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Cognitive impairment in SCA3: A multi-center cohort study with demographic, imaging, and biomarker correlates

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ABSTRACT

Background: Cognitive deficits are common in spinocerebellar ataxia type 3 (SCA3), but their neurobiological correlates remain largely unknown.
Objectives: To investigate cognitive performance in a large international cohort of SCA3 mutation carriers covering the entire disease course and to explore associations with posterior cerebellar volumes, basal ganglia and thalamus volumes, and plasma neurofilament light chain (NfL) concentration.
Methods: The Montreal Cognitive Assessment (MoCA) was used to evaluate cognitive impairment in this prospective, observational cohort study involving 13 ataxia referral centers. Standardized motor assessments, brain MR imaging, and peripheral blood biosampling were also performed.

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Results: MoCA data were collected from 61 pre-ataxic SCA3 mutation carriers, 231 ataxic SCA3 patients, and 111 healthy controls. After adjustments for educational level and age, there were significant differences in MoCA total score, as well as visuospatial/executive, attention, language, and abstraction subscores, between healthy controls and ataxic, but not pre-ataxic individuals. MoCA scores declined with ataxia severity, especially in patients with a lower educational level. Patients with a MoCA score < 26 had lower pallidal volumes and higher plasma NfL concentrations than those with a score ≥ 26. However, only the interaction term between ataxia severity and educational level was independently associated with cognitive performance in multivariable regression analyses containing demographic, clinical, volumetric, and biochemical parameters.
Conclusion: Cognitive deficits in SCA3 generally appear after clinical ataxia onset and progress in parallel with ataxia severity, especially in patients with a lower cognitive reserve. Other measured biochemical and imaging parameters did not have a significant additional contribution.

1. Introduction

The involvement of the cerebellum in non-motor functions has been increasingly acknowledged over the past couple of decades, especially since the first delineation of the "cerebellar cognitive affective syndrome" (CCAS) (Schmahmann and Sherman, 1998; Schmahmann et al., 2019). Schmahmann and Sherman demonstrated in a seminal paper that patients with isolated cerebellar pathology commonly exhibit impairments in specific cognitive and behavioral domains, including executive functions, linguistic processing, visuospatial abilities, and emotional regulation (Schmahmann and Sherman, 1998). Disturbed connections between the posterior lobe of the cerebellum and prefrontal, posterior parietal, superior temporal, and paralimbic cortices have been hypothesized as the underlying anatomical substrate of these non-motor features (Schmahmann et al., 2019). Importantly, cognitive complaints are also prevalent from the cerebellar patient and caregiver perspectives and negatively impact functioning in daily life (Reumers et al., 2024).

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is one of the most common causes of dominantly inherited ataxia worldwide. It is a progressive polyglutamine disorder that results from a CAG repeat expansion in the *ATXN3* gene. In addition to cerebellar and spinal cord degeneration, SCA3 is characterized neuropathologically by involvement of the brainstem, substantia nigra, pallidum, thalamus, and different parts of the peripheral nervous system (Koeppen, 2018; Seidel et al., 2012; Rezende et al., 2024).

Since the beginning of this century, several studies have evaluated cognitive performance in patients with SCA3 using extensive test batteries, mostly in small cohorts up to 30 patients. Neuropsychological assessments revealed mixed findings, including deficits in timed verbal attention tests, processing speed, phonemic and/or semantic fluency, visuospatial and constructional tasks, immediate and/or delayed verbal recall, cognitive flexibility, and/or response inhibition (Zawacki et al., 2002; Burk et al., 2003; Kawai et al., 2004; Klinke et al., 2010; Braga-Neto et al., 2012; Lopes et al., 2013; Feng et al., 2014; Tamura et al., 2018; Garrard et al., 2008). Although the combination of cerebellar and basal ganglia pathology in SCA3 may contribute to the heterogeneity in cognitive profiles (Yap et al., 2022), the majority of studies lacked additional brain imaging to better understand the primary source of cognitive dysfunction in this complex multisystemic disorder. Moreover, except for one recently published study, the relationship between cognitive deficits and plasma biomarkers of neurodegeneration has not been examined thus far (Petit et al., 2025). Accordingly, structural, biochemical, and demographic correlates of cognitive impairment in SCA3 remain largely unknown. In this study, we aimed to (i) investigate cognitive performance in a large international cohort of SCA3 mutation carriers spanning the disease spectrum and (ii) explore associations with posterior cerebellar volumes, basal ganglia and thalamus volumes, plasma neurofilament light chain (NfL) concentration, and educational level.

