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Assessing the link between cerebellar volume and cognitive function in Alzheimer's disease: a pilot study

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The cerebellum, long recognized for its role in motor functions, has become increasingly acknowledged for its involvement in a broader spectrum of cognitive functions. Given the cerebellum's strong neuronal connections with cerebral regions affected by neurodegenerative diseases, this study investigated the cerebellar contribution to cognitive decline in Alzheimer's disease (AD). This study retrospectively analysed 127 individuals with subjective cognitive decline (SCD, *n* = 46), mild cognitive impairment due to AD (MCI, *n* = 24), and AD dementia (ADD, *n* = 57). Grey and white matter volumes of the whole cerebellum and its lobules were examined and correlated with cognitive scores. Significant grey matter atrophy was observed in posterior cerebellar regions (including crus II, lobule VIIa, VIIIa, VIIIb, and X), particularly between SCD and ADD, but not between MCI and ADD. Additionally, cerebellar volume positively correlated with cognitive function in SCD, MCI and ADD. These findings support the hypothesis that cerebellar atrophy is associated with cognitive symptoms of neurodegenerative diseases like AD.

Keywords Alzheimer's disease (AD), Brain volume, Atrophy, Cerebellum, Cognitive decline

Alzheimer's disease (AD) is a prevalent neurodegenerative brain disorder characterised by progressive structural and functional alterations in the brain[1,2]. Central to AD's pathology is the accumulation of amyloid plaques and neurofibrillary tangles, which gradually damage neurons, axons, and synapses. This process of neurodegeneration results in significant atrophy in regions such as the hippocampus, posterior cingulate cortex, and precuneus[3]. Clinically, these changes are reflected in a spectrum of cognitive deficits, including disturbances in memory, language, orientation, and attention, as well as alterations in mood, behaviour, and personality[4]. Interestingly, the pattern of brain atrophy in AD reflects the connectivity patterns seen in healthy individuals, particularly in the default mode network (DMN)[5]. This network typically shows reduced activity during attention-demanding tasks but increases during complex cognitive activities related to memory or abstract thinking[3,6]. This suggests a link between AD's pathology and pre-existing brain architecture.

The cerebellum was traditionally considered unaffected by neurodegeneration in AD. However, recent studies suggest it undergoes pathological changes similar to those in the cortex[4]. Beyond its role in motor control, the cerebellum is increasingly recognized for its involvement in non-motor functions like cognition and sleep[4]. These non-motor functions—such as executive control, social-linguistic processes, and working memory—are thought to be organised into a threefold spatial representation within the posterior cerebellum[7–9]. Buckner et al.[7] first identified this organization using resting-state fMRI, demonstrating that cerebellar functional networks mirror cerebral cortical hierarchies. They observed that motor regions were localized to lobules I–VI/VIII, while higher-order cognitive and affective networks, such as the DMN, were found in Crus I/II and lobule

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IX. Guell et al.[8] further confirmed this architecture through task-based fMRI, showing that distinct cerebellar subregions (lobules VI/Crus I, Crus II/VIIB, and IX/X) are activated during language, working memory, and social-emotional tasks, with their connectivity profiles matching frontoparietal and default-mode networks. Nettekoven et al.[9] recently validated the tripartite model across seven task-fMRI datasets.

Particularly noteworthy is lobule VII, specifically Crus I/II, which is of significant interest due to its functional connections with key DMN nodes, such as the posterior cingulate cortex and medial prefrontal cortex[7,10,11]. These regions are crucial for episodic memory, largely through their interactions with the hippocampus[3].

Given the DMN's critical role in higher-order cognitive functions and its vulnerability in AD, the involvement of Crus I/II in this network suggests that structural or functional impairments to Crus I/II could disrupt DMN dynamics, thereby contributing to the cognitive symptoms observed in AD. Disruptions in connectivity between Crus I/II and cortical DMN regions have been documented in AD, correlating with impaired cognitive functioning[11–13].

