**Reference values for the Cerebellar Cognitive Affective Syndrome Scale: Age and education matter.**

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**List of Abbreviations**

CCAS = Cerebellar Cognitive Affective/ Schmahmann Syndrome

Cer = cerebellar patient

Con = control

DFG = Deutsche Forschungsgemeinschaft (German Research Foundation)

DRKS = Deutsches Register Klinischer Studien (German Clinical Study Register)

Fig. = figure

MSA-C = multiple system atrophy – cerebellar type

SAOA = sporadic adult onset ataxia of unknown etiology

SD = standard deviation

SCA = spinocerebellar ataxia

UMEA = University Medicine Essen Clinician Scientist Academy

US (-American) = United States (American)

yrs = years

n = number

**This letter refers to “The cerebellar cognitive affective/ Schmahmann syndrome scale”, by Hoche et al. (doi: 10.1093/brain/awx317).**

During the last decades, many studies have yielded evidence for cerebellar involvement in cognitive, emotional and affective processes besides the well-known cerebellar contribution to motor performance and learning (Koziol *et al.*, 2014; Marien *et al.*, 2014; Van Overwalle *et al.*, 2014; Strata, 2015; Adamaszek *et al.*, 2017; Kansal *et al.*, 2017; Guell *et al.*, 2018; King *et al.*, 2019). Cerebellar diseases can result in executive, linguistic and visuospatial dysfunctions as well as problems with the regulation of emotion and affect. This combination of non-motor symptoms has been named *Cerebellar Cognitive Affective/ Schmahmann Syndrome (CCAS)* (Schmahmann and Sherman, 1998)*.* For many years, diagnosis has relied on non-standardized bedside cognitive examination and, if available, detailed neuropsychological test batteries. Recently, a short and easily applicable bedside test (CCAS Scale) published by Hoche et al. (2018) in *Brain* has been developed to screen for CCAS. The CCAS Scale is already in widespread use. We therefore believe that it is important to share our recent findings that the reference values published by Hoche and colleagues may apply only within a limited age and education range, while their more universal application may lead to a substantial number of false positive test results.

The original CCAS Scale has been developed in an US-American cohort of 77 patients with various cerebellar diseases and 58 healthy controls (exploratory cohort) and has then been validated in another US-American cohort of 39 adult cerebellar patients and 55 healthy controls (validation cohort). The CCAS Scale consists of twelve test items that capture deficits in the core domains of CCAS. Single CCAS Scale test items can either be passed or failed. Based on how many test items have been failed, the presence of a CCAS is considered possible (one item failed), probable (two items failed) or definite (three or more items failed). The scale showed good values for selectivity (that is the ability to distinguish between patients and controls, or in other words preventing controls from being diagnosed as patients; exploratory cohort: possible/ probable/ definite CCAS: 74/ 94/ 100 %; validation cohort: 78/ 93/ 100 %) and reasonable values for sensitivity (that is the probability that a patient is identified as a patient; exploratory cohort: 85/ 58/ 48 %; validation cohort: 95/ 82/ 46 %). The CCAS Scale outperformed other screening instruments of cognitive dysfunction, i.e. Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005) or Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) which did not reliably differentiate between patients with cerebellar disorders and healthy individuals (Hoche *et al.*, 2018).

As yet, the CCAS Scale has only been available in American English. We have recently generated a German version of the scale using a standardized translation procedure (Thieme *et al.*, 2020). To date, 107 patients with various forms of cerebellar degeneration, including hereditary ataxias (n = 82, predominately spinocerebellar ataxia type 3 (SCA3), SCA6 and Friedreich’s ataxia), non-hereditary ataxias (n = 15, predominantly sporadic adult onset ataxia of unknown etiology (SAOA) and multiple system atrophy – cerebellar type (MSA-C)) and acquired ataxias (n = 3), as well as patients with cerebellar stroke (n = 7), and 97 healthy matched controls have been tested with the German CCAS Scale.

Using the same cut-off values of single test items and the same criteria to define a possible (one item failed), probable (two items failed) or definite (three or more items failed) CCAS, we found significantly lower values for selectivity (present study: 32/ 64/ 84 %) compared to the original US-American validation study (validation cohort: 78/ 93/ 100 %). Values for sensitivity were comparable (present study: 92/ 70/ 48 %; original US-American validation cohort: 95/ 82/ 46 %).