2. Methods

2.1. Study design and participants

The study population comprised (i) pre-ataxic SCA3 mutation carriers, defined by a Scale for the Assessment and Rating of Ataxia (SARA) score < 3 points (Maas et al., 2015), (ii) ataxic SCA3 patients, defined by a SARA score ≥ 3 points, and (iii) healthy controls without a history of neurological or psychiatric disorders who participated in the European Spinocerebellar ataxia type 3 / Machado-Joseph Disease Initiative (ESMI). Baseline data of this prospective observational cohort study were collected between November 2016 and August 2021 at eleven European and two US ataxia referral centers. MRI and NfL data of the full ESMI cohort have been published previously (Berger et al., 2025; Garcia-Moreno et al., 2022). The study was approved by the local ethics committees of the participating centers. Written informed consent was obtained from each participant prior to enrolment.

2.2. Clinical assessment

The Montreal Cognitive Assessment (MoCA) was used in ESMI to evaluate cognitive performance (Nasreddine et al., 2005). Its short administration time, availability in various languages, and assessment of multiple cognitive domains make MoCA a practical instrument to use in multi-center studies with lengthy protocols. We excluded patients who were physically unable to perform the first three tasks from analyses on MoCA total score rather than rate their visuospatial/executive subscore as 0/5 and thereby automatically assume they have severe visuospatial and executive deficits. In this way, we aimed to reduce the impact of upper limb ataxia on cognitive scores as much as possible. The correlations shown therefore represent the most conservative estimates. We used data collected from these individuals from all other MoCA domains that do not rely on upper limb function.

Ataxia severity was quantified with the SARA score, ranging from 0 (no ataxia) to 40 points (severe ataxia) (Schmitz-Hubsch et al., 2006). The extent of extracerebellar involvement and number of depressive symptoms were evaluated with the Inventory of Non-Ataxia Signs (INAS) and Patient Health Questionnaire-9 (PHQ-9), respectively (Jacobi et al., 2013; Kroenke et al., 2001). Estimated time to disease onset in pre-ataxic individuals was calculated using an established equation based on CAG repeat length of the expanded allele and actual age (Tezenas du Montcel et al., 2014).

2.3. MRI scans of the brain

We used a highly standardized MRI protocol with the exact same sequence details on each of the operating scanners, which were all Siemens 3 T machines. T1-weighted MR images (192 slices, matrix size $= 256 \times 256$, voxel size $= 1\ mm^3$, repetition time $= 2500$ ms, echo time $= 4.37$ ms, inversion time $= 1100$ ms) were acquired at 10 out of 13 ESMI sites. Pilot scans with phantoms and human subjects were performed in each of these centers prior to the enrolment of participants. All

acquisition parameters were automatically checked for every subject, and scans were excluded if any sequence parameters deviated from the predefined protocol. Volumetric readouts were not specifically harmonized in ESMI. Quality control was carried out continuously throughout the study.

Volumes of the thalamus, caudate nucleus, putamen, and pallidum, as well as estimated Total Intracranial Volume (eTIV), were obtained with FreeSurfer software. CerebNet was used to subsegment the cerebellum at the lobular level, resulting in a total of 25 cerebellar cortical and 2 cerebellar white matter labels (Faber et al., 2022). The former were combined to produce total cerebellar gray matter, while summation of the latter yielded total cerebellar white matter. In addition, volumes of the anterior lobe (i.e., lobules I-V), superior posterior lobe (i.e., lobules VI, Crus I, Crus II, and VIIB), and inferior posterior lobe (i.e., lobules VIIIA, VIIIB, and IX) were calculated. To account for interindividual differences in head size, all cerebellar and subcortical volumes were divided by eTIV.

2.4. Neurofilament light chain

The methodology concerning the collection, processing, and storage of blood samples has been described elsewhere in detail (Garcia-Moreno et al., 2022). Plasma NfL concentrations were measured using the Neurology 4-Plex A kit on the Simoa HD-1 Analyzer (Quanterix, Billerica, MA, USA). Measurements were performed in duplicate for each sample, and average values were taken.