In addition to functional alterations, structural changes in Crus I/II have also been documented in AD. Zhou et al.[13] found a significant reduction in grey matter (GM) volume in Crus I/II in both AD dementia (ADD) patients and those with mild cognitive impairment (MCI), suggesting an early and progressive involvement. Conversely, Toniolo et al.[14] reported a reduction in volume in Crus I exclusively among ADD patients, while MCI patients exhibited a different pattern of cerebellar atrophy. Furthermore, Guo et al.[15] observed distinct patterns of atrophy in Crus I in ADD compared to other forms of dementia, such as frontotemporal dementia, suggesting a specific involvement of the cerebellum, particularly the Crus I region, in AD pathology. However, while a number of studies emphasize the posterior cerebellum, particularly Crus I/II, as being highly susceptible to volumetric changes in AD, how the cerebellum is affected by the disease and at which stage remain subjects of ongoing debate[16–21].

Furthermore, whether cerebellar volume changes correlate with cognitive changes in AD remains uncertain, as the evidence is limited and inconsistent. While some studies have found positive correlations between specific cerebellar regions—such as the right hemisphere, posterior lobe, and vermis—and cognitive performance on measures like the Mini-Mental State Examination (MMSE) and its language subscale[21,22]other studies have not identified such associations[23]. Further complicating the picture, Lin et al.[18] reported that larger cerebellar grey matter (GM) volume was associated with poorer cognitive performance, as assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale 13 (ADAS-cog 13), in individuals with MCI, but not in those with ADD or in healthy controls (HC). In ADD, smaller cerebellar GM volume was linked to more severe executive dysfunction, as measured by the Trail Making Test A and B[18]. Despite the inconsistencies, these findings suggest that cerebellar pathology may play a role in AD, potentially disrupting the cerebro-cerebellar network and contributing to further cognitive decline.

Beyond its pathological involvement, recent research has introduced the concept of cerebellar cognitive reserve (CCR) in AD[24]. This concept, akin to the cognitive reserve hypothesis traditionally applied to cortical structures, can be defined as the adaptability and resilience of cerebellar structure and function in response to both beneficial (such as environmental and cognitive enrichment), and adverse conditions (such as neurodegenerative pathology)[24]. According to this hypothesis, individuals with preserved or larger cerebellar volumes, and with stronger cerebro-cerebellar connectivity, may be better equipped to compensate for neurodegenerative changes, thereby delaying the onset of clinical symptoms and slowing cognitive decline[24]. For example, studies have shown that larger cerebellar volumes are associated with improved cognitive performance in early AD, particularly among individuals with low amyloid burden[25]. However, this protective effect appears to diminish as the disease progresses to more advanced stages[25]. Additionally, factors like intellectual engagement may enhance CCR by fostering structural and functional plasticity within the cerebellum[26].

Given the complexity of these findings, the precise role of cerebellar volume in AD pathology, and whether it serves a protective or detrimental function, remain unclear. Therefore, this study aims to explore the cross-sectional relationships between cerebellar volume alterations, particularly in DMN-associated areas, and cognitive function in biomarker-confirmed and clinically diagnosed (probable AD without biomarker confirmation) AD patients. The study focuses on (1) identifying significant cerebellar volume differences, including both grey and white matter volume (WM), among three diagnostic groups—subjective cognitive decline (SCD), MCI due to AD, and ADD—and (2) correlating these volume differences with neuropsychological test scores. Based on existing literature, we anticipated that individuals with MCI and/or ADD would show significant differences in whole cerebellar volume and grey matter compared to those with SCD. We specifically expected to find differences in the posterior cerebellum, especially in crus I/II, and that these changes would correlate with cognitive changes across the Alzheimer's disease continuum.

Results

Sample characteristics

For this study, we selected the following demographic and clinical variables: age, sex (a biological attribute, classified as either male or female based), level of education, presence of alcohol abuse and the number of days between the administration of neuropsychological testing and the MRI scan. The level of education was classified as Lower education for individuals with Basic and/or Secondary (high school) education, and Higher education for individuals with a Bachelor and/or Master, and/or PhD degree. Alcohol abuse was assessed based on self-reported information from the patient or documentation in their medical file, and it was classified as currently present, having occurred in the past, or never present. These variables were chosen due to their known associations with brain structure, particularly the volume of the cerebellum, and their potential impact on cognitive function assessments[26–31].

