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Research Report

Cognitive impairment in young adults following cerebellar stroke: Prevalence and longitudinal course



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ABSTRACT

Introduction: Cognitive impairment is a well-known result of a stroke, but for cerebellar stroke in young patients detailed knowledge on the nature and extent of cognitive deficits is limited. This study examined the prevalence and course of cognitive impairment in a large cohort of patients with cerebellar stroke.

Methods: Sixty young (18–49 years) cerebellar stroke patients completed extensive neuropsychological assessments in the subacute (<9 months post-stroke) and/or chronic phase (≥9 months post-stroke). Performance and course were assessed using standardized scores and Reliable Change Index analyses. Associations between cognitive deficits and lesion locations were explored using subtraction analyses, and associations with subjective cognitive complaints and fatigue were examined.

Results: Sixty patients (52% male) were included with a mean age at event of 43.1 years. Cognitive impairment was observed in 60.3% of patients in the subacute phase and 51.2% during the chronic phase. Deficits were most frequent for visuo-spatial skills and executive functioning (42.5–54.6%). Both improvement and decline were observed over time, in 17.9% and 41.0% of participants, respectively. Cognitive deficits seem to be associated with lesions in certain cerebellar regions, however, no distinct correlation was found for a specific subregion. Subjective cognitive complaints were present in the majority of participants (61

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–80.5%) and positively correlated with fatigue in both phases ($\rho = -.661$ and $\rho = -.757$, $p < .001$, respectively).

Discussion: Cognitive impairment in cerebellar stroke patients is common, with deficits most pronounced for visuo-spatial skills and executive functioning, as in line with the Cerebellar Cognitive Affective Syndrome. The course of cognitive performance was heterogenous, with cognitive decline despite the fact that no recurrent strokes occurred. No clear association between lesion location and cognitive deficits was observed. Subjective cognitive complaints and fatigue were prevalent and positively correlated. Clinicians could use this information to actively screen for and better inform patients about possible cognitive sequelae.

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1. Introduction

The incidence of stroke in young adults is increasing, and so is the number of persons that face its life-long consequences (Ekker et al., 2019). Besides motor outcomes, cognitive impairment (CI) is a known consequence of stroke, which is estimated to affect half of persons with young stroke (18–50 years) (Weterings et al., 2023). A recent study showed that up to 37% of stroke patients had cognitive impairments in the first months after stroke, with deficits that could involve all cognitive domains (Schellekens et al., 2022). Symptoms may even be present up till many years after the event (Schaapsmeeders et al., 2013). Although cognitive impairments after stroke may have a profound impact, studies that relate cognitive impairments to specifically the cerebellum are limited. Our study examines cognitive impairments after a stroke in the cerebellum, which occurs in 2–10% of strokes (Amarenco et al., 1994; Tohgi et al., 1993).

Although the cerebellum is typically linked to motor function, there is increasing evidence for a role of the cerebellum in cognition (Schmahmann et al., 2019). The cognitive domains affected by cerebellar lesions include executive function, spatial cognition, affective processing, and language, and have been described as the Cerebellar Cognitive Affective Syndrome (CCAS) (Schmahmann & Sherman, 1998). Research into the non-motor consequences of cerebellar strokes is, however, overall limited and includes mainly small studies and case reports. Only a few larger studies have been conducted to date, but not all cognitive domains that might be affected were extensively evaluated, and time of assessment after the event differed largely between studies (Malm et al., 1999; Moliis et al., 2021; Taskiran-Sag et al., 2020; van der Giessen et al., 2023). In general, cognitive and affective symptoms following cerebellar strokes are argued to be mild and transient (Alexander et al., 2012; Gok-Dursun et al., 2021; Taskiran-Sag et al., 2020), but several studies indicate that severe and long-term cognitive deficits may be present in some patients (Abderrakib et al., 2022; Maeshima & Osawa, 2007; Mariën et al., 2009; Ruffieux et al., 2017). Since empirical evidence is limited, the prevalence, severity, course, and underlying mechanisms of cognitive impairment after cerebellar strokes remain largely unclear (Alexander et al., 2012; Kalashnikova et al., 2005). However, several factors seem to play a role, such as stroke location – especially lesions in the

posterior lobe of the cerebellum are associated with cognitive symptoms (Chirino-Pérez et al., 2021; Stoodley & Schmahmann, 2010) – and the delay time from stroke to cognitive assessment. Previous evidence points to improvement over time, probably due to compensatory mechanisms (Kalashnikova et al., 2005; Schmahmann & Sherman, 1998). Furthermore, fatigue and subjective cognitive complaints are known to be prevalent after stroke, but results about their association with cognitive function as measured using performance tests are mixed (Maaijwee et al., 2014; Schellekens et al., 2022; van Rijsbergen et al., 2014).

Cognitive impairment significantly affects quality of life by limiting daily functioning, social interaction, and hampering return to work, therefore it is relevant to systematically investigate cognitive impairment (CI) after cerebellar stroke (Malm et al., 1999). This study reports the prevalence and longitudinal course of CI in a large cohort of young stroke patients with cerebellar lesions, with use of a wide range of standardized neuropsychological tests. In addition, we provide an overview of magnetic resonance imaging (MRI)-derived lesion locations associated with cognitive impairment. Finally, associations with subjective cognitive complaints and fatigue were explored.

2. Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of the study procedures or analysis plans was preregistered prior to the research being conducted.