2.5. Statistical analysis

All statistical analyses were conducted in SPSS Statistics (IBM, version 29). Demographic characteristics between the three groups of participants were compared using analysis of variance for continuous variables and chi-square tests for categorical variables. Between-group differences in MoCA total score, as well as individual domain scores, were assessed with analysis of covariance (ANCOVA), adjusting for age and educational level. Associations between cognitive performance and ataxia severity were evaluated with Pearson correlation coefficients. We further explored if the relationship between both variables is different for individuals with lower or higher educational level, thereby using the established cutoff of 12 years and including the interaction term between SARA score and educational level in a linear regression analysis (Nasreddine et al., 2005). ANCOVAs were used to compare basal ganglia, thalamus, and (posterior) cerebellar volumes (covariates: age and educational level), and plasma NfL concentrations (covariates: age and repeat length (Wilke et al., 2020)) between cognitively impaired and cognitively unimpaired patients. The latter distinction was based on the originally proposed and still most commonly applied MoCA cutoff score of 26 points (Nasreddine et al., 2005). Finally, stepwise linear regression analyses were performed to identify demographic, clinical, imaging, and biochemical parameters that are independently associated with MoCA score.

3. Results

3.1. Demographic and clinical characteristics of participants

MoCA data were collected from 61 pre-ataxic SCA3 mutation carriers, 231 ataxic SCA3 patients, and 111 healthy controls. Demographic and clinical characteristics of participants are summarized in Table 1. The number of educational years was higher in healthy controls compared with pre-ataxic SCA3 mutation carriers ($p < 0.001$) and ataxic individuals ($p < 0.001$). There was no difference in educational years between the pre-ataxic and ataxic group ($p = 0.47$). Pre-ataxic subjects were younger than ataxic patients ($p < 0.001$) and healthy controls ($p < 0.001$). The ataxic group was slightly but significantly older than the control group ($p = 0.024$). There were no sex differences between the three groups ($p = 0.08$).

Table 1
Demographic and clinical characteristics of study participants.

	Healthy controls ($n = 111$)	Pre-ataxic SCA3 ($n = 61$)	Ataxic SCA3 ($n = 231$)
Age (y)	47.7 ± 14.0	35.5 ± 8.9	51.3 ± 11.3
Male, n (%)	50 (45.0)	23 (37.7)	122 (52.8)
CAG repeat length, longer allele	N/A	67.9 ± 3.7	69.0 ± 4.4
Disease duration (y), estimated[#]	N/A	−5.4 ± 9.4	12.8 ± 10.1
SARA score	0.4 ± 0.7	1.0 ± 0.9	13.5 ± 7.4
Disease stage, n (%)			
No gait difficulties	96 (86.5)	47 (77.0)	4 (1.7)
Gait difficulties	0 (0)	14 (23.0)	126 (54.5)
Loss of independent gait	0 (0)	0	65 (28.1)
Confined to wheelchair	0 (0)	0	34 (14.7)
Information missing	15 (13.5)	0	2 (0.9)
Education (y)	18.5 ± 4.1	13.2 ± 4.3	11.9 ± 5.3
8MWT (s)	4.9 ± 2.6	4.9 ± 1.1	8.1 ± 4.9
9HPT, dominant hand (s)	19.6 ± 3.1	21.6 ± 3.9	42.3 ± 26.5
PATA rate	29.8 ± 6.7	28.1 ± 7.3	22.0 ± 6.9
INAS count	0.6 ± 0.9	1.3 ± 1.1	5.0 ± 2.5

Data are presented as mean ± SD or frequency (percentage).
SCA3 = spinocerebellar ataxia type 3; SARA = Scale for the Assessment and Rating of Ataxia; 8MWT = 8 m walk test; 9HPT = nine-hole peg test; INAS = Inventory of Non-Ataxia Signs.
[#] According to the equation by Tezenas du Montcel and colleagues based on CAG repeat length and actual age (Tezenas du Montcel et al., 2014).

Visuospatial/executive domain data from 10 patients were excluded because of severe upper limb ataxia, which impaired their ability to perform the Trail Making Test-B, copy a cube, and draw a clock. For those patients, we did not calculate a MoCA total score.

MRI scans were performed in 25 pre-ataxic SCA3 mutation carriers and 72 SCA3 patients. Plasma NfL data were available from 30 pre-ataxic and 149 ataxic SCA3 mutation carriers.

