Brain and Cognition 173 (2023) 106102

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

The CODECS study: COgnitive DEficits in Cerebellar Stroke

Ruben S. van der Giessen [a,*], Djaina Satoer [b], Peter J. Koudstaal [a]

[a] Department of Neurology, Erasmus University, Rotterdam, The Netherlands
[b] Department of Neurosurgery, Erasmus University, Rotterdam, The Netherlands

ARTICLE INFO

Keywords:
Cerebellar stroke
Cognition
Cerebellum
Cerebellar cognitive affective syndrome
Female

ABSTRACT

Part of the extra-pyramidal system, the cerebellum is more and more recognized by its non-motor functions known as the cerebellar cognitive affective syndrome. Several studies have identified disturbances specifically in executive and attentional functions after focal cerebellar lesions. However, most studies were performed in small and heterogeneous patient groups. Furthermore, there is a substantial variation in the methodology of assessment. Here, we present the results of a large and homogeneous cohort of patients with isolated uniform cerebellar lesions. After three months post-stroke all patients underwent structural neuroimaging to confirm an isolated lesion and were given neuropsychological testing. The results show that cerebellar lesions relate to mild but long-term cognitive impairment in a broad spectrum of neurocognitive functions compared to normative values. These findings confirm involvement of the cerebellum in cognitive processing and supports the theory of 'dysmetria of thought' based upon uniform cerebellar processing in multiple cognitive domains. This study highlights the following results: 1-Cognitive impairments after isolated cerebellar stroke is confirmed in several cognitive domains. 2-Semantic and phonemic fluency are most affected in cerebellar stroke patients. 3-Verbal deficits show an age-independent long term effect post-stroke and should be studied further in depth. 4-Cognitive disorders after cerebellar stroke are more prominent in women than men.

1. Introduction

In the last decades non-motor aspects of the extra-pyramidal systems such as the basal ganglia and cerebellum have received increasing interest. For example, the recognition of cognitive disturbance in Parkinson's disease is already well established in clinical care. Also, the notion of non-motor cerebellar functions was recognized from the early nineties commonly referred to as the cerebellar cognitive affective syndrome. However, the concept was initially based upon occasional observations and several case reports (Lagarde et al., 2009; Schmahmann, 1991). An initial study of Schmahmann was conducted in a heterogeneous group of 20 patients with stroke, post infectious and neurodegenerative causes and neoplasms. Furthermore, the onset of examination varied from a week up to six years after diagnosis (Schmahmann, 1998). Although consecutive studies have confirmed disturbances specifically in executive and attentional functions after focal cerebellar lesions, there is some variation in the methodology of assessment. All studies were performed with either heterogeneous groups or relatively small group sizes (Bolceková et al., 2017; Chirino-Perez et al., 2022; Taskiran-Sag et al., 2020; Ziemus OB et al., 2007).

Several studies included a wide range of patients and etiologies such as mixed tumor patients (Alexander, 2012; Baillieux, 2010; Gottwald et al., 2004) or variable upper brainstem lesions in the same cohort (Malm et al., 1998). One study admitted both adults and children (Tavano et al., 2007). Other studies did include solitary cerebellar stroke patients, but post-onset times varied from acute to chronic stage (up to more than a year) (Kalashnikova, 2005; Richter et al., 2007).

Furthermore, several studies lumped focal lesions and general degenerative disease. Most studies reported no domain specific cognitive disturbances after cerebellar lesions despite attempts to localize deficits (Grimaldi, 2012). This may be due to the unique neuronal structure of the cerebellum. The cerebellar cortex has a uniform cytoarchitecture which processes all signals similarly, while the outcome seems dependent on the function of the specific cerebro-cerebellar loop (Ito, 2008; Strick et al., 2009). The cerebellum, therefore, may contribute to the executive function of multiple cognitive domains. Because of the homogeneity of the cerebellar anatomy, executive problems in all cognitive domains such as language, memory, spatial function and problem solving are indeed expected. However, since the cerebellum acts as a parallel system to fine-tune motor behavior rather

* Corresponding author.
E-mail address: r.vandergiessen@erasmusmc.nl (R.S. van der Giessen).

https://doi.org/10.1016/j.bandc.2023.106102
Received 10 May 2023; Received in revised form 28 September 2023; Accepted 21 October 2023
Available online 2 November 2023

than generating direct motor output, the effect of lesions is expected to be more subtle than cortical lesions. The same can be assumed in lesions leading to cognitive disorders. Additionally, the cerebellum is known for its plasticity, proven by significant motor recovery after damage which also limits the magnitude of disturbances (Sokolov et al., 2014). The assessment of the impact of cerebellar lesions therefore requires a larger sample size. Cerebellar lesions can cause overt neuropsychological deficits, especially with regard to language deficits, in children compared to less prominent deficits in adults (Bianchi et al., 2019; Levisohn, 2000). Studies show that cerebellar lesions in children, can demonstrate long-lasting neurocognitive impairments, with most striking prominent personality changes and mutism (Levisohn, 2000; Panagopoulos & Gavra, 2023; Schmahmann, 2020; Wells & Khademiain, 2008). All these characteristics directly imply that interpreting the cognitive contribution of the cerebellum requires a larger and homogeneous study group at a fixed post-lesion time point. In our study children were excluded to retain a homogeneous group and since cerebellar stroke in children is rare. Furthermore, any involvement of other brain structures must be excluded, such as cerebral cortex in SCA-patients, brainstem compression in tumor-patients and non-localizing infections.

We investigated a large homogeneous group of isolated cerebellar stroke adult patients confirmed by imaging, who were all tested at fixed moments after stroke onset. We hypothesized that cognitive impairments are found in isolated cerebellar stroke patients and that they demonstrate a specific cerebellar cognitive pattern of mild but broad cognitive impairment.

2. Methods

2.1. Subject selection and study design

We included patients with focal cerebellar lesions who were admitted to the Neurology department of Erasmus Medical Centre between April 2015 and April 2021. Exclusion criteria were the existence of extra-cerebellar lesions, pre-existent neurocognitive or psychiatric disorders and age younger than 18 years. Furthermore, patients with compression of the fourth ventricle or adjacent brainstem structures were excluded. The study was approved by the local Medical Ethics Committee (MEC-2013–462) and all patient gave written informed consent. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All patients were given a standard neurological examination and a fluency test within 24 h after hospital admission. During admission all patients underwent structural neuroimaging by means of Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) scan to confirm and specify an isolated cerebellar lesion. All patients were investigated by means of a standard neuropsychological protocol at three months. Reorganization and recovery occur after stroke, such as perilesional edema and tissue reperfusion, which takes up to several weeks to months, therefore neuropsychological testing was performed in a stable phase at three months (Rossini CC et al., 2003). A verbal fluency assessment was performed immediately after stroke, at 3 and 6 months to monitor long-term effects. This single test was used as a follow-up because its frequently observed and prominent impairment in cerebellar patients (Leggio et al., 2000; Mariën, 2014; Smet, 2007). Therefore, it was considered suitable to demonstrate the clinical course of cognitive impairment (Alexander, 2012; Baillieux, 2010; Lezak et al., 2012; Malm et al., 1998; Schmahmann, 1991). We compared all results with normative values corrected for sex, age and level of education. We did not focus on other aspects of the proposed cerebellar cognitive and affective syndrome such as affective or social disturbances mentioned in other studies (Clausi et al., 2019; Van Overwalle et al., 2020).