2.1. Study design and participants

For this study, data of the ‘Observational Dutch Young Symptomatic Stroke study’ (ODYSSEY) were used. This prospective, multi-centre cohort study in the Netherlands investigates the prognosis and risk factors of young stroke patients. Details were described in the protocol by Arntz et al. (2014). In short, participants were aged 18–49 years and had first-ever strokes with corresponding confirmation on brain imaging. Participants with ischaemic and haemorrhagic strokes isolated to the cerebellum were selected for this study.

The presence of additional lesions in the cerebrum (e.g., thalamus) was an exclusion criterion, except for micro-infarctions in frontal, parietal, temporal and occipital areas. In- and exclusion criteria were established prior to data analysis.

The ODYSSEY was approved by the medical ethics committee Arnhem-Nijmegen (NL41531.091.12) and all participants provided written informed consent. If the patient was unable to provide written informed consent because of motor impairments, the patient's legal representative provided consent. Raw data are not publicly available due to ethical barriers (no consent from participants), but can be requested from the corresponding author under the condition of a data sharing agreement.

2.2. Neuropsychological assessment

Cognitive function was examined using an extensive set of neuropsychological tests, as described in detail previously (Arntz et al., 2014). The major cognitive domains were included: executive functioning (Semantic Fluency test, abbreviated Stroop Colour Word test – interference, Brixton Spatial Anticipation test), episodic memory (Rey Auditory Verbal Learning Test – 3 trial version), attention and working memory (Digit Span test), information processing speed (abbreviated Stroop Colour Word test, Symbol Digit Modalities test), visuo-spatial skills (Rey Osterrieth Complex Figure – copy, Star Cancellation test), and language (Token test) (Kessels et al., 2018). Legal copyright restrictions prevent public archiving of the various neuropsychological tests used in this research, which can be obtained from the copyright holders in the cited references. Parallel versions were used for tests to minimize material-specific carry-over effects. Assessments took place at least one month after the event in the subacute and chronic phase, which we defined as <9 and ≥9 months post-stroke, respectively. In addition, general cognition was assessed using the Mini Mental State Examination (MMSE).

Test outcomes were transferred into standardized z-scores with use of normative data adjusted for age, sex, and education. The Advanced Neuropsychological Diagnostics Infrastructure (ANDI) database was used for the majority of tests (de Vent et al., 2016). For the Symbol-Digit Modalities Test and the Stroop Colour-Word Test, z-scores were calculated as described before by Schellekens et al. (2022). Since performance on the Star Cancellation test for visual neglect is highly negatively skewed, z-scores cannot be used. Therefore, we applied the common cut-off value for this test, whereby cognitive impairment is defined as a score below 44 points (Friedman, 1992). To correct for outliers, all z-scores below –3 or above 3 were adjusted to –3 and 3, respectively. Composite mean z-scores per cognitive domain were calculated. If one test score was missing because it was not performed, the composite z-score was based on the remaining tests of that domain. Missing test scores were because of motor deficits or refusal of the patient, or due to technical issues. Cognitive impairment on a test was defined as a z-score below –1.5 SD, while z-scores between –1.0 and –1.5 SD were defined as a below average performance (Sachdev et al., 2004). To describe the severity of cognitive impairment in the participants,

Vascular Cognitive Disorder (VCD) was determined using the diagnostic criteria of the International Society for Vascular Behavioural and Cognitive Disorders (VASCOG) (Sachdev et al., 2014). A composite z-score between –1.5 and –2.0 SD in one or more cognitive domains was defined as *mild* VCD. A composite z-score below –2.0 SD in one or more cognitive domains was defined as *major* VCD (Jak et al., 2009).

For analyses on the course of cognitive performance over time, the Reliable Change Index (RCI) was calculated per test. Subsequently, composite domain scores and a total score were calculated by averaging the test scores. The RCI equation by Chelune et al. was used, which takes practice effects and measurement errors into account (Chelune et al., 1993). The Star Cancellation test was excluded for RCI analyses because of its non-normal distribution. Normative data was used to calculate RCI scores for all cognitive domains, details of sources and RCI computation are provided in the [Supplemental material, Table S1](#). RCI scores larger than 1.96 or below –1.96 are considered as a reliable cognitive recovery or decline, respectively (Chelune et al., 1993). When the score was within this range, there was no reliable difference between the two timepoints.

2.3. Demographic and stroke-related information

Additional measures included demographic information about sex, age, and time intervals between assessments. Education level was defined with use of the classification of the Dutch educational system (Verhage, 1965), ranging from 1 (only primary education) to 7 (university degree). Stroke severity was reported with use of the National Institutes of Health Stroke Scale (NIHSS), and the aetiology of stroke was assessed based on the modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (Hennerici, 2009). Depressive symptoms were assessed using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

2.4. Subjective cognitive complaints and fatigue

To evaluate subjective cognitive complaints, a semi-structured questionnaire was administered (Maaijwee et al., 2014). This consisted of 15 questions regarding cognitive complaints in the past month. In addition to the total score, scores of the memory-related complaints were calculated, as well as executive complaints. Fatigue was assessed with the Checklist Individual Strength (CIS20-R), using the total score and the subscale for subjective fatigue (Vercoulen et al., 1994). A subscale score below 27 points was considered normal, and scores between 27 and 35 points indicate increased fatigue. When the score was higher than 35 points, this was marked as severe fatigue.