3.2. Cognitive performance in pre-ataxic and ataxic SCA3 mutation carriers

Adjusting for the number of educational years and age, ANCOVA revealed significant differences in MoCA total score between the three groups ($F(2, 383) = 13.8$, $p < 0.001$, partial $\eta^2 = 0.07$). Post-hoc Bonferroni tests showed lower scores in SCA3 patients (mean ± SD, 25.31 ± 4.14) compared with healthy controls (mean ± SD, 27.57 ± 2.23; $p < 0.001$) and pre-ataxic individuals (mean ± SD, 27.66 ± 1.79; $p < 0.001$). There was no difference in MoCA total score between pre-ataxic mutation carriers and healthy controls ($p = 0.99$). Regarding the individual cognitive domains, significant between-group differences were found for visuospatial/executive score ($F(2, 383) = 11.3$, $p < 0.001$, partial $\eta^2 = 0.06$), attention score ($F(2, 394) = 7.5$, $p < 0.001$, partial $\eta^2 = 0.04$), language score ($F(2, 394) = 13.9$, $p < 0.001$, partial $\eta^2 = 0.07$), and abstraction score ($F(2, 394) = 6.4$, $p = 0.002$, partial $\eta^2 = 0.03$) (Table 2). SCA3 patients performed significantly worse than healthy controls on these four domains (all p values < 0.005) and performed worse than pre-ataxic individuals on visuospatial/executive ($p = 0.004$), attention ($p = 0.011$), and language domains ($p = 0.001$). There were no differences in any of the MoCA domain scores between pre-ataxic mutation carriers and healthy controls ($p = 0.99$). Furthermore, after adjustments for age and education, MoCA score was not associated with the estimated number of years to disease onset within the group of pre-ataxic individuals ($r = -0.10$, $p = 0.48$).

Table 2
MoCA scores of healthy controls, pre-ataxic SCA3 mutation carriers, and ataxic SCA3 patients.

	Healthy controls ($n = 111$)	Pre-ataxic SCA3 ($n = 61$)	Ataxic SCA3 ($n = 231$)
Visuospatial / executive	4.64 ± 0.63	4.48 ± 0.83	3.86 ± 1.48
Naming	2.94 ± 0.24	2.95 ± 0.22	2.84 ± 0.46
Attention	5.67 ± 0.69	5.62 ± 0.69	5.16 ± 1.25
Language	2.46 ± 0.75	2.33 ± 0.79	1.97 ± 0.85
Abstraction	1.84 ± 0.42	1.74 ± 0.51	1.56 ± 0.68
Delayed recall	3.89 ± 1.38	4.18 ± 0.87	3.52 ± 1.40
Orientation	5.96 ± 0.30	5.97 ± 0.18	5.90 ± 0.34
Total score	27.57 ± 2.23	27.66 ± 1.79	25.31 ± 4.14
MoCA < 26	19 (17.1)	7 (11.5)	80 (36.2)

Data are presented as mean ± SD or frequency (percentage). Significant between-group differences were found in visuospatial/executive, attention, language, and abstraction scores.

3.3. Cognitive performance versus ataxia severity

MoCA total score in ataxic SCA3 mutation carriers was inversely correlated with SARA score ($r = -0.44$, $p < 0.001$) (Fig. 1). This association between cognitive performance and ataxia severity remained after adjusting for age ($r = -0.43$, $p < 0.001$) and was more pronounced in patients with twelve years of education or less ($r = -0.52$, $p < 0.001$) than in those with more than twelve years of education ($r = -0.26$, $p < 0.001$). Linear regression analysis showed that the interaction term between SARA score and educational level was associated with MoCA score ($p < 0.001$), which indicates that the difference in magnitude of both correlations is statistically significant. When visuospatial/executive subscores were left out, associations between MoCA total score and SARA score remained significant in the whole group of patients ($r = -0.40$, $p < 0.001$), as well as in both subgroups (twelve years of education or less: $r = -0.47$, $p < 0.001$; more than twelve years of education: $r = -0.24$, $p = 0.006$).

3.4. Cognitive performance versus MRI volumes

Relative volumes of all posterior cerebellar lobules, as well as those of the thalamus, putamen, caudate nucleus, and pallidum, were lower in SCA3 patients than in healthy controls (Supplementary Figs. 1, 2, and 3). However, after adjusting for age and educational level, only pallidal volume was significantly reduced in cognitively impaired compared with cognitively unimpaired SCA3 patients ($F(1, 62) = 5.3$, $p = 0.025$, partial $\eta^2 = 0.08$) (Fig. 2). There were no volumetric differences between cognitively impaired and cognitively unimpaired patients in any of the other subcortical structures, superior posterior lobe, inferior posterior lobe, total cerebellar gray matter, and total cerebellar white matter.