Table 1
Demographic results of CODECS cohort showing age, education, type of stroke, stroke volume, TOAST classification and clinical outcomes such as mRS, NIHSS and ICARS.

	Total	Female	Male
n =	52 (100 %)	20 (38 %)	32 (63 %)
Age (years)	62 ± 12	64 ± 16	62 ± 15
Education (years)	12.8 ± 4	11.4 ± 3	13.3 ± 4
Type of stroke			
-Infarction	86 % (n = 45)	85 % (n = 17)	87 % (n = 28)
-Bleeding	14 % (n = 7)	15 % (n = 3)	13 % (n = 4)
Stroke volume (cm3)	19.9 ± 19	23.9 ± 17	17.9 ± 19
TOAST-classification:			
1-large artery	1 %	0 %	3 %
2-cardio embolism	2 %	0 %	3 %
3-small vessel	70 %	65 %	68 %
4-other causes	25 %	25 %	24 %
5-unknown causes	2 %	10 %	3 %
mRS	1.4 ± 1.1	1.1 ± 1.2	1.6 ± 1.1
NIHSS	0.6 ± 0.8	0.7 ± 0.9	0.6 ± 0.9
ICARS	5.9 ± 7.8	6.7 ± 6.5	5.4 ± 8.4

2.2. Cognitive and functional measures

All patients underwent two general cognitive screening tools, the Frontal Assessment Battery (FAB) as a brief standardized test for frontal executive dysfunction and the Montreal Cognitive Assessment (MoCA), a bedside test used to detect mild cognitive impairments (Dubois et al., 2000; Nasreddine & Bédirian, 2005). For the FAB-score a cut-off of 13.5 was used to define a mild cognitive impairment (MCI) (Appollonio et al., 2005; Lipton et al., 2005). The MoCA score was corrected for level of education. Selective attention and inhibitory capacity were more specifically investigated by means of the Stroop Color-Word Test (Hammes, 1971), whereas the Trail Making Test (TMT) was used for visual attention and mental flexibility (Reitan, 1958). Scores on both tests were corrected for age, sex and level of education. All tests were performed at 3 months. Verbal functioning was assessed by the Verbal Fluency Test. Both semantic and letter fluency were included (Lezak et al., 2012). The Verbal fluency test was tested at 0, 3 and 6 months as a follow-up test. A Five-point test was added at 3 months during the study to discriminate verbal fluency deficits from (non-verbal) executive deficits. In the Five-point Test, a standardized test measuring figural fluency, the subject has to draw as many unique figures within a standard five point box (Tucha et al., 2012). Both tests were also corrected for age, sex and level of education. To exclude possible current depression (score ≥ 7) all patients completed the Hospital Anxiety and Depression Scale (HADS) (Zigmond, 1983). All patients filled in a questionnaire with regard to behavioral changes. Handedness was assessed by the Edinburgh Handedness Inventory. The International Cooperative Ataxia Rating Scale (ICARS) was used to quantify the cerebellar ataxia as a measure of motor severity. For each patient the modified Rankin Scale and National Institutes of Health Stroke Scale was assessed.

2.3. Statistical analysis

Semantic and phonemic fluency tests were repeated at 0, 3 and 6 months. To demonstrate any long-term effect these follow-up tests were analyzed using a two-way ANOVA with repeated measures. Correlation between cognitive tests, stroke volume and ICARS was measured with Pearson correlation coefficient. Differences per age group in verbal fluency was measured with a one-way ANOVA test. The analysis for difference between male and female was calculated by the Odds ratios. The normal distribution of the variables was tested before proceeding with parametric tests. All measurements were analyzed with SPPS Statistics 28.0.1.0 x64.

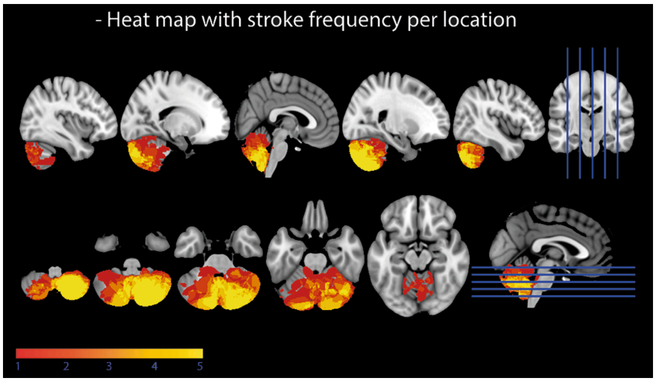

Fig. 1. Figure demonstrating a heat map based on MRI stroke frequency per location in the brain. Scale bar depicts the number of strokes in color (red: n = 1, yellow: n ≥ 5). Most of the cerebellum is covered anatomically. The heat map shows that all strokes are restricted to the cerebellum. With courtesy to N.A. Weaver for the analysis of the heat map. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4. Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to the privacy of research participants.

3. Results

3.1. Patients' characteristics

A total of 52 patients with isolated cerebellar stroke were included in the study. Demographic characteristics are summarized in Table 1. The age range of the study group was 21–91 years (mean age 62.8 years). Thirty-two patients were men with an average age of 62 years (mean 62; SD 15; range 37–91) and 20 patients were women with an average age of 64 years (mean 64; SD 16; range 21–85) (Table 1). There were no significant differences between the groups in age (*t*-test; two-tailed, unpaired, p = 0.535). The mean level of education was 12.8 years. All cerebellar strokes were confirmed with CT (n = 20) or MRI-imaging (n = 32) and involvement of other brain regions was excluded. None of the patients met the criteria for a current depression according to the HADS.

3.2. Cross-sectional results of the neuropsychological battery

We used a neuropsychological battery at 3 months to analyze the patient cognitive profile. With regard to the FAB-test all patients showed a mean value of 14.2 ± 3.2 (normal FAB score ≥ 14). Only 12 % (6 of 50 patients) had a maximal score, whereas 36 % (18 of 50 patients) had a range at or below a level of MCI (<13.5). Most cerebellar patients exhibited problems with mental flexibility and inhibitory control. Of all subtests environmental autonomy was not disturbed in most cases (Fig. 1). The mean score on the MoCA was 24,1 ± 3.6, which is at the level of a mild cognitive impairment (normal MoCA score ≥ 25). Although the subtests cannot be considered as individual cognitive domains, most patients demonstrated a disturbed memory recall, visuospatial ability and language problems. The least affected subtest was orientation, which was disturbed in only 13 % (n = 7) of the patients (Fig. 2). Although the Stroop interference score showed a reduced average score of 56.2 ± 24.8, only two percent of the patients scored below the 10th percentile and 26 % of the patients scored below the 25th percentile (Fig. 3). Three patients did not perform the Stroop test: one because of colorblindness and two because of fatigue. There was a significant positive correlation between FAB and Stroop interference score (Pearson's r 0.366; p = 0.012). The Trailmaking Test BA showed a mean score of 34.2 ± 33.6. Almost half of all patients (48 %) scored below the 25th percentile and 40 % scored below 10th percentile. The Trailmaking Test A shows a mean of 32th percentile below the normative value (mean 32.4 ± 30.6) while 52 % scores below the 10th percentile. No major behavioral changes were reported in the questionnaires. Because movement disorders may impact the performance of neuropsychological tests, we performed an ICAR-score. In general negative trends in relation to cognitive tests are found, however a significant correlation was