As depicted in Table 1, the analyses revealed a significant difference in age, level of education and cognitive functioning between the diagnostic groups. We found an age gradient among the three diagnostic groups with

	SCD		MCI		ADD			
	M	SD	M	SD	M	SD	F	*p*
Age	61.6	8.7	75	5.3	76.7	8.6	47.551	< 0.001*
sMMSE	28.5	0.9	25.7	2.2	20	5.1	35.792	< 0.001*
ACE-R	92.3	3.3	74	11.5	57	16	38.638	< 0.001*
	n		n		n			
Sex							5.666	0.059
Male	24		12		20			
Female	21		11		42			
Educational level							22.170	0.005 *
Lower education [a]	17		14		43			
Higher education[b]	25		9		16			
Alcohol abuse							3.402	0.493
Never	29		14		33			
In the past	0		1		4			
Current	6		3		9			

Table 1. Demographics, mean (M), and standard deviations (SD) of cognitive test scores (sMMSE and ACE-R) across diagnosis groups (SCD, MCI, and AD). [a]Lower education = Basic and/or Secondary (high school) education. [b]Higher education = Bachelor and/or Master and/or PhD.

SCD being generally younger patients than MCI ($p < 0.001$) and ADD ($p < 0.001$) patients. However, we did not find a significant age difference between the MCI and ADD groups. Regarding education levels, individuals with dementia were more likely to have lower educational levels compared to those with SCD. Specifically, 60% of the SCD group had higher education qualifications, while 73% of the dementia group had lower educational levels. Additionally, there were significant differences in standardised MMSE (sMMSE) and ACE-R scores across the three groups ($p < 0.001$). No significant differences were observed in gender distribution or alcohol abuse behaviour.

We opted to control for the days between neuropsychological testing and MRI in the correlation analysis as this variable exhibited a standard deviation of 110, indicating considerable variability in the time interval between these assessments (see supplementary table S1). The wide range (0 to 861 days) suggests that while some participants underwent testing shortly after their MRI, others experienced more delay. However, it is worth noting that the larger gaps were observed in a minority of patients ($N = 8$), with the majority of participants being tested either soon after or within a more moderate time frame relative to their MRI.

Cerebellum volume differences across diagnostic categories

Based on the one-way ANOVA results presented in Table 2, significant differences were observed among 14 cerebellar regions with effect sizes ranging from small to moderate, especially between SCD and ADD groups. The dementia group generally exhibited lower volumes compared to the SCD group. Additionally, significant differences were observed in the left and right lobule X between the SCD and MCI groups, with both lobules showing significantly lower volumes in the MCI group as compared to the SCD group. No significant differences were observed in the white matter volume of the entire cerebellum. Additionally, no significant differences were found in the grey matter volumes of the following posterior lobules: Left VI, Vermis VI, Right VI, Left Crus I, Right Crus I, Vermis Crus II, Right Crus II, Vermis VIIb, Vermis VIIa, Vermis VIIIb, Left IC, Vermis IX, Right IX, Vermis X, as well as all anterior regions (see supplementary table S2).

A one-way ANOVA was performed to examine lateralization patterns by comparing the differences between the left and right parts of the cerebellum. However, none of the tests showed significant results. While no lateralization patterns were identified, analysing the percentages of volume loss unveiled varying degrees of decline across distinct cerebellar regions. Particularly, the right parts of the lobule X, VIIb, VIIIa and VIIIb regions displayed a tendency of higher percentages of volume loss compared to their left hemisphere counterparts.

ANCOVA results, controlling for age and education (see Table 3), revealed that the overall model was significant across all regions, indicating that the combination of diagnosis, age and educational level significantly predicted cerebellar volume. The analysis indicates that age is the only significant predictor of cerebellar volume in the multivariate model. Education and diagnosis did not significantly contribute to cerebellar volume in this model, suggesting that age was the primary driver of the observed effects on cerebellar volume. This was further confirmed by the significant main effect of age in nearly all regions, except the left crus II and left and right VIIIb, with older age being associated with smaller cerebellar volumes.