3.5. Cognitive performance versus plasma NfL concentration

After controlling for age and repeat length (Wilke et al., 2020), mean plasma NfL concentrations were higher in cognitively impaired than cognitively unimpaired SCA3 patients ($F(1, 124) = 4.8$, $p = 0.031$, partial $\eta^2 = 0.04$) (Fig. 2I).

3.6. Predictors of cognitive performance in SCA3 patients

Stepwise multivariable linear regression analysis was performed to identify factors affecting MoCA score in SCA3 patients. Age, educational level, SARA score, the interaction between SARA score and educational level, repeat length of the expanded allele, pallidal volume, plasma NfL concentration, PHQ-9 score, and INAS count were selected as independent variables. Of these variables, only the interaction term between SARA score and educational level was independently associated with MoCA score ($p < 0.001$), explaining 40% of the variance in a model that includes the main effects (SARA score [$p = 0.008$] and educational level [$p = 0.65$]) along with the interaction term ($p < 0.001$).

4. Discussion

Leveraging multimodal data from the international ESMI cohort, this study examined imaging, biochemical, and demographic correlates of cognitive impairment in SCA3 mutation carriers across the disease spectrum. The main findings can be summarized as follows. First, reduced cognitive performance was found in ataxic, but not pre-ataxic SCA3 mutation carriers on the group level. Second, cognitive performance decreases with increasing ataxia severity, especially in SCA3 patients with a lower educational level. Third, the second conclusion does not appear to depend on any of the structural and biochemical factors examined in this study, as associations between MoCA score, volumetric MRI parameters, and plasma NfL concentration were not retained in multivariable regression models.

The MoCA was used as a screening instrument for cognitive dysfunction in our multi-center study because other more specific bedside tools for cerebellar patients were lacking at the time ESMI was launched. In the meantime, the cerebellar cognitive affective syndrome scale (CCAS-S) has been developed, validated, translated into various languages, and shown to detect cognitive deficits in patients with different types of ataxia across the globe (Petit et al., 2025; Bolzan et al., 2024; Corben et al., 2024; Hoche et al., 2018; Maas et al., 2021; Naeije et al., 2020; Reumers et al., 2025; Rodriguez-Labrada et al., 2022; Selvadurai et al., 2024; Thieme et al., 2022). Although the CCAS-S only contains cognitive domains that are affected in patients with cerebellar disorders and is therefore a more sensitive screening instrument than the MoCA, the original development and validation study of the CCAS-S interestingly also showed significant differences in MoCA score between cerebellar patients and healthy controls, as well as impairments

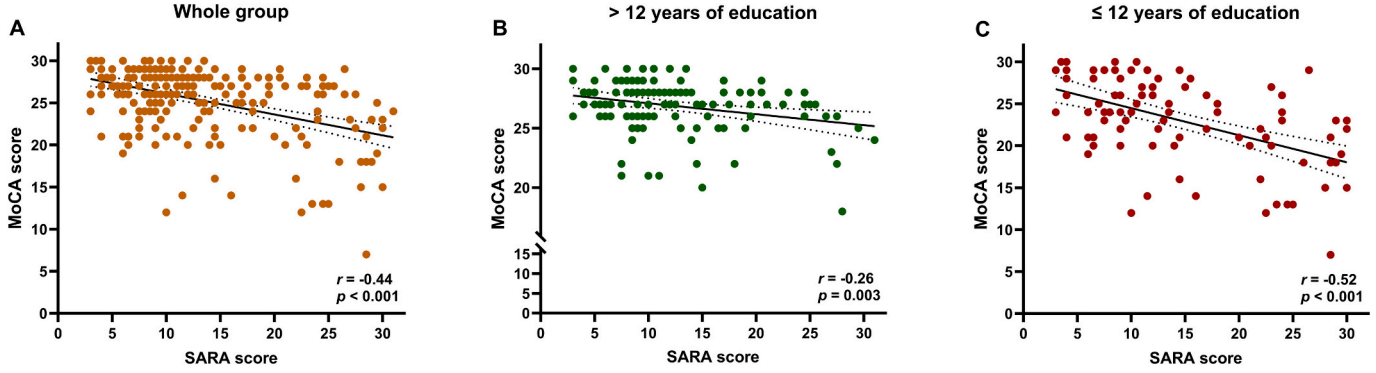

Fig. 1. Associations between MoCA total score and Scale for the Assessment and Rating of Ataxia (SARA) score for the whole group of ataxic SCA3 mutation carriers (A), those with > 12 years of education (B), and those with ≤ 12 years of education (C).