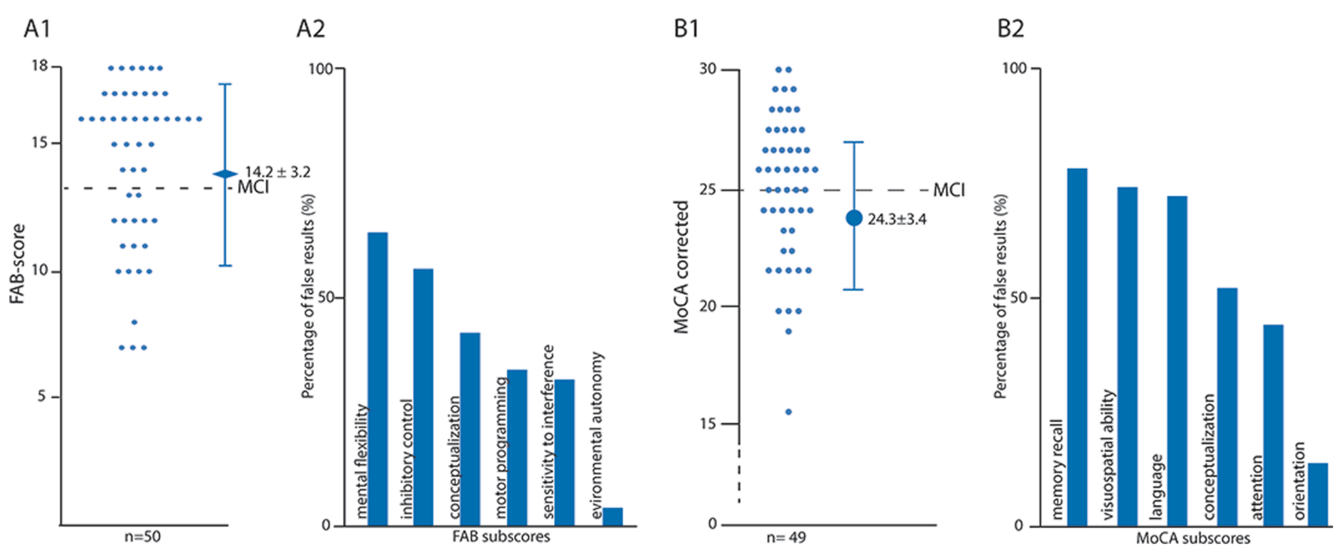

Fig. 2. A1. Graph showing FAB-scores of all cerebellar stroke patients. The dotted line depicts the threshold of Mild Cognitive Impairment (at FAB-score < 13.5). The mean value of FAB-score is 14.2 ± 3.2. Although the score is near the threshold, it is not in the range van MCI. A2. Histogram demonstrating the percentage of negative results of the FAB-sub scores. The graph shows that cerebellar patients have more problems with mental flexibility, inhibitory control and conceptualization. To lesser extent there are difficulties with motor programming and sensitivity to interference. While environmental autonomy is in almost all patients normal. B1. Graph showing corrected MoCA-scores of all cerebellar stroke patients. The dotted line depicts the threshold of Mild Cognitive Impairment (at MoCA-score 25). The mean value of corrected MoCA-score is 24.3 ± 3.4 which is within the MCI range. B2. Histogram showing the percentage of negative results of the MoCA-sub scores. The graph shows that cerebellar patients have the most problems with memory recall, visuospatial ability and language. To lesser extent there are difficulties with conceptualization and attention. While orientation is hardly affected in cerebellar patients.