2.5. Neuroimaging

All participants underwent brain imaging as part of routine clinical care. As MRI scans were performed in multiple medical centres in the Netherlands, scan protocols were slightly different. Lesions were visually identified and delineated on either diffusion-weighted imaging (DWI) or fluid-attenuated

inversion recovery (FLAIR) sequences using ITK-SNAP software (Yushkevich et al., 2006). DWI sequences were used when the scan was performed within two weeks after the event, otherwise FLAIR sequences were used. Lesions were masked on the axial slice images but checked in sagittal and coronal directions. Binary lesion masks were normalized to an adult Montreal Neurological Institute (MNI152 1 mm) template and visually inspected for accurateness. Segmentations in MNI space were manually adjusted when necessary and lesion volumes were calculated. To relate lesion location to the patients' cognitive performance, a simple voxel-wise lesion subtraction analysis was performed (Karnath et al., 2020). In this method, the lesion overlap map of patients without cognitive deficits is subtracted from the lesion overlap map of patients with cognitive deficits. The resulting map highlights specific areas more frequently lesioned in patients with cognitive impairment than without. This descriptive method was favoured over more sophisticated methods, due to small group sizes. Overlap of the lesioned voxels was examined using the non-parametric Brunner–Munzel rank-order test, to determine significant relationships between the lesioned areas and cognitive impairment. False-discovery rate (FDR) corrections with α set at .01 and the maximum number of permutations (8000) were employed, and only voxels damaged $\geq 10\%$ of the patients were included in the analysis. MRICron (version 2016) and MRICroGL were employed to create lesion overlap maps and perform analyses.

2.6. Statistical analyses

Analyses were performed using IBM SPSS Statistics (v27.0), MATLAB (R2022a, MathWorks), and RStudio 3.6.2. Analysis codes and scripts are available on the publicly accessible digital repository 'Open Science Framework' (OSF; <https://osf.io/utvw6/>). Statistical significance was set at .05 (two-tailed) for all tests and Bonferroni corrections were applied for multiple testing. Descriptive statistics were used to obtain information on prevalence and course of cognitive performance. Continuous variables were presented as medians and interquartile ranges (IQR) and ordinal variables as frequencies with percentages. Mann–Whitney *U* tests were performed to compare groups with and without CI, since variables were not normally distributed. Spearman correlations (ρ) were performed to investigate associations between subjective cognitive complaints, fatigue, and neuropsychological test outcomes. These can be interpreted using Cohen's (1988) rule of thumb for effect sizes: small ($|\rho| = .1$), medium ($|\rho| = .3$) and large ($|\rho| = .5$) (Kraemer et al., 2003). All analyses were performed again to explore the possible impact of additional micro-infarctions on cognitive functioning, after excluding patients with additional micro-infarctions.

3. Results

Of the total number of participants from the ODYSSEY study who underwent neuropsychological testing ($n = 807$), 60 participants with cerebellar strokes were identified. The majority of participants ($n = 54$) had ischaemic lesions, of which 50 were isolated to the cerebellum. Four participants had

additional micro-infarctions in occipital, frontal or parietal regions, as assessed by an experienced neurologist. Six participants had cerebellar haemorrhage. Participant characteristics are described in Table 1. Neuropsychological tests were performed by 58 participants in the subacute phase and by 41 participants in the chronic phase, two of whom did not perform the tests in the subacute phase.

3.1. Cognitive impairment

Cognitive impairment was present in 35/58 (60.3%) participants during the subacute phase. Sixteen (45.7%) of them were classified as having major VCD and 19 (54.3%) as having mild VCD. During the chronic phase, 21/41 (51.2%) participants had CI, 10 (47.6%) of whom were classified as having major VCD and 11 (52.4%) as having mild VCD. The numbers of patients per group are visualized in Fig. 1 for the participants in whom neuropsychological tests were administered in both the subacute and chronic phase ($n = 39$). Nine participants improved on cognitive function and went from a classification of major VCD to mild VCD or from mild VCD to unimpaired. However, ten participants worsened with respect to cognitive function in the absence of a recurrent stroke. Participants with mild or major VCD and unimpaired participants did not statistically

Table 1 – Participant and stroke characteristics.

N	60
Male	31 (52%)
Age at event, y	43.1 (38.5–46.2)
Age at initial testing, y	43.4 (38.7–46.1)
Time after event of assessment in subacute phase, days ($n = 58$)	91.5 (53.8–125.3)
Time after event of assessment in chronic phase, days ($n = 41$)	494.0 (428.0–599.0)
Interval time of assessments between subacute and chronic phase, days ($n = 39$)	413.0 (372.0–473.0)
Education level [1–7]	5 (5–6)
MMSE score at baseline	28.0 (26.0–29.0)
NIHSS score at admission	1 (0–2)
MINI – depressive symptoms present	6 (10%)
TOAST classification of subtype of ischaemic stroke ($n = 54$)	
- Likely atherothrombotic	5 (9%)
- Small vessel disease	1 (2%)
- Cardioembolic	10 (18%)
- Rare causes	17 (32%)
- Cryptogenic	18 (33%)
- Multiple causes	3 (6%)
Aetiology cerebellar haemorrhage ($n = 6$)	
- Small vessel disease/hypertensive microangiopathy	1 (17%)
- Arteriovenous malformation	1 (17%)
- Cavernous malformation	1 (17%)
- Drug abuse	1 (17%)
- Unknown	2 (33%)

Variables presented as medians and interquartile ranges (IQR) or as frequencies with percentages. MMSE = Mini-Mental State Examination; NIHSS = National Institutes of Health Stroke Scale; MINI = Mini International Neuropsychiatric Interview; TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