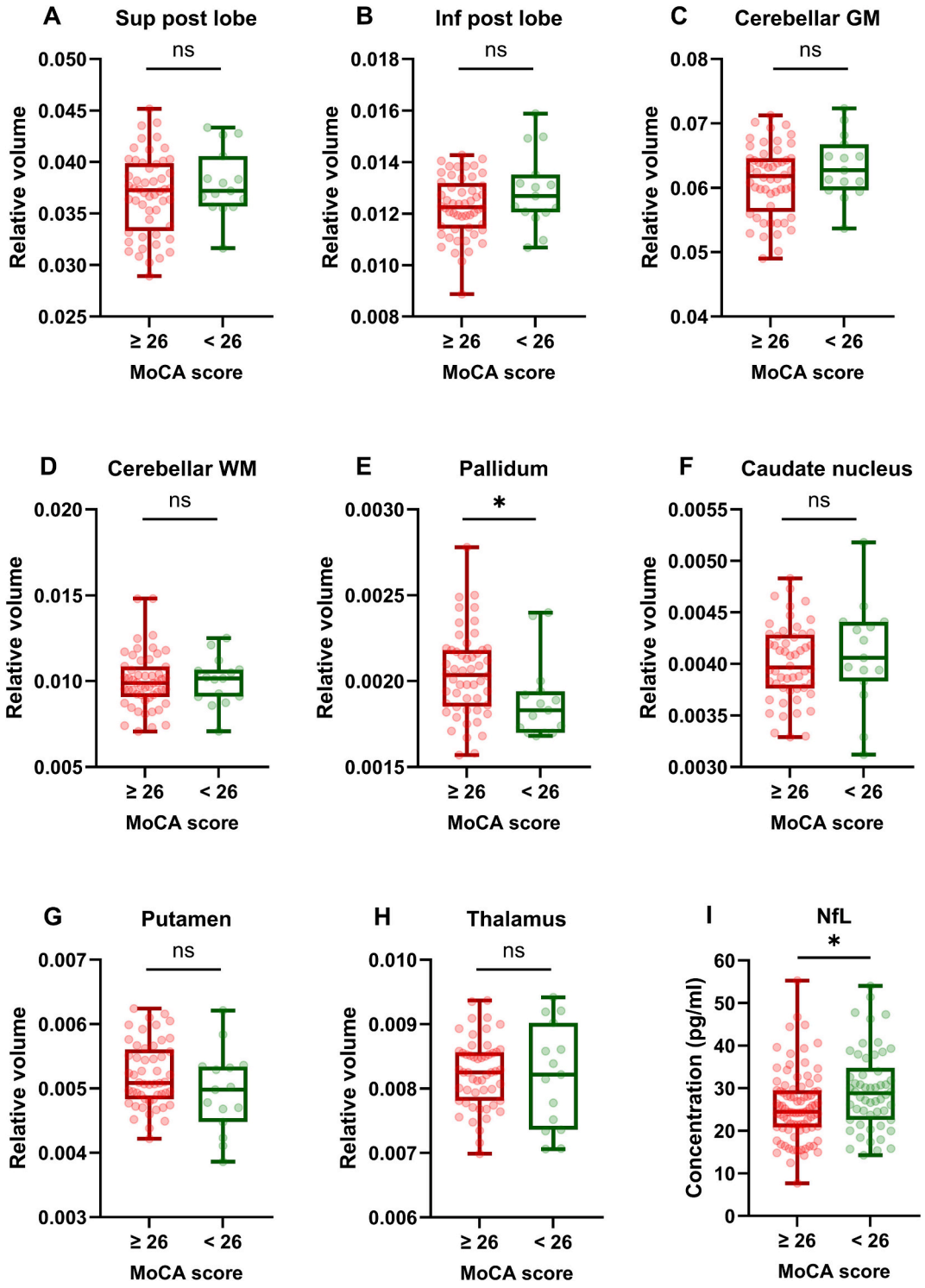

Fig. 2. Volumes of cerebellar (A-D) and subcortical structures (E-H), as well as plasma neurofilament light chain (NfL) concentrations (I), in cognitively impaired versus cognitively unimpaired SCA3 patients.
Asterisks indicate adjusted p values < 0.05.

on a number of MoCA subscores (Hoche et al., 2018). In accordance with the concept and core domains of CCAS, we found significant differences between ataxic SCA3 mutation carriers and healthy controls on visuo-spatial/executive, language, attention, and abstract reasoning tests (Schmahmann and Sherman, 1998). On the other hand, there were no between-group differences in spatiotemporal orientation, delayed recall, and a pictured animal naming task, which together comprise almost half of the maximum 30 points of MoCA.