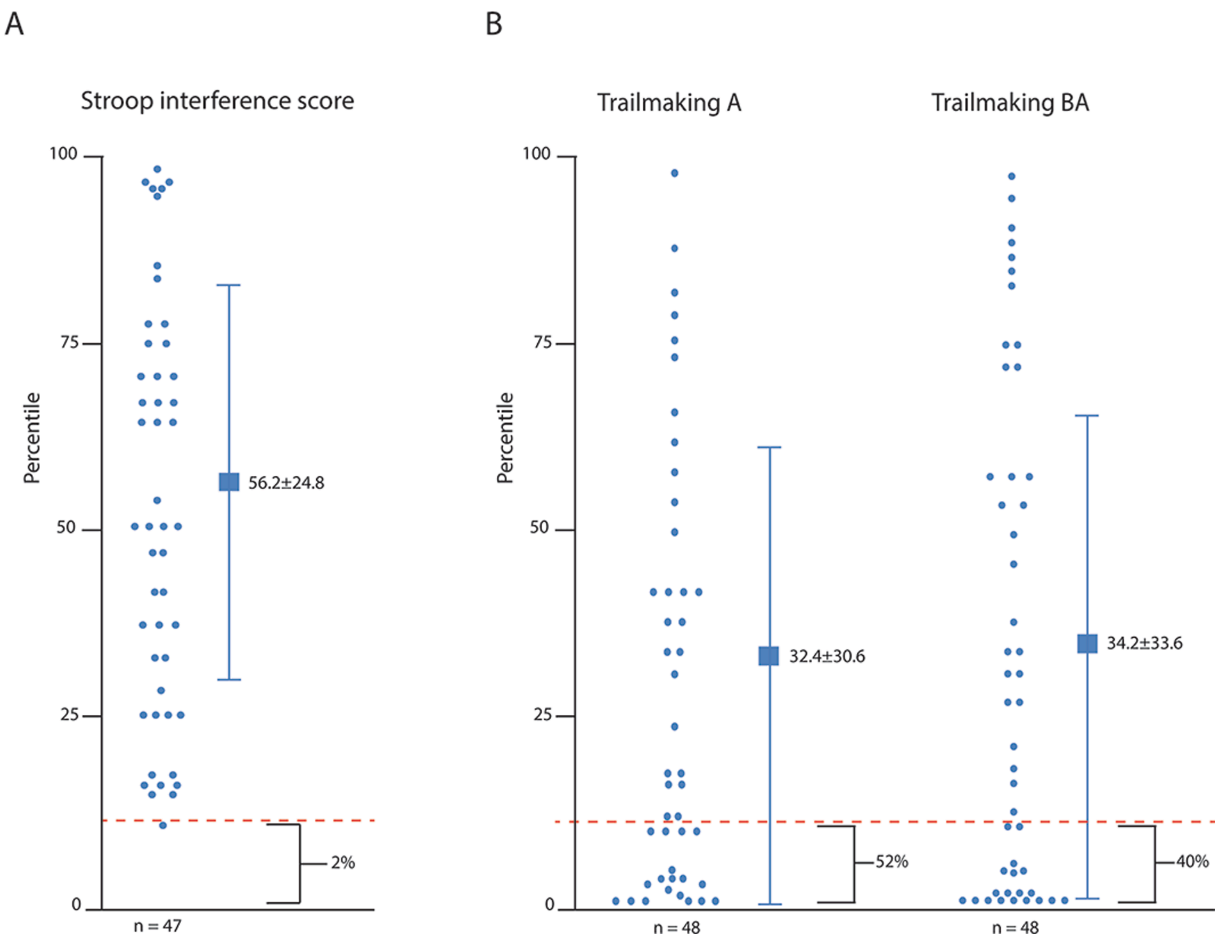

Fig. 3. A. graph showing the interference scores of the Stroop test of 47 cerebellar stroke patients. On average cerebellar patients perform 56 % below the normative value. The first quartile comprises 26 % of the patients (the threshold is depicted by the dotted line). Only 10 % (6/47 patients) score within normal range. B. graph showing the scores of Trailmaking test A and Trailmaking test BA of 48 cerebellar stroke patients. At the Trailmaking test A cerebellar patients perform with a mean of 32th percentile below the normative value (mean 32.4 ± 30.6) and 52 % scores below the 10th percentile. At the Trailmaking BA on average cerebellar patients perform at 34th percentile below the normative value (mean 34.2 ± 33.6) and below the 10th percentile comprises 40 % of the patients (the threshold is depicted by the dotted line).

observed between ICARS and FAB, MoCA and Phonemic fluency. We found no significant correlation between stroke volume and cognitive outcome (Fig. 4). The mean mRS-score was between one and three (1.4 ± 1.1 at 3 months) which suggests that there is no major influence on daily routine. The NIHSS score was also very low (0.6 ± 0.8 at 3 months) (Table 1). However, this test is designed for anterior stroke, and is therefore less sensitive for posterior strokes. The Five Point test shows a mean score of 39.2 ± 31.3 with near half of all patients scoring below 25th percentile (45 %) and 21 % below 10th percentile (Fig. 5A). Additionally, to enable further understanding of mechanisms of cognitive deficits and their changes after the cerebellar stroke, all strokes were classified with the TOAST classification (see Table 1). The majority of strokes had an etiology of small vessel disease or other causes (such as vertebral artery dissection). However, there was no significant difference in cognitive outcome between these groups.

3.3. *Verbal fluency and long term follow-up*

The fluency test demonstrated a mean score of 30.5 ± 26.8 for semantic fluency and 33.9 ± 30.2 for phonemic fluency. In both tests more than half of all patients scored below the 25th percentile (resp. 60 % and 54 %) whereas 38,5% and 23 % respectively scored below the 10th percentile (Fig. 5A). During follow-up patients still showed deficits after six months post-stroke with the verbal fluency tests (Fig. 5B1). Although there was some improvement in the verbal fluency tests after six months, this was not significant (ANOVA semantic fluency p = 0.79, phonemic fluency p = 0.195). Because a more pronounced effect of cerebellum on cognition has been shown in children we looked at verbal fluency in different age groups. Although there seemed a trend with regard to worse fluency at younger age, there was no significant difference between the age groups in both semantic and phonemic fluency (ANOVA; one-way; p = 0.835, p = 0.202 respectively) (Fig. 5B2). With regard to fluency tests both semantic and phonemic fluency in general showed a pathological impairment (resp. Z-score: −2.6 and −2.2) (Fig. 6A). Although nonverbal fluency seemed less affected than verbal fluency, there was a significant positive correlation between semantic fluency and nonverbal fluency (Pearson's r 0.390; p = 0.011). Further analysis showed the odds of cognitive disorders tends more to women compared to men. Phonemic fluency, in particular, was significantly more affected in women (odds ratio [OR], 3.0; 95 % CI, 1.0–9.8) (Fig. 6B). There was no significant difference in ICARS, stroke volume or stroke etiology between women and men that could explain this difference (ICARS men vs women: 5.4 ± 8.4 vs 6.7 ± 6.5, *t*-test; two-tailed, unpaired, p = 0.579, stroke volume men vs women: 17.9 ± 19.0 cm^3 vs 23.9 ± 17.5 cm^3, *t*-test; two-tailed, unpaired, p = 0.372, see Table 1).

3.4. *Relation with clinical and neurological variables*

The FAB test, which is sensitive for testing frontal executive dysfunction, did not show a clinical impairment (Z-score: −1,2).

