**−0.525**	**.002**	111	**−0.376**	**< .001**	31	**−0.507**	**.004**	128	**−0.475**	**< .001**
PHQ-9 total	40	**−0.421**	**.007**	32	−0.153	.404	93	**−0.291**	**.005**	27	−0.361	.064	113	**−0.220**	**.019**
FSS total	45	−0.239	.114	28	−0.341	.076	105	**−0.334**	**< .001**	30	−0.327	.077	116	**−0.240**	**.009**
S-Factor*	45	−0.105	.492	30	−0.384	**.036**	107	**−0.295**	**.002**	26	.098^	.643	N/A	N/A	N/A
CCAS-S total fail score															
CAG repeat expansion	54	0.094	.499	42	0.088	.579	120	0.108	.241	43	−0.091	.563	N/A	N/A	N/A
AO	46	0.118	.437	36	0.260	.125	114	**−0.187**	**.046**	32	0.050	.786	127	0.035	.697
Disease duration	46	0.153	.310	36	0.153	.373	114	**0.274**	**.003**	32	0.310	.084	125^	0.145	.106
SARA total	44	**0.558**	**< .001**	23	0.388	.067	96	**0.292**	**.004**	29	0.218	.256	109	**0.419**	**< .001**
BARS total	14	0.080	.787	18	0.422	.081	33	**0.410**	**.018**	28	**0.446**	**.018**	73	**0.363**	**.002**
FSA	48	**0.483**	**< .001**	33	**0.366**	**.036**	111	**0.357**	**< .001**	31	**0.485**	**.006**	128	**0.442**	**< .001**
PHQ-9 total	40	**0.325**	**.041**	32	0.118	.520	93	**0.240**	**.021**	27	0.343	.080	113	0.183	.052
FSS total	45	0.096	.529	28	0.247	.205	105	**0.297**	**.002**	30	**0.378**	**.039**	116	0.162	.082
S-Factor*	45	0.267	.077	30	0.264	.158	107	**0.350**	**< .001**	26	−.036^	.861	N/A	N/A	N/A

AO age at disease onset, *SARA* Scale for the Assessment and Rating of Ataxia, *BARS* Brief Ataxia Rating Scale, *FSA* Functional Staging of Ataxia, *PHQ-9* Patient Health Questionnaire-9, *FSS* Fatigue Severity Scale

*S-Factor = ((length of CAG repeat expansion−maximum normal repeat length) /maximum normal repeat length) × (current age−age at disease onset) × 10)

^= correlation following removal of single influential outlier. Significant *p*-values at < .05 are bolded