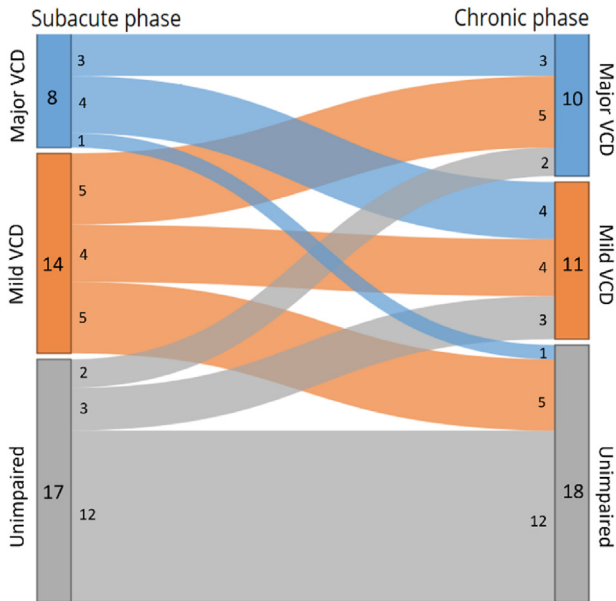


Fig. 1 – Sankey diagram. Shows groups of participants in whom cognitive assessments were performed in the subacute and chronic phase and their course over time in terms of classification mild or major VCD.

differ in terms of NIHSS score, MINI score, or TOAST classification ($p = .144$, $p = .063$, and $p = .682$, respectively).

Impaired performance (below average or cognitive impairment) was most frequently observed in visuo-spatial skills and executive functioning (>50%). When looking at the domain of executive functioning, especially the performance on the Semantic Fluency test was commonly impaired. The proportion of participants with impaired test performance

decreased from the subacute to the chronic phase for all cognitive domains. For visuospatial skills and executive functioning, the proportion of below average performance increased at the expense of cognitive impairment. The most outspoken recovery was found for episodic memory; here, 29.3% of participants had impaired episodic memory in the subacute phase compared to 14.6% in the chronic phase. All test results are presented in Fig. 2 and in Supplementary Table S2.

Analyses were performed again excluding four participants who had additional micro-infarctions in extracerebellar regions. Two of the patients performed assessments at both time points and had normal cognitive function. The other two patients had major VCD and were both only assessed in the subacute phase. The results of these analyses remained similar, with CI present in 33/54 (61.1%) patients during the subacute phase, and in 21/39 (53.8%) in the chronic phase. One excluded patient in this analysis had cognitive deficits in the domains of attention and working memory, and language. The other excluded patient had deficits in the domains of visuo-spatial skills, executive functioning, information processing, episodic memory, and language.

3.2. Longitudinal course of cognitive function

Reliable improvement and decline of cognitive function over time was shown by RCI scores for the participants with assessments in both phases ($n = 39$). Overall, seven participants (17.9%) had a significant improvement of cognitive function in at least one domain, and sixteen participants (41.0%) a significant decline in at least one domain. All participants with significant improvement over time had impaired performance in the subacute phase, but some patients with cognitive impairment in the subacute phase showed a significant

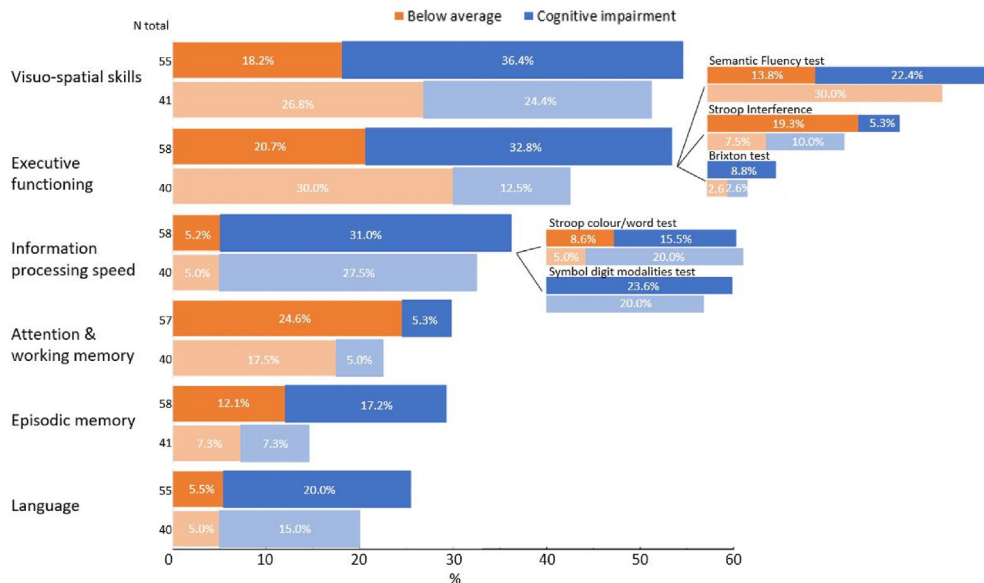


Fig. 2 – Impaired cognitive performance. Percentages are shown per cognitive domain for the subacute (upper row, dark colour) and chronic (lower row, light colour) phase. Additionally, the percentage of impairment is shown per test for the domains with multiple tests; executive functioning and information processing speed. N total refers to the number of participants who completed neuropsychological tests in the concerning domain and phase.