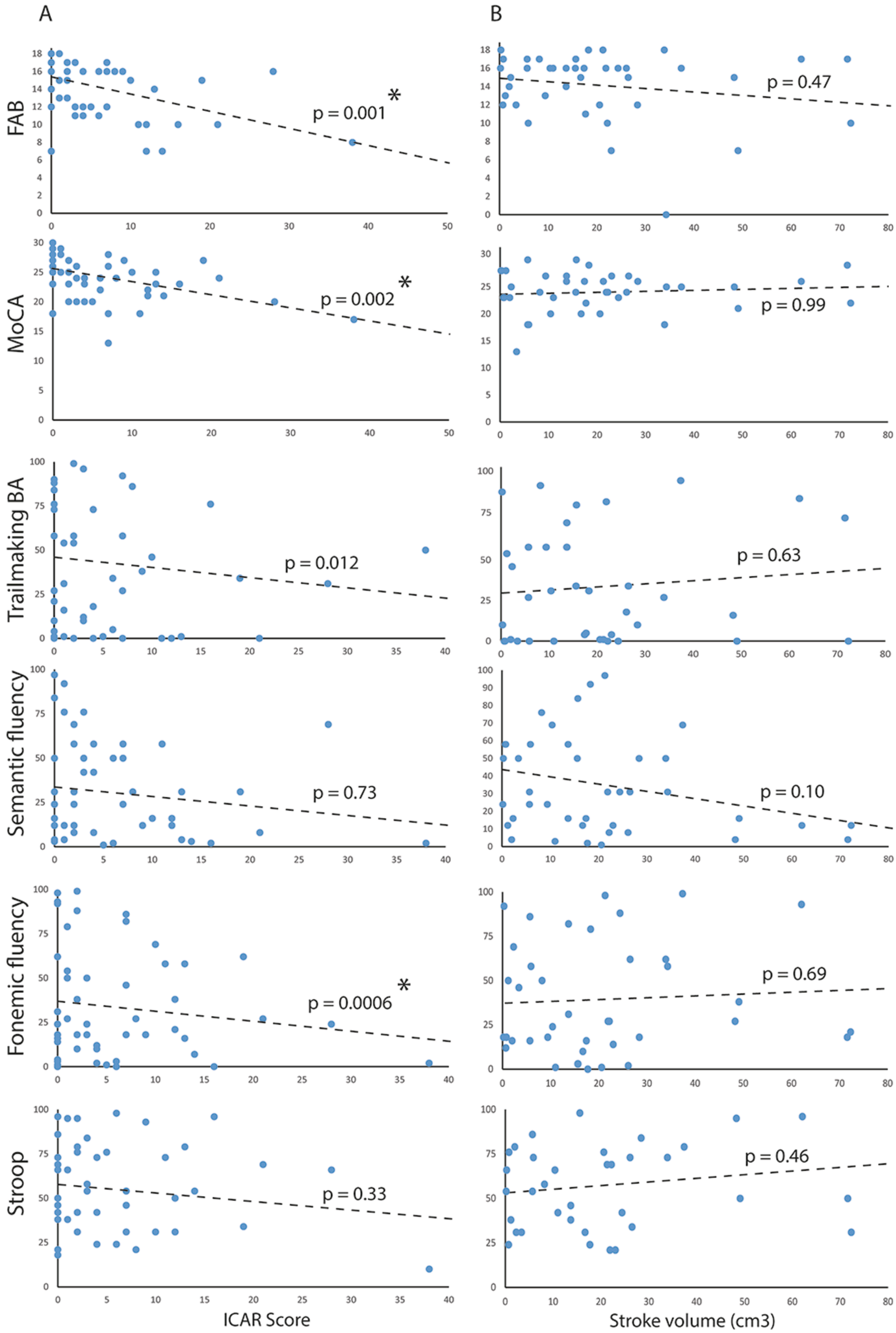

Fig. 4. A graphs showing correlation between ICAR score and results of cognitive tests. All graphs show a negative trend with regard to the ICAR score. The FAB test, MoCA and Phonemic fluency (resp. p = 0.001, p = 0.002 and p = 0.0006) show a significant correlation with the ICARS. B. graphs demonstrating correlation between stroke volume and results of cognitive tests. Only the FAB, Semantic fluency show a negative trend with regard to stroke volume. There is no significant correlation between stroke volume and cognitive results.

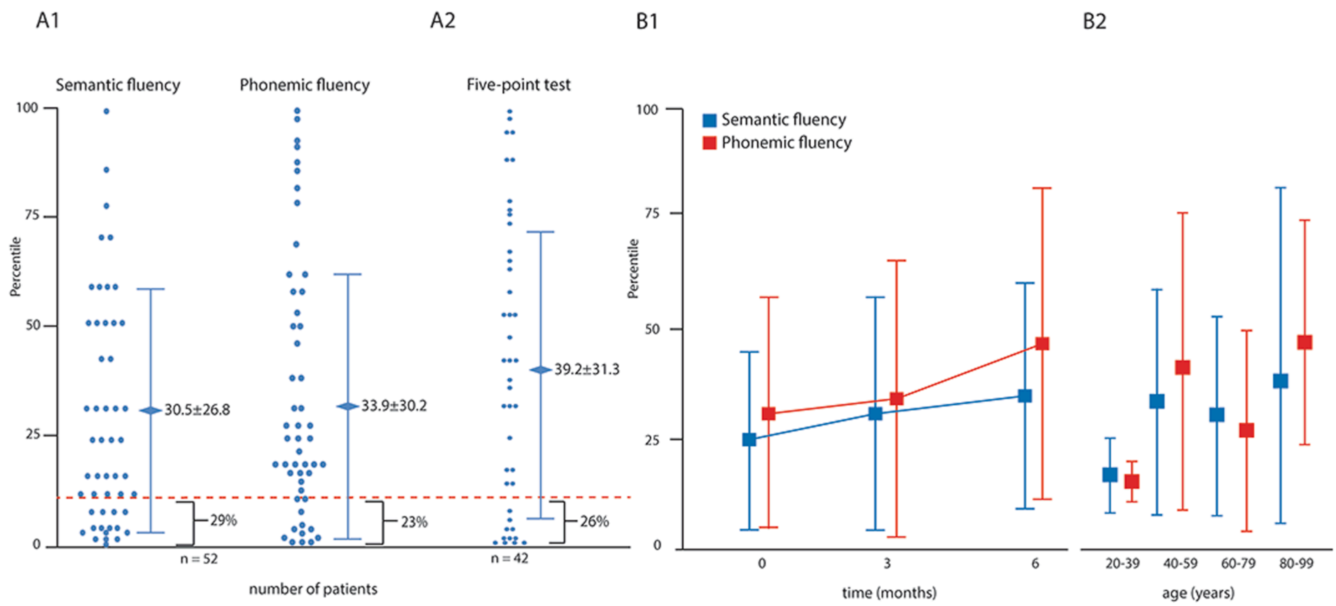

Fig. 5. A1-graph showing the percentile of verbal fluency. For semantic fluency the patients perform 30.5 % below the normative value (mean 30.5 ± 26.8). The first quartile comprises 60 % of the patients (the threshold is depicted by the red dotted line). For phonemic fluency the patients perform 33.9 % below the normative value (mean 33.9 ± 30.8). The first quartile comprises 54 % of the patients (the threshold is depicted by the red dotted line). A2-Scores of the five-point test of 42 cerebellar stroke patients. The first quartile comprises 45 % of the patients (the threshold is depicted by the dotted line). Patients perform 39.2 % below the normative value (mean 39.2 ± 30.1.3). B1-Mean percentile of the fluency tests after 0, 3 and 6 months. The follow-up does not show a significant improvement. However, a non-significant positive trend is present. B2-graph showing the age-dependent percentiles of verbal fluency. In the age of 20–39 there seems a lower percentile of both semantic and phonemic fluency. There is however no significant difference between the age groups. Although the graph suggests a positive trend toward better verbal fluency with increasing age. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

However, there was quite a considerable range within subjects. The MoCA which detects general cognitive impairment scored at the level of a clinical impairment (Z-score: −1,6). Tests for executive functioning and problem solving such as the Stroop interference score showed a clinical impairment (Z-score: −1.8). Furthermore, the Trail Making Test BA showed even a more significant clinical impairment (Z-score: −2.0) (Fig. 6A). In general, none of the patients showed complete normal neuropsychological results in all neuropsychological tests. Seven patients who tested within a normal range of the FAB and MoCA still showed disturbances (z-score ≤ 1.5) in semantic and/or phonemic verbal fluency or Trail Making Test BA.

4. Discussion

4.1. General results

In this prospective study, we demonstrate significant cognitive impairments in a large and homogeneous cohort of isolated cerebellar stroke patients. We found impairments in several cognitive domains which confirms previous limited or heterogeneous studies in cerebellar patients. It demonstrates that the cerebellum is indeed involved in cognitive processing based on isolated cerebellar lesions.