Despite the lack of statistical significance, the multivariate tests revealed a medium effect size for diagnosis, suggesting that diagnosis still contributes meaningfully to the variance in cerebellar volumes across regions. While the effect sizes were smaller in the between-subjects tests for individual cerebellar regions, they still indicated small to very small effects, which still point to subtle variations in cerebellar volumes across diagnostic groups.

	SCD		MCI		ADD					CI (95%)		
	M	SD	M	SD	M	SD	F	*p*	η2	Lower	Upper	Volume loss in %
Whole cerebellum	147.48	12.08	142.90	11.03	140.89	13.91	3.419	0.036	0.052	0.000	0.135	SCD-ADD: 4.47%
Grey Matter	122.01	9.83	118.49	8.97	116.21	11.57	4.394	0.014	0.058	0.000	0.143	SCD-ADD: 4.75%
Left Crus II	10.89	1.29	10.21	1.69	10	1.65	4.719	0.011	0.065	0.002	0.154	SCD-ADD: 8.17%
Left VIIb	4.50	0.62	4.26	0.64	4.09	0.66	3.823	0.024	0.076	0.006	0.168	SCD-ADD: 9.11%
Right VIIb	4.97	0.74	4.76	0.81	4.43	0.76	3.826	0.024	0.092	0.013	0.188	SCD-ADD: 10.86%
Left VIIIa	5.08	0.84	4.88	0.71	4.63	0.62	4.341	0.015	0.075	0.006	0.166	SCD-ADD: 8.86%
Right VIIIa	4.55	0.68	4.34	0.61	4.09	0.62	5.073	0.008	0.096	0.015	0.194	SCD-ADD: 10.11%
Left VIIIb	3.37	0.46	3.40	0.40	3.16	0.45	6.269	0.003	0.058	0.000	0.143	SCD-ADD: 6.22%
Right VIIIb	3.16	0.42	3.08	0.35	2.92	0.44	5.001	0.008	0.067	0.003	0.156	SCD-ADD: 7.59%
Left X	0.54	0.10	0.46	0.10	0.46	0.13	6.580	0.003	0.101	0.017	0.199	SCD-ADD: 14.81% SCD-MCI: 14.81%
Right X	0.54	0.09	0.45	0.09	0.47	0.11	3.819	0.025	0.117	0.026	0.219	SCD-ADD: 14.81% SCD-MCI: 16.67%
Posterior Cerebellum	104.60	8.58	101.11	8.60	99.05	10.39	4.476	0.013	0.066	0.003	0.155	SCD-ADD: 5.31%
Left Cerebellum	49.69	4.30	48.08	4.20	46.86	5.05	6.929	0.001	0.071	0.004	0.161	SCD-ADD: 5.7%
Right Cerebellum	49.29	3.85	47.58	4.35	46.83	5.02	8.208	< 0.001	0.058	0.000	0.143	SCD-ADD: 4.99%

Table 2. Mean volume of the 14 cerebellar regions showing significant differences according to diagnosis (SCD, MCI, ADD), ANOVA results, effect sizes, confidence intervals and percentages volume loss between groups with significant differences (SCD-ADD and SCD-MCI).