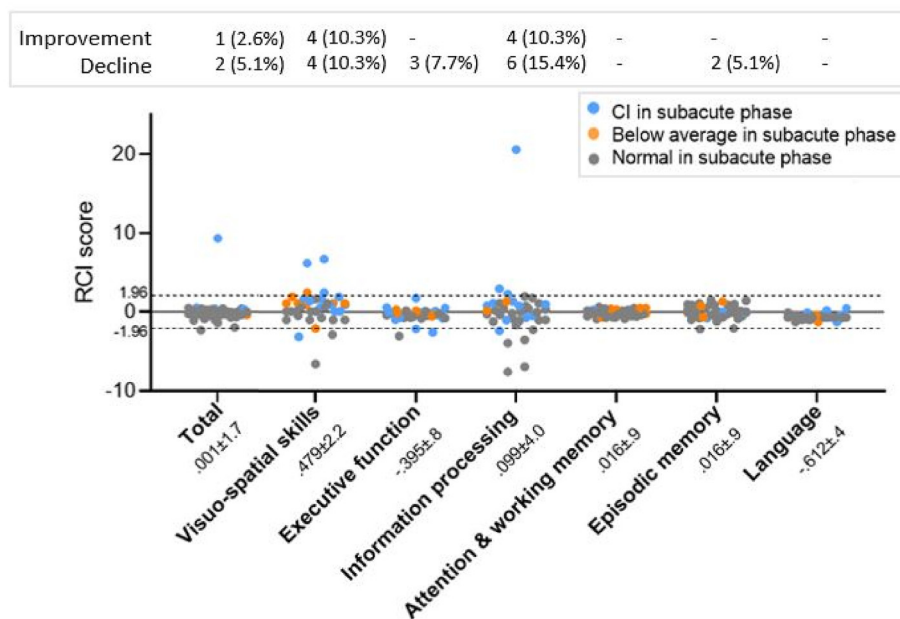


Fig. 3 – RCI scatterplots per cognitive domain. Orange and blue colours show participants with performance below average and cognitive impaired in that domain in the subacute phase, respectively. Below each cognitive domain, mean and standard deviation of all RCI scores are provided. At the top, numbers and percentages of participants with significant improvement and decline per cognitive domain are provided.

decline. Scatterplots of RCI scores and means per domain are visualized in Fig. 3.

3.3. Lesion location

Imaging data for segmentation were available for 50 participants; other scans were not appropriate for lesion delineation, because DWI or FLAIR sequences were not available. Details on lesions and imaging per group are listed in Table 2. Median

lesion volume, lesion side, presence in deep cerebellar nuclei, affected lobe, vascular territory, and time of imaging after the event was not statistically different between the groups with versus without CI (all $p > .05$), and no correlation between lesion volume and cognitive impairment was found ($p = .067$).

Lesion overlap maps for both groups are visualized in Fig. 4. The groups were compared voxel-wise using subtraction analyses, for overall cognition and stratified per cognitive domain, shown in Fig. 5. For overall cognition, several areas in

Table 2 – Lesion and imaging description for all participants, participants with CI (CI group; VCD in subacute and/or chronic phase), and participants without CI (No CI group).

	All participants (n = 50)	CI group (n = 33)	No CI group (n = 17)
DWI/FLAIR sequence, n	39/11	25/8	14/3
Time of imaging after event, days	3.0 (1.0–7.0)	3.0 (1.0–8.0)	2.0 (.5–6.5)
Lesion volume, mL	4.45 (1.67–14.52)	4.53 (1.83–21.90)	3.51 (1.05–11.74)
Lesion side			
- Left	16 (32%)	11 (33%)	5 (29%)
- Right	26 (52%)	17 (52%)	9 (53%)
- Bilateral	8 (16%)	5 (15%)	3 (18%)
Lesion present in deep cerebellar nuclei	20 (40%)	13 (39%)	7 (41%)
Affected lobe			
- Anterior only	23 (46%)	14 (43%)	9 (53%)
- Posterior only	14 (28%)	9 (27%)	5 (29%)
- Both	13 (26%)	10 (30%)	3 (18%)
Vascular territory ^a			
- PICA	21 (42%)	15 (45%)	6 (35%)
- SCA	28 (56%)	19 (58%)	9 (53%)
- AICA	21 (42%)	15 (45%)	6 (35%)

Variables presented as counts, medians, and interquartile ranges (IQR) or as frequencies with percentages. CI = cognitive impairment; VCD = vascular cognitive disorder; DWI = diffusion-weighted imaging; FLAIR = Fluid-Attenuated Inversion Recovery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery; AICA = anterior inferior cerebellar artery.

^a Commonly, more than one vascular territory was involved. Numbers are provided for when the lesion was at least in that territory.

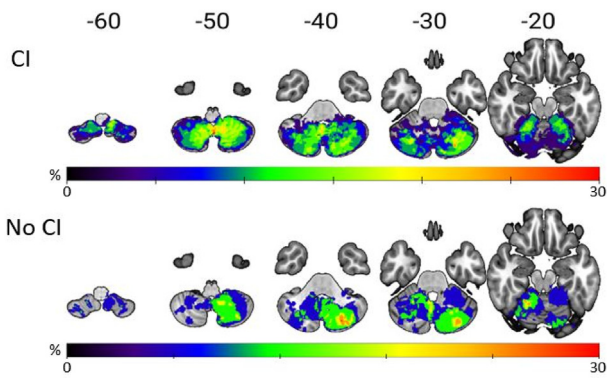


Fig. 4 – Lesion overlap maps. Overlap maps are shown of the group with CI (n = 33) and without CI (n = 17), respectively. Values reflect the percentage of patients with overlapping lesions. Numbers above the slices correspond with z-coordinates in MNI space. Images are provided in radiological convention (i.e., the left hemisphere is depicted on the right and vice versa).

the right posterior cerebellar hemisphere are shown to be up to 24% more frequently lesioned in the group with CI than the group without CI. In the domains of executive functioning, information processing speed, and language, lesions are also observed to be more frequent in the right posterior hemisphere. On the other hand, deficits in the domain of visuo-

spatial skills are more associated with lesions in the left hemisphere. The overlap of lesioned voxels were examined using the Brunner–Munzel test, but no significant associations were found between lesioned areas and cognitive impairment.