The results show that the impairments are general but more subtle compared to impairments resulting from a correlating cortical area. For instance, the FAB test did not show clinical impairment. However, the wide range of disturbances in our study suggests that the cerebellum is in some way involved in frontal executive functioning. The MoCA, Stroop test and Trail Making Test all scored at the level of a clinical impairment. A recent study in a smaller sample of isolated cerebellar strokes in the chronic stage confirms that MoCA and CCAS-S reveal cognitive impairments in patients (Chirino-Perez et al., 2022). With regard to fluency tests both semantic and phonemic fluency showed even a pathological impairment. In general, most patients showed significant cognitive deficits in a broader spectrum of neuropsychological tests such as executive functioning and inhibitory control, mental flexibility, visuospatial skills and verbal fluency. The Trailmaking A demonstrates that cerebellar patients also have problems with processing speed. This broad involvement in cognitive functioning supports the concept of 'Universal Cerebellar Transform' (UCT) in which a standard computing process subserves cerebellar modulation in movement, cognition and emotion. Furthermore, this process is similar in all cognitive domains (Guell & Schmahmann, 2018; Mitoma et al., 2020). Our study demonstrates that cognitive symptoms in cerebellar disorders fit the range of mild cognitive impairments which is in agreement with the cerebellum as a parallel system. The results support the hypothesis of a Cerebellar Cognitive and Affective Syndrome as proposed by Schmahmann. (Argyropoulos et al., 2020; Hoche et al., 2018).

4.2. Study limitations

We did not investigate the lateralized functional organization of the cerebellum in contrast to other studies (Hokkanen et al., 2006). This study shows a large variation in severity between patients. This variation suggests that stroke location and size are important which was also proposed previously by others (Hokkanen et al., 2006; Stoodley et al., 2016; Stoodley, 2010). Preliminary analysis in our study showed no significant correlation between stroke size or location (left vs right hemisphere respectively, FAB-scores 13.5 ± 3.8 vs 14.7 ± 2.8, MoCA 24.7 ± 3.3 vs 23.2 ± 4.2, TMT 34.0 ± 33.1 vs 34.8 ± 37.4, Semantic fluency 29.8 ± 23.8 vs 34.5 ± 31.4, Phonemic fluency 35.3 ± 31.5 vs 32.5 ± 31.4, Stroop 48.9 ± 23.5 vs 60.3 ± 25.3). However a larger sample size maybe necessary to show significant differences because of the mild cognitive impairments found. We did not compare vermian versus hemispheric or anterior versus postero-lateral localization because the sample size did not allow this analysis. Further extension of the study in the future may reveal such lateralization. However, even small studies in children show a prominent lateralizing effect, suggesting a developmental aspect (Wells & Khademiain, 2008) Another

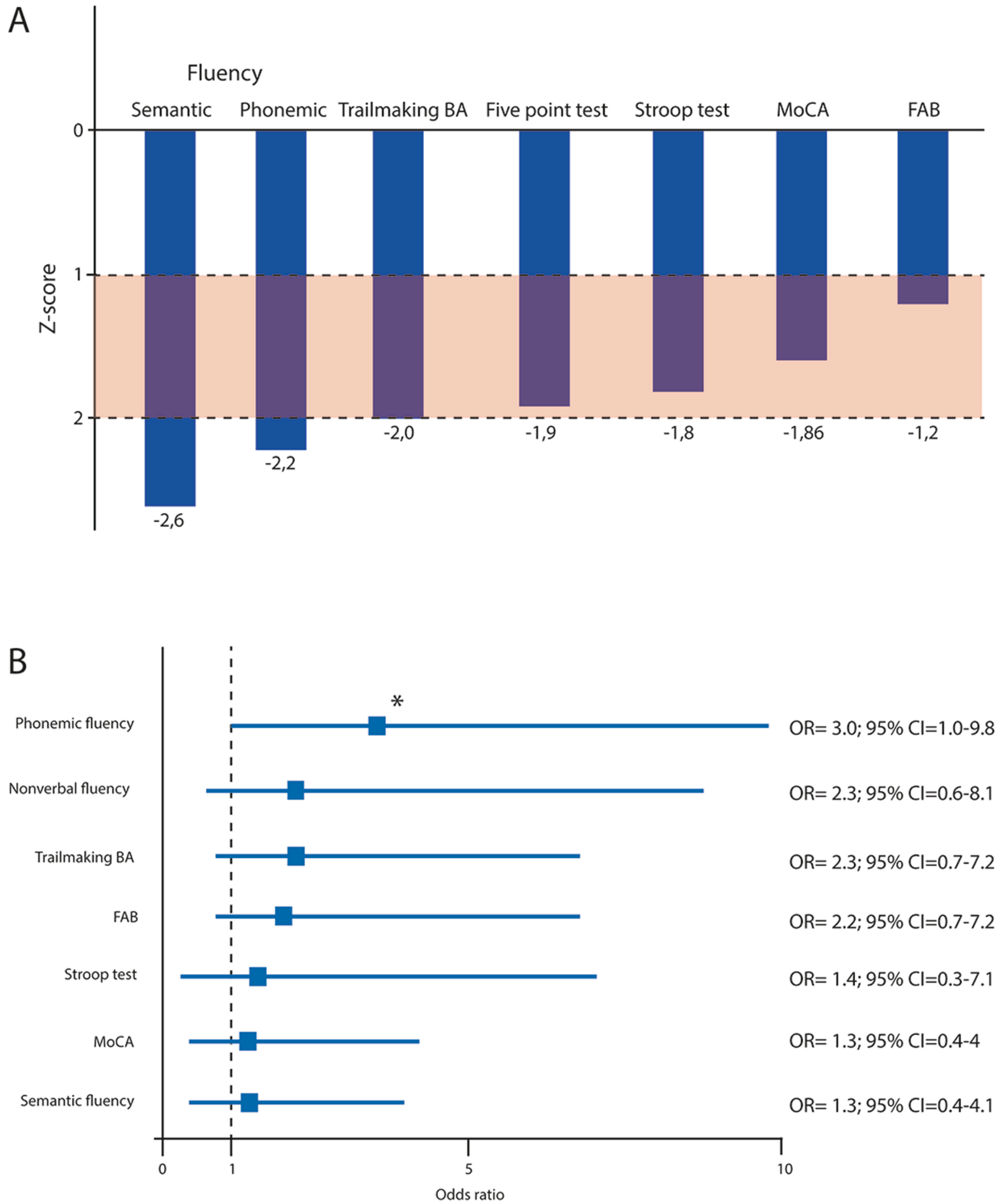

Fig. 6. A-Histogram depicting the Z-score for each test. The pink area shows the threshold ranging from a clinical impairment to a pathological impairment. All tests at least demonstrate a clinical impairment. Both semantic and phonemic fluency show a level at pathological impairment. B-Results of the association between sex and cerebellar cognitive outcomes after stroke. The odds of cognitive disorders show a trend towards women, compared to men. Phonemic fluency is significantly greater in women (OR = 3.0; 95 % CI = 1.0–9.8). All cognitive tests, except for semantic fluency, are ranked in order of the strongest to the smallest odd ratio. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

limitation of the study is the correlation between the ICAR score and language tasks and FAB score. Although these tests are specially designed to tests cognitive abilities one can argue that motor skills may somehow influences the outcome of these tests.