Age effects likely explain the differences in selectivity in our German study cohort compared to the validation cohort tested by Hoche and colleagues (2018). Their control participants were on average significantly younger than their patients with cerebellar disease (patients: 55.0 ± 12.5 years, range: 31 – 75; controls: 40.4 ± 16.2 years, range not reported; two-tailed: p-value < 0.001). Age was not significantly different between groups in our study (patients: 55.5 ± 13.3 years, range: 22 – 84; controls: 52.6 ± 18.1 years, range 21 – 90; two-tailed t-test: p = 0.190).

We observed an age-dependent decline in CCAS Scale performance in healthy controls which has not been reported by Hoche *et al.* (2018). The number of failed CCAS test items showed a significant positive correlation with increasing age in controls (R = 0.479, p < 0.001; Spearman’s correlation coefficient; **Fig. 1A**). A similar trend was observed in patients but did not reach significance (R = 0.184, p = 0.058), possibly due to the additional contributory component of disease per se, in addition to age. Healthy participants above the age of 50 years failed on average 1.9 test items (SD: 1.5, range: 0 – 6). This effect was more pronounced in healthy participants above the age of 60 years who failed on average 2.1 test items (SD: 1.6, range: 0 – 6; **Fig. 2A**). The number of false positive test results in healthy controls increased with age (false positive controls < 50 years: possible/ probable/ definite CCAS: 48/ 13/ 0 %; false positive controls > 60 years: 83/ 61/ 36 %).

Furthermore, in our study, patients and controls with lower education level performed worse when tested with the CCAS Scale than participants with higher education level. The number of failed CCAS test items was negatively correlated with increasing years of education both in controls and patients (controls: R = -0.314, p = 0.002; patients: R = -0.324, p = 0.001; Spearman’s correlation coefficient; **Fig. 1B**). For example, healthy controls with less than 13 years of education failed on average more test items (mean: 2.6 ± 1.8, range: 1 – 6) than healthy controls with 15 or more years of education (failed items: 1.0 ± 1.2, range: 0 – 5; **Fig. 2B**). The number of false positive test results was higher in controls with a lower education level (< 13 years of education: possible/ probable/ definite CCAS: 100/ 57/ 36 %) compared to controls with a higher education level (> 15 years of education: 57/ 28/ 13 %).

This dependency of CCAS Scale performance on both age and education is in line with other extensive test batteries and bedside tests of cognitive function, e.g. Wechsler Adult Intelligence Scale 4th edition (Wechsler, 2008), Delis-Kaplan Executive Function System (Delis *et al.*, 2001), Demtect (Kalbe *et al.*, 2004) or Montreal Cognitive Assessment (Nasreddine *et al.*, 2005). Accordingly, reference values published for these cognitive test instruments are age- and/ or education-dependent.

Our findings demonstrate that age- and education-dependent reference values need to be developed for the CCAS Scale. The cut-off values given in the original study in an US-American population likely apply only for patients with cerebellar disease who are younger than 50 years of age and with a higher education level.

**Figures**

**Figure 1: Age and education effects on CCAS Scale performance.** Scatter plots showing the relation (**A**) between the number [n] of failed test items and age in years [yrs], and (**B**) between the number of failed test items and years of education in healthy controls (blue dots) and cerebellar patients (yellow dots). The number of failed test items increased with increasing age and decreased with increasing years of education.

**Figure 2: CCAS Scale performance in subgroups of different age and education level.** Cumming estimation plots showing the number [n] of failed test items in healthy controls (Con; blue dots) and cerebellar patients (Cer; yellow dots) shown for different age groups (**A**) and education levels (**B**). Graphs have been generated online using <https://www.estimationstats.com>; Ho *et al.*, 2019). Dots on upper panels represent raw data from individual participants. Gapped lines indicate means and standard deviations. Lower panels show the observed differences between groups: Black dots represent mean differences and error bars 95 % confidence intervals. Filled curves represent the bootstrapped sampling distribution of the observed data.

**Ethics approval and consent to participate**

This study has been approved by the responsible ethics committee at the Essen University Hospital (coordinating study center; local ethics number: 18-8444-BO) as well as the ethics committees at the University Hospitals of Aachen, Bonn, Düsseldorf and Tübingen (participating study centers). All participating patients and healthy control subjects were provided with a full verbal explanation of the study and the information sheet. Written informed consent was given before any study specific procedures started. The study was conducted in accordance with the Declaration of Helsinki.

**Study registration**

The study is registered at the German Clinical Study Register (<https://www.drks.de>; DRKS-ID:  DRKS00016854).

**Data availability**

Data underlying the statistics and the figures is available from the corresponding author upon reasonable request.

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**Competing interests**

The authors report no competing interests.

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