3.4. Subjective cognitive complaints and fatigue

In the subacute phase (n = 58), subjective memory complaints were present in 44 (75.9%) patients, and complaints related to executive function in 38 (65.5%). Increased fatigue was present in 15 (25.9%) persons, and severe fatigue in 21 (36.2%). In the chronic phase (n = 41), subjective memory and executive complaints were present in 33 (80.5%) and 25 (61.0%) participants, respectively. Increased fatigue was present in 12 (29.3%) persons, and severe fatigue in 10 (24.4%).

Reporting more subjective memory complaints was significantly correlated with a lower performance on attention and working memory tests ($\rho = -.423, p = .001$) during the subacute phase, but not during the chronic phase ($\rho = -.249, p = .122$). A similar result was found for subjective executive complaints and executive functioning, which were correlated in the subacute phase ($\rho = -.388, p = .003$) but not in the chronic phase ($\rho = -.305, p = .053$). More subjective cognitive complaints were significantly correlated with a lower overall cognitive performance in the subacute ($\rho = -.447, p < .001$) and chronic ($\rho = -.614, p < .001$) phase, with correction for fatigue and age. The total score of the fatigue questionnaire was also

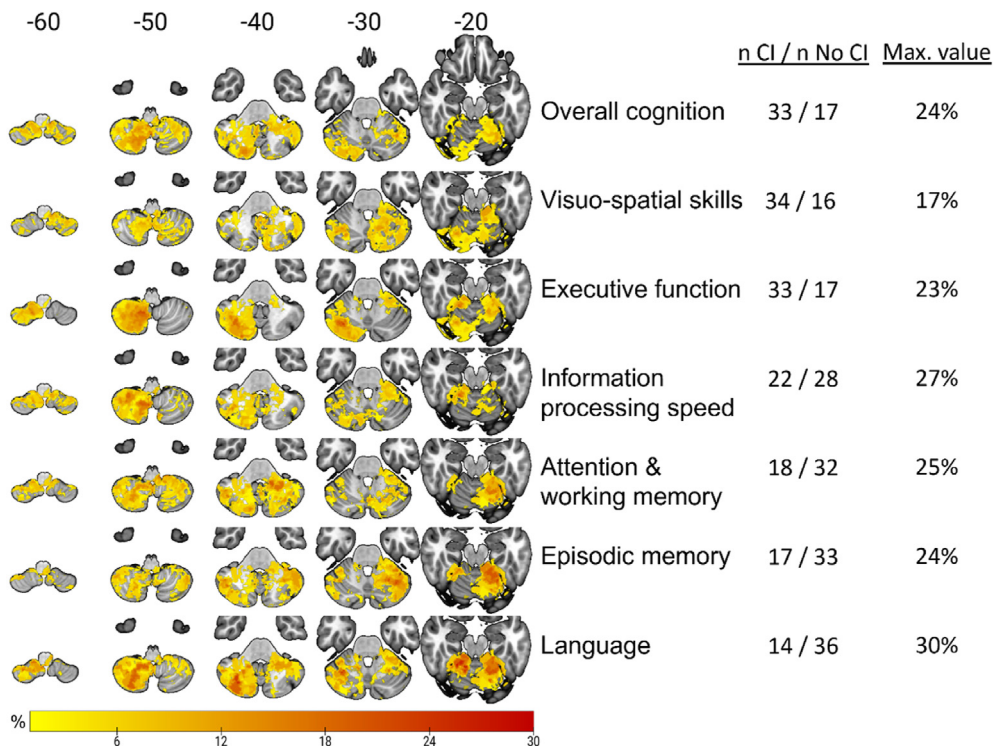


Fig. 5 – Subtraction analyses. Outcomes of the subtraction analyses are shown, for overall cognition and the separate cognitive domains. Numbers of participants with CI and no CI are provided, and the maximal values. Values reflect the relative frequency of damage of a voxel. E.g., a value of 30 reflects that the particular voxel is damaged 30% more frequently in patients with CI than in those without CI. Numbers above the slices correspond with z-coordinates in MNI space. Images are provided in radiological convention (i.e., the left hemisphere is depicted on the right and vice versa).

negatively correlated with overall cognitive performance in the subacute ($\rho = -.344, p = .015$) and chronic ($\rho = -.389, p = .017$) phase. More subjective cognitive complaints were moderately associated with higher scores on the fatigue questionnaire in the subacute ($\rho = -.661, p < .001$) and chronic phase ($\rho = -.757, p < .001$).

4. Discussion

In this group of young adults with cerebellar strokes, we found cognitive impairments in the subacute phase in 60.3% of the participants, and in 51.2% during the chronic phase. Both improvement and decline of cognitive performance was observed. Cognitive deficits were most frequently observed in the domains of visuo-spatial skills and executive functioning (42.5–54.6%). This is a relatively large longitudinal study of young adults with a stroke confined to the cerebellum, with more extensive neuropsychological assessment than in previous studies (Malm et al., 1999; Taskiran-Sag et al., 2020; van der Giessen et al., 2023). Hoche et al. (2018) also conducted a large study into cognitive function in 77 patients with cerebellar pathology, but their sample only consisted of a small proportion of (pure) cerebellar stroke patients (Hoche et al., 2018). Our study provides an accurate view of the prevalence and severity of cognitive deficits after cerebellar strokes, and the persistence of these deficits over time. This information would help in the diagnosis and management of cognitive symptoms in patients who have experienced a cerebellar stroke.