4.3. Follow up and language deficits

Although this study did not focus on affective disturbances, no major behavioral changes were reported at three or at six months follow-up. However, fluency tasks were the most prominently disturbed and persistent in follow-up. Although, there was some improvement after six months, there was no significant difference (Fig. 5B). Compared to children, the cognitive profile (language, visuospatial and verbal memory impairments) and its long lasting effect after cerebellar lesions is similar to adults. However, specific characteristics such as pronounced personality changes and severe speech retardation, seen in children, were not observed in our study. A deficit commonly seen among children with cerebellar lesions called cerebellar mutism is not common in adults. In this study, we found only one patient with a short-lasting mutism. The mutism resolved spontaneously within 3 months. It should be noted that this was the youngest patient in the cohort (21 years). Still, there is a remarkable difference in language impairments between children and adults after cerebellar lesions which suggests a developmental shift in the contribution of cerebellar involvement directed to a more cerebral involvement. Studies in children confirm younger age as one of the risk factors for developing a cerebellar mutism after cerebellar lesions (Levisohn, 2000; Panagopoulos & Gavra, 2023). The language deficits are in agreement with the cerebellar cognitive affective scale, which has a focus on the verbal fluency task, specifically designed to detect cognitive disorders in cerebellar disease (Hoche et al., 2018). Although the verbal fluency task is often considered as a test to assess word retrieval, it also measures memory, and executive functions including logical thinking and problem solving (Shao et al., 2014). Since there was a significant correlation between verbal and nonverbal fluency, it can be argued that lack of fluency is a deficit in executive functioning. For example this test encourages the use of executive skills like flexible thinking, set switching, self-regulation and –monitoring. On the other hand, studies in healthy participants and several clinical case studies point towards involvement of the cerebellum in several language functions, the so-called "linguistic cerebellum", in addition to verbal fluency, such as word repetition, morpho-syntactic processing, reading and writing (Mariën, 2014). We conducted therefore a follow-up study with a more in-depth language testing to reveal the more exact cerebellar involvement in language-processing.

4.4. Sex differences in cerebellar cognitive deficits

Research shows that women have substantial differences in stroke risk factors with regard to men. Moreover, there are differences in presentation and stroke outcomes in women. To our knowledge there are no studies regarding sex differences in cerebellar stroke. We found a trend that cognitive disorders were more prominent in women than men after isolated cerebellar stroke. This is, however, in line with a recent study showing women had worse cognitive outcomes than men at 90 days generally post stroke (Dong et al., 2020). An additional cause in sex difference in cerebellar strokes might be that the cerebellum is sensitive for female sex hormones such as estrogen and estradiol, especially during cerebellar development (Hoche et al., 2012). There were no significant differences in stroke etiology, stroke volume or clinical outcome in women (Table 1).

4.5. Conclusion

In summary, this large homogenous study confirms a standardized role of the cerebellum in various cognitive processes described by previous smaller studies, reports and a *meta*-analysis (Ahmadian et al., 2019). In contrast to most other studies, all patients had an isolated acute cerebellar lesion which means that the etiology and disease process are similar. Unlike tumors, which cause slow compression with coping mechanisms or inflammation and degenerative diseases that affect other pathways outside the cerebellum, all lesions in this study were similar, both anatomically and pathophysiologically. This study demonstrates that focal cerebellar lesions with a uniform etiology can lead to cognitive deficits without the involvement of other brain structures. Specifically, with regard to verbal fluency this study demonstrates an important role of the cerebellum with long term effects post-stroke (up to half a year). Although cognitive impairments in cerebellar stroke are less specific and more subtle as in cortical stroke, this study shows that the cerebellum is generally involved in cognitive processing, especially in language, with a tendency to be more prominent in women.

CRediT authorship contribution statement

Ruben S. van der Giessen: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Methodology, Writing – original draft. **Djaina Satoer:** Data curation, Formal analysis, Writing – review & editing. **Peter J. Koudstaal:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

The authors want to acknowledge Maaike Scheele and Naziha Bouyakoub-El Ghannouti for their contribution in taking the patients tests and helping in setting up the CODECS study.

Funding

This study was supported by grant no. 514 of the Fund of Stichting Coolsingel.

References

Ahmadian, N., van Zandvoort, M., & Robe, P. A. (2019). The Cerebellar Cognitive Affective Syndrome-a Meta-analysis. *Cerebellum, 18*(5), 941–950.
Alexander, M. P. (2012). Cognitive impairments due to focal cerebellar injuries in adults. *Cortex, 48*(8), 980–990.
Appollonio, I., Isella, V., Piamarta, F., Consoli, T., Villa, M. L., Forapani, E., Russo, A., & Nichelli, P. (2005). The Frontal Assessment Battery (FAB): normative values in an Italian population sample. *Neurological Science., 26*, 108–116.
Argyropoulos, G., Adamaszek, M., Leggio, M., Manto, M., Masciullo, M., Molinari, M., Stoodley, C., Van Overwalle, F., Ivry, R., & Schmahmann, J. (2020). The Cerebellar Cognitive Affective/Schmahmann Syndrome: a Task Force Paper. *Cerebellum, 19*(1), 102–125.
Baillieux, H. (2010). Cognitive and affective disturbances following focal cerebellar damage in adults: A neuropsychological and SPECT study. *Cortex, 46*(7), 869–879.
Bianchi, D. P. F., Chieffo, R., Frassanito, P., Di Rocco, C., & Tamburrini, G. (2019). Cerebellar mutism: the predictive role of preoperative language evaluation. *Child Nerv Syst., 36*(6), 1153–1157.
Bolceková, E. M. M., Van Tran, Q., Kukal, J., Ostrý, S., Kulišťák, P., & Rusina, R. (2017). Cognitive impairment in cerebellar lesions: A logit model based on neuropsychological testing. *Cerebellum Ataxias., 4*(13).
Chirino-Perez, A. M.-M. O., Munoz-Lopez, J. I., Hernandez-Castillo, et al. (2022). Mapping the Cerebellar Cognitive Affective Syndrome in Patients with Chronic Cerebellar Strokes. *Cerebellum, 21*(2), 208–218.
Clausi, S. O. G., Lupo, M., Siciliano, L., Bozzali, M., & Leggio, M. (2019). The Cerebellar Predictions for Social Interactions: Theory of Mind Abilities in Patients With Degenerative Cerebellar Atrophy. *Frontiers in Cellular Neuroscience, 8*(12), 510.
Dong, L., Morgenstern, L., & Lisabeth, L. D. (2020). Poststroke Cognitive Outcomes: Sex Differences and Contributing Factors. *Journal of the American Heart Association, 9*(14).
Dubois, M., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: A frontal assessment battery at bedside. *Neurology, 55*, 1621–1626.
Gottwald, B., Wilde, B., Mihajlovic, Z., & Mehdorn, H. M. (2004). Evidence for distinct cognitive deficits after focal cerebellar lesions. *Journal of Neurology, Neurosurgery, and Psychiatry, 75*(11), 1524–1531.
Grimaldi, G. M. M. (2012). Topography of cerebellar deficits in humans. *Review cerebellum., 11*(2), 336–351.
Guell, X. G. J., & Schmahmann, J. D. (2018). Embodied cognition and the cerebellum: Perspectives from the Dysmetria of Thought and the Universal Cerebellar Transform theories. *Cortex, 100*, 140–148.
Hammes, J. G. W. (1971). *Stroop Kleur Woord Test*. Lisse: Swets and Zeitlinger BV.
Hedges, V. L., Meisel, R. L., & Mermelstein, P. G. (2012). The cerebellum as a target for estrogen action. *Frontiers in Neuroendocrinology., 33*(4), 403–411.
Hoche, F. G. X., Vangel, M. G., Sherman, J. C., & Schmahmann, J. D. (2018). The cerebellar cognitive affective/Schmahmann syndrome scale. *Brain, 141*(1), 248–270.
Hokkanen, L. S., Kauranen, V., Roine, R. O., Salonen, O., & Kotila, M. (2006). Subtle cognitive deficits after cerebellar infarcts. *European Journal of Neurology, 13*(2), 161–170.
Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nature Reviews. Neuroscience, 9*(4), 304–313.
Kalashnikova, L. A. (2005). Cognitive impairments in cerebellar infarcts. *Neurosi Behav Physiol., 35*(8), 773–779.