On the group level, pre-ataxic SCA3 mutation carriers did not perform worse than healthy controls on any of the individual MoCA domains. Although it could be hypothesized that the MoCA lacks the required granularity or specificity to already detect abnormalities in pre-ataxic subjects, three previous CCAS-S studies from the US ($n = 15$), Brazil ($n = 35$), and a combined French-German-American cohort ($n = 45$) similarly did not report significant differences with healthy controls on any of the item scores, total score, and the number of failed tests

(Petit et al., 2025; Bolzan et al., 2024; Selvadurai et al., 2024). On the individual level, our data also do not support an association between the number of years to estimated motor onset and cognitive performance in SCA3. Together with (1) observed differences in cognitive performance between the pre-ataxic and ataxic group and (2) associations between cognitive dysfunction and ataxia severity in the latter, this finding suggests that overt cognitive deficits in SCA3 generally emerge during the ataxic stage and gradually worsen over time. Importantly, the inability to execute motor tasks because of too severe upper limb ataxia cannot explain the association between motor and cognitive dysfunction, because these individuals were excluded from analyses on MoCA total score.

Based on post-mortem research, degeneration of structures in the cerebello-thalamo-cortical pathway and cortico-basal ganglia-thalamo-cortical loop has been thought to underlie cognitive impairment in SCA3 (Koeppen, 2018; Seidel et al., 2012). Thus far, only few studies examined associations between the cognitive performance of these patients and (micro)structural brain changes in vivo (Petit et al., 2025; Wu et al., 2017; Ye et al., 2024). Our MRI findings confirm the presence of widespread atrophy of the basal ganglia, thalamus, and cerebellum in SCA3. In the subset of SCA3 patients who underwent brain imaging in our study, pallidal volume was the only MRI parameter that tended to be lower in cognitively impaired individuals. The pallidum is known to be affected early in the disease course of SCA3 and was the only region, together with the putamen, to exhibit a significant change in gray matter volume after two years of follow-up in the EUROSCA study (Faber et al., 2021; Reetz et al., 2013). We cannot conclude, however, that pallidal degeneration is the actual driver of cognitive decline, as this finding could merely reflect an imaging marker of disease progression. Indeed, pallidal volume was not retained as an independent predictor of MoCA score in the final multivariable regression models. We did not observe differences in posterior cerebellar volumes between cognitively impaired and cognitively unimpaired SCA3 patients. This is in line with recent findings of Petit and colleagues in a subgroup of 65 SCA3 mutation carriers who underwent structural brain imaging and were administered the CCAS-S, and could suggest that cognitive performance in SCA3 is determined by other factors than those captured by volumetric MRI measurements (Petit et al., 2025). Alternatively, it is possible that the concomitant involvement of multiple structures in the cerebello-thalamo-cortical and cortico-basal ganglia-thalamo-cortical pathways obscures associations between cognitive performance and individual volumes. Our observations, as well as those of Petit and colleagues (Petit et al., 2025), contrast with another recent study from China that showed lower volumes of bilateral lobule VI, right Crus I, right lobule IV, and the left caudate nucleus in cognitively impaired SCA3 patients (Ye et al., 2024). Volume loss of these regions was associated with worse performance on different neuropsychological tests, evaluating verbal learning and memory, visuospatial skills, phonemic fluency, attention, and processing speed. Possible reasons for the discrepancy in findings include differences between studies in (i) cognitive tests and (ii) demographic and clinical characteristics of participants (i.e., older, more severely affected patients with smaller repeat lengths in our study).