The prevalence of cognitive impairment in cerebellar patients during the subacute phase (60.3%) is comparable to that of the entire cohort of the ODYSSEY study, in which two-thirds of all individuals with strokes had CI (Schellekens et al., 2022). Another recent study found a higher prevalence in cerebellar stroke patients; 84% had definite CCAS, as measured by the French version of the CCAS scale (Abderrakib et al., 2022). However, their sample size was relatively small ($n = 25$), and that version of the CCAS scale has not been validated yet (Abderrakib et al., 2022). In our sample of cerebellar stroke patients, 51.2% had CI in the chronic phase. This prevalence, based on an extensive neuropsychological assessment that is far more sensitive for CI than short screening tools, is substantially higher than previously assessed in patients with strokes across all brain regions (34.5%). This suggests that CI in the chronic phase is more common after cerebellar strokes compared to strokes anywhere (Schaapsmeeders et al., 2013). However, in the previous study, CI was defined less strict, and a longer follow-up period was considered (11 years). Furthermore, our results show that CI is also common in relatively mild strokes, having low NIHSS scores. Cognitive performance in our sample was re-evaluated after excluding patients with extra-cerebellar micro-infarctions. Results remained similar, therefore we consider the impact and possible bias of these micro-infarctions as negligible.

Cognitive performance was most frequently impaired on the domains of visuo-spatial skills and executive function. This pattern differs from persons with strokes in other brain regions, in which executive functioning is typically not

commonly affected, despite being assessed with the same neuropsychological tests (Schaapsmeeders et al., 2013; Schellekens et al., 2022). Although the prevalence of CI is similar between cerebellar strokes and strokes in other brain regions, the affected cognitive domains differ. When comparing our sample to the complete ODYSSEY cohort with strokes anywhere, the high prevalence of deficits in visuo-spatial skills and processing speed is similar (Schellekens et al., 2023). A difference is the prevalence of executive dysfunction (around 50% in our subsample and <20% in the full ODYSSEY cohort), and attention and working memory (approximately twice as often in our sample). However, this difference has not been studied through analyses and therefore only highlights a potential discrepancy. Our results correspond with the characteristically affected domains in CCAS, except for language impairment (Schmahmann & Sherman, 1998). Language deficits were not as common as expected in our results, which might be explained by the fact that the language domain was ascertained only by the token test that assesses language comprehension. CCAS-related linguistic deficits mainly concern language expression, such as verbal fluency and agrammatism (Schmahmann & Sherman, 1998). However, other tasks are also verbal in nature, notably the semantic fluency test assessing word generation, but this test was grouped under executive function in line with previous reports from our group (Schellekens et al., 2022). Linguistic deficits in relation to cerebellar dysfunction have, however, been clearly described in previous studies, indicating involvement of different language impairments (Guell et al., 2015; van Gaalen et al., 2014).

Regarding our neuroimaging results, no clear association between lesion location and the occurrence of CI was observed. Previous studies reported specific cognitive deficits linked to lesion side, especially for the right cerebellar hemisphere (Alexander et al., 2012; Chirino-Pérez et al., 2021; Liu et al., 2022), but have to be interpreted with care since not all studies found an association with the right hemisphere, and they were mostly based on smaller samples than our study (Erdal et al., 2021; Richter et al., 2007). However, lesion side is not always found to affect cognitive performance (Tedesco et al., 2011). In our study, lesions associated with overall cognitive impairment seem to be slightly more frequent in the right posterior cerebellar hemisphere, as visualized with subtraction analysis. This is also seen when looking at impairment in the domains of executive functioning, information processing speed, and language. The association of language deficits with the right cerebellar hemisphere can be explained by the fact that the cerebellar hemispheres predominantly connect to the contralateral cerebral hemispheres, in this case the left, language-dominant cerebral hemisphere. In line, visuo-spatial deficits are more associated with left cerebellar lesions, which is in agreement with previous findings (Stoodley & Schmahmann, 2009). However, the relative frequencies in which specific locations are affected more in patients with CI than without CI were low (17–30%). Moreover, when examining the relation between lesioned areas and cognitive impairment using the Brunner–Munzel test, no statistically significant results were found. Therefore, evidence for a distinct relationship between CI and lesion location remains inconclusive based on our

sample. The degree of overlap in cerebellar areas observed in this study were previously noted by [Stoodley et al. \(2016\)](#) as well. It seems likely that CI is a consequence of disturbances on the network level between cerebellum and cerebrum ([Habas, 2021](#); [Mitoma et al., 2020](#)). Previous work has shown that the cerebellum connects to association areas of the cerebral cortex and forms a closed-loop circuit, which is considered a key component of cerebellar cognition ([Strick et al., 2009](#)). The cerebellar area most prominently related to cognitive dysfunction in our sample is suggested to be functionally connected to the executive control network in the brain, as supported by functional MRI studies ([Alahmadi, 2023](#); [Habas, 2021](#)). The localization and characterization of cognitive and affective processing in the cerebellum has also been studied in a large fMRI study, showing that these are represented in distinct connections from the cerebellum to the cerebral cortex ([Guell et al., 2018](#)). Future studies in large samples should hence focus on the complex interconnectivity of networks in cerebellar-related pathways.