Lagarde, J., Hantkie, O., Hajjioui, A., & Yelnik, A. (2009). Neuropsychological disorders induced by cerebellar damage. *Annals of Physical and Rehabilitation Medicine, 52*(4), 360–370.

Leggio, M. G. S. M., Petrosini, L., & Molinari, M. (2000). Phonological grouping is specifically affected in cerebellar patients: A verbal fluency study. *Journal of Neurology, Neurosurgery, and Psychiatry, 69*(1), 102–106.

Levisohn, L. (2000). Neuropsychological consequences of cerebellar tumour resection in children: Cerebellar cognitive affective syndrome in a paediatric population. *Brain, 123*(5), 1041–1050.

Lezak, M. H. D., Bigler, E., & Tranel, D. (2012). *Neuropsychological Assessment*. New York, NY: Oxford University Press.

Lipton, A. M., Ohman, K. A., Womack, K. B., Hynan, L. S., Ninman, E. T., & Lacritz, L. H. (2005). Subscores of the FAB differentiate frontotemporal lobar degeneration from AD. *Neurology, 65*(5), 726–731.

Malm, J., Kristensen, B., Karlsson, T., Carlberg, B., Fagerlund, M., & Olsson, T. (1998). Cognitive impairment in young adults with infratentorial infarcts. *Neurology, 51*(2), 433–440.

Mariën, P. (2014). Consensus Paper: Language and the Cerebellum: An Ongoing Enigma. *The Cerebellum, 13*, 386–410.

Mitoma, H., Buffo, A., Gelfo, F., Guell, X., Fuca, E., Kakei, S., et al. (2020). Consensus Paper. Cerebellar Reserve: From Cerebellar Physiology to Cerebellar Disorders. *The Cerebellum, 19*(1), 131–153.

Nasreddine, Z. S., & Bédirian, V. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *JAGS., 53*, 695–699.

Panagopoulos, D. S. G., Gavra, M., et al. (2023). The entity of Cerebellar Mutism Syndrome: A Narrative Review Centered on the Etiology, Diagnostics, Prevention, and Therapeutic Options. *Children, 10*(83), 1–14.

Reitan, R. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills, 8*(271–276).

Richter, S. G. M., Aslan, B., Wilhelm, H., Schoch, B., Dimitrova, A., Gizewski, E., Ziegler, W., Karnath, H., & Timmann, D. (2007). Cognitive functions in patients with MR-defined chronic focal cerebellar lesions. *Journal of neurology., 254*(9), 1193–1203.

Rossini CC, P. M., Pauri, F., & Baron, J. (2003). Post-stroke plastic reorganisation in the adult brain. *Lancet Neurology, 2*(8), 493–502.

Schmahmann, J. D. (1991). An emerging concept: The cerebellar contribution to higher function. *Archives of Neurology., 48*(11), 1178–1187.

Schmahmann, J. D. S. J. (1998). The cerebellar cognitive affective syndrome. *Brain, 121*(4), 561–579.

Schmahmann, J. D. (2020). Pediatric post-operative cerebellar mutism syndrome, cerebellar cognitive affective syndrome, and posterior fossa syndrome: Historical review and proposed resolution to guide future study. *Child Nerv Syst., 36*(6), 1205–1214.

Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in Psychology, 5*(772).

Smet, H.J.D. (2007). The cerebellum and Language: the story so far. 59(4).

Sokolov, A. A., Erb, M., Grodd, W., Tatagiba, M. S., Frackowiak, R. S., & Pavlova, M. A. (2014). Recovery of biological motion perception and network plasticity after cerebellar tumor removal. *Cortex, 59*, 146–152.

Stoodley, C. J. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex, 46*(7), 831–844.

Stoodley, C. J., MacMore, J. P., Makris, N., Sherman, J. C., & Schmahmann, J. D. (2016). Location of lesion determines motor vs. cognitive consequences in patients with cerebellar stroke. *Neuroimage Clin., 12*(12), 765–775.

Strick, P. L., Dum, R. P., & Fiez, J. A. (2009). Cerebellum and nonmotor function. *Annual Review of Neuroscience, 32*, 413–434.

Taskiran-Sag, A. U. U. H., Ahmet Uyanik, S., & Oztekin, N. (2020). Prospective investigation of cerebellar cognitive affective syndrome in a previously non-demented population of acute cerebellar stroke. *Journal of stroke and cerebrovascular diseases., 29*(8).

Tavano, A., Grasso, R., Gagliardi, C., Triulzi, F., Bresolin, N., Fabbro, F., & Borgatti, R. (2007). Disorders of cognitive and affective development in cerebellar malformations. *Brain, 130*(Pt 10), 2646–2660.

Tucha, L., Aschenbrenner, S., Koerts, J., & Lange, K. W. (2012). The five-point test: Reliability, validity and normative data for children and adults. *PLoS One1, 7*(9), e46080.

Van Overwalle, F. M. M., Cattaneo, Z., Clausi, S., Ferrari, C., Gabrieli, J. E. D., Guell, X., Heleven, E., Lupo, M., Ma, Q., Michelutti, M., Olivito, G., Pu, M., Rice, L. C., Schmahmann, J. D., Siciliano, L., Sokolov, A. A., Stoodley, C. J., van Dun, K., Vandervert, L., & Leggio, M. (2020). Consensus Paper: Cerebellum and Social Cognition. *Cerebellum, 19*(6), 833–868.

Wells, E. M., Khademiain, Z. P., et al. (2008). The cerebellar mutism syndrome and its relation to cerebellar cognitive function and the cerebellar cognitive affective disorder. *Developmental Disabilities Research Reviews., 14*, 221–228.

Ziemus OB, B., Luerding, R., Schlosser, R., Schuierer, G., Bogdahn, U., & Greenlee, M. W. (2007). Impaired working-memory after cerebellar infarcts paralleled by changes in BOLD signal of a cortico-cerebellar circuit. *Neuropsychologia, 15*(45(9)), 2016–2024.

Zigmond, A. S. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361–370.