In recent years, plasma NfL has emerged as a promising biomarker of neuroaxonal damage in SCA3. Its concentrations have been shown to correlate with proximity to estimated disease onset in preclinical SCA3 mutation carriers and with ataxia severity in clinically manifest disease (Garcia-Moreno et al., 2022; Wilke et al., 2020; Li et al., 2019; Peng et al., 2020). Here, we report significantly higher plasma NfL levels in cognitively impaired compared with cognitively unimpaired patients, also after adjustments for age and repeat length, suggesting more widespread or increased rates of neuronal degeneration in these individuals who also had more severe motor symptoms. However, similar to pallidal volume, plasma NfL was not retained as an independent predictor of MoCA score when other demographic and clinical factors were added to the regression models. Weak but significant correlations between CCAS-S score and plasma NfL were recently described in patients with SCA3 and SCA7 but not in SCA1 and SCA2 (Petit et al., 2025).

Our study has several limitations. First, restricted time during study visits because of a variety of other assessments did not allow us to conduct a more comprehensive cognitive examination, and the CCAS-S had not been published when ESMI started. As alluded to above, we acknowledge that the MoCA may not be the most suitable tool to evaluate cognitive deficits in cerebellar patients. This would have required extensive neuropsychological examinations (Reumers et al., 2025), which are not feasible in multinational ataxia studies such as ESMI. Nonetheless, our findings of impaired cognitive performance on visuospatial/executive, attention, language, and abstraction subscores of the MoCA are in good accordance with the domains that are typically affected in CCAS. However, some of MoCA's other domains are not typically impaired in cerebellar patients, while domains, such as semantic fluency, are not part of the scale. On the other hand, while the CCAS-S is increasingly used, failures at one or more of its items are also common in healthy individuals as well as cerebellar patients without evidence for CCAS on a gold standard neuropsychological examination, resulting in suboptimal specificity of the current version of the scale (Maas et al., 2021; Reumers et al., 2025; Rodriguez-Labrada et al., 2022; Thieme et al., 2022). Second, ancillary investigations, in particular structural imaging of the brain, could not be performed at all study sites. Third, longitudinal assessments are required to capture the progression of cognitive changes over time, as well as associations with motor deterioration and biomarker changes. Fourth, NfL measurements were not performed in cerebrospinal fluid (CSF). However, previous studies in different neurodegenerative diseases, including SCA3, have established close correlations between plasma and CSF NfL concentrations (Li et al., 2019; Aamodt et al., 2021; Mattsson et al., 2017).

In conclusion, this multi-center study has provided a better understanding of cognitive impairment in SCA3 and its relationship with demographic, clinical, structural, and biochemical variables. Our results indicate that cognitive deficits in general appear after ataxia onset and progress in parallel with ataxia severity, especially in patients with a lower cognitive reserve. Furthermore, pallidal volume and plasma NfL concentration differed between cognitively impaired and cognitively unimpaired patients, but educational level and ataxia severity – two parameters readily available at the outpatient clinic – appear to be the primary determinants of cognitive performance in SCA3 and could guide proactive screening of cognitive impairment.

CRediT authorship contribution statement

Roderick P.P.W.M. Maas: Writing – original draft, Formal analysis, Conceptualization. **Hector Garcia-Moreno:** Writing – review & editing, Investigation. **Jennifer Faber:** Writing – review & editing, Investigation. **Carlos Gonzalez:** Writing – review & editing, Investigation. **Ludger Schöls:** Writing – review & editing, Investigation. **Jeroen J. de Vries:** Writing – review & editing, Investigation. **Khalaf Bushara:** Writing – review & editing, Investigation. **Kathrin Reetz:** Writing – review & editing, Investigation. **Chiadi U. Onyike:** Writing – review & editing, Investigation. **Heike Jacobi:** Writing – review & editing, Investigation. **Friedrich Erdlenbruch:** Writing – review & editing, Investigation. **Jon Infante:** Writing – review & editing, Investigation. **Magda M. Santana:** Writing – review & editing, Investigation. **Jeannette Hübener-Schmid:** Writing – review & editing, Investigation. **Luís Pereira de Almeida:** Writing – review & editing, Investigation, Funding acquisition. **Manuela Lima:** Writing – review & editing, Investigation, Funding acquisition. **Paola Giunti:** Writing – review & editing, Investigation, Funding acquisition. **Thomas Klockgether:** Writing – review & editing, Investigation, Funding acquisition. **Bart P.C. van de Warrenburg:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

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Appendix

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2026.107301.

Data availability

Anonymized data will be shared by the corresponding author on reasonable request from a qualified investigator after approval by the executive board of the ESMI Consortium.

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