The course of cognitive function was heterogeneous in our cohort since both improvement and decline were observed. Most significant improvement was found in the domains of visuo-spatial skills and information processing speed. Surprisingly, cognitive decline was also common, despite the absence of a recurrent stroke. The patients with significant cognitive improvement over time all had CI in the subacute phase, which could be expected as the capacity of improvement is also greater. Previous studies on the course of cognition after cerebellar strokes only found improved or stable cognitive function over time, but no decline ([Erdal et al., 2021](#); [Hokkanen et al., 2006](#); [Neau et al., 2000](#)). However, these studies used less strict methodology than RCI analyses, which may explain the different outcomes. In addition, our outcomes are in line with findings from all strokes of the ODYSSEY cohort, also measured with RCI analyses ([Schellekens et al., 2023](#)). Both improvement and decline was observed here as well, which were most common in the domains of processing speed and visuospatial skills.

Subjective cognitive complaints and fatigue were present in most participants during both the subacute and chronic phase, which is in line with previous literature ([Maaijwee et al., 2014](#); [Schellekens et al., 2022](#)). We found moderate to large associations between subjective complaints, objective cognitive performance, and fatigue.

A strength of our study is the relatively large sample size for cerebellar strokes to assess neuropsychological performance, with use of an extensive neuropsychological test battery instead of a short screening tool. By making use of large normative data sets, z-scores were corrected for age, sex, and education level. This gave us the opportunity to provide an accurate reflection of cognitive performance in each individual patient, covering a wide range of cognitive domains. The longitudinal design to evaluate cognitive performance in both the subacute and chronic phase is another strength of our study, as is the use of RCI scores, which reflect reliable differences over time because these correct for measurement errors and learning effects. This study has several limitations as well. First, longitudinal data were limited to thirty-nine participants, as some participants were unable to or refused to complete neuropsychological assessments in both the

subacute and chronic phase. However, these participants did not have CI more frequently than the participants who completed assessments in both phases. Second, our study lacks information on previous cognitive function, hence we are not able to conclude that the impairment is a pure consequence of the cerebellar stroke. Premorbid cognitive decline is also known to be a risk factor for cognitive dysfunction ([del Ser et al., 2005](#)). However, due to the young age of our participants, we expect the chance of any premorbid cognitive disorder to be low. Furthermore, no data were available about mediators of cognitive recovery, such as rehabilitation therapies focused on cognition. At last, we lacked information on affect and social cognition, which would have been valuable due to its association with CCAS. However, this study was not designed for investigating CCAS specifically, but cognitive functioning in a broad way.

5. Conclusion

In conclusion, our study found that nearly two thirds of cerebellar stroke patients had CI in the subacute phase, and approximately half of them in the chronic phase. Cognitive deficits after cerebellar strokes are common, even in patients with relative mild strokes and low NIHSS scores. Deficits were most pronounced in the domains of visuo-spatial skills, executive functioning, and information processing speed. These results clearly show that cognitive impairment is a common consequence of cerebellar stroke. Clinicians should be aware of this since cognitive complaints in relation to cerebellar lesions are mostly neglected as the cerebellum is particularly linked to motor performance. Neurologists could use this information in the clinic to better inform cerebellar patients about possible cognitive symptoms. Future research focussing on the role of the cerebellum in cognitive impairment in terms of cerebellar-related networks should be performed in larger samples. More research is required to unravel potential underlying mechanisms.

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TOP guidelines statement

No part of the study procedures or analyses was preregistered prior to the research being conducted. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

CRediT authorship contribution statement

Stacha F.I. Reumers: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis,

Conceptualization. **Mijntje M.I. Schellekens**: Writing – review & editing, Methodology, Investigation, Conceptualization. **Selma Lugtmeijer**: Writing – review & editing, Visualization. **Roderick P.P.W.M. Maas**: Writing – review & editing. **Jamie I. Verhoeven**: Writing – review & editing. **Esther M. Boot**: Writing – review & editing. **Merel S. Ekker**: Writing – review & editing. **Anil M. Tuladhar**: Writing – review & editing. **Bart P.C. van de Warrenburg**: Writing – review & editing, Supervision, Conceptualization. **Dennis J.L.G. Schutter**: Writing – review & editing, Supervision, Conceptualization. **Roy P.C. Kessels**: Writing – review & editing, Supervision, Conceptualization. **Frank-Erik de Leeuw**: Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

AT is a junior staff member of the Dutch Heart Foundation (grant number 2016T044). FEDL is a clinical established investigator of the Dutch Heart Foundation (grant number 2014T060).

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Appendix A. Coinvestigators

The ODYSSEY study group consists of members from multiple medical centres in the Netherlands. Including: Mayte E. van Alebeek and Anouk van Norden (Amphia hospital), Paul J.A.M. Brouwers and Renate M. Arntz (Medisch Spectrum Twente), Gert W. van Dijk (Canisius-Wilhelmina hospital), Rob A.R. Gons and Inge W.M. van Uden (Catharina hospital), Tom den Heijer (Franciscus Gasthuis & Vlietland), Paul L.M. de Kort (Elisabeth-TweeSteden hospital), Karlijn F. de Laat (Haga hospital), Sarah E. Vermeer (Rijnstate hospital), Marian S.G. van Zagten (Jeroen Bosch hospital), Marieke J.H. Wermer (Leiden University Medical Centre), Paul J. Nederkoorn (Amsterdam University Medical Centre), Frank G. van Rooij (Medical Centre Leeuwarden), Ido R. van den Wijngaard (Haaglanden Medical Centre).

Supplementary data

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