	Diagnosis*age			Diagnosis			Age			Level of education		
	F	*p*	η2	F	p	η2	F	*p*	η2	F	p	η2
Multivariate tests												
Wilk's Lambda	0.868	0.661	0.118	0.980	0.490	0.123	3.386	< 0.001	0.326	0.853	0.763	0.108
Test of between-subjects effects												
Whole cerebellum	0.158	0.854	0.003	0.299	0.742	0.005	12.791	< 0.001	0.103	1.126	0.348	0.039
Grey Matter	0.206	0.814	0.004	0.290	0.749	0.005	12.090	< 0.001	0.098	1.230	0.302	0.042
Left Crus II	0.436	0.648	0.008	0.498	0.609	0.009	1.473	0.227	0.013	0.239	0.916	0.009
Left VIIb	0.643	0.528	0.011	0.696	0.501	0.012	5.944	0.016	0.051	0.969	0.428	0.034
Right VIIb	0.361	0.698	0.006	0.443	0.643	0.008	7.368	0.008	0.062	0.315	0.867	0.011
Left VIIIa	0.816	0.445	0.014	0.909	0.406	0.016	6.353	0.013	0.054	1.383	0.244	0.047
Right VIIIa	0.217	0.805	0.004	0.273	0.762	0.005	4.933	0.028	0.043	1.524	0.200	0.052
Left VIIIb	0.908	0.406	0.016	0.811	0.447	0.014	0.392	0.532	0.004	0.860	0.491	0.030
Right VIIIb	0.083	0.921	0.001	0.105	0.900	0.002	0.847	0.359	0.008	0.848	0.498	0.030
Left X	0.450	0.639	0.008	0.365	0.695	0.007	20.585	< 0.001	0.156	0.449	0.773	0.016
Right X	0.677	0.510	0.012	0.817	0.444	0.015	13.478	< 0.001	0.108	0.276	0.893	0.010
Posterior cerebellum	0.291	0.748	0.005	0.338	0.714	0.006	13.050	< 0.001	0.105	0.921	0.454	0.032
Left cerebellum	0.201	0.818	0.004	0.209	0.812	0.004	11.671	< 0.001	0.095	0.918	0.456	0.032
Right cerebellum	0.574	0.565	0.010	0.689	0.504	0.012	14.182	< 0.001	0.113	0.934	0.447	0.033

Table 3. ANCOVA results and effect sizes (η2) when controlling for age.

Additionally, no significant interaction was found between diagnostic status and age ($p = 0.611$, $\eta^2 = 0.118$), suggesting that the effect of diagnosis on cerebellar volume, or lack thereof, does not change depending on the person's age.

As seen in Table 4, the correlation analysis revealed a negative correlation between age and cerebellar region volumes, indicating a consistent relationship between these variables.

To validate our cerebellar volume findings, we conducted a control analysis comparing hippocampal volumes across the diagnostic groups (SCD, MCI, and ADD). A one-way ANOVA revealed a significant difference in hippocampal volume between the groups ($p < 0.001$). Post hoc analyses confirmed a stepwise decline in hippocampal volume from SCD to MCI and from MCI to ADD. Regression analysis showed that both diagnosis ($p < 0.001$, $\eta^2 = 0.277$) and age ($p = 0.020$, $\eta^2 = 0.043$) were significant predictors of hippocampal volume. A model including age alone explained 28.6% of the variance in hippocampal volume ($R^2 = 0.286$), while adding diagnosis as a predictor increased the explained variance to 47.8% ($R^2 = 0.478$), indicating a substantial contribution of diagnosis to hippocampal volume differences beyond age. To quantify the degree of atrophy relative to the

	Age	
	Pearson correlation	p(2-tailed)
Whole cerebellum	− 0.465	< 0.001*
Grey Matter	− 0.451	< 0.001*
Posterior cerebellum	− 0.459	< 0.001*
Left cerebellum	− 0.461	< 0.001*
Right Cerebellum	− 0.447	< 0.001*
Left Crus II	− 0.309	< 0.001*
Left VIIb	− 0.371	< 0.001*
Right VIIb	− 0.412	< 0.001*
Left VIIIa	− 0.370	< 0.001*
Right VIIIa	− 0.408	< 0.001
Left VIIIb	− 0.232	< 0.001*
Right VIIIb	− 0.206	0.020*
Left X	− 0.550	< 0.001*
Right X	− 0.546	< 0.001*

Table 4. Pearson correlation between age and volume of cerebellar regions.

SCD group, we calculated the percentage volume loss: MCI showed a 9.27% reduction, ADD showed a 19.48% reduction, and the difference between MCI and ADD was 11.22%, all statistically significant ($p < 0.001$).

Link between cerebellar volume and cognitive performance

Partial correlations

A partial correlation analysis (two-tailed), adjusting for the time interval between MRI scans and neuropsychological testing, was performed to examine the relationship between sMMSE and ACE-R test scores and the cerebellar regions exhibiting significant volume differences. In the MCI group, sMMSE scores showed significant positive correlations with the grey matter volume ($r = 0.484$ $p = 0.027$), posterior cerebellum ($r = 0.514$, $p = 0.017$), left cerebellum ($r = 0.559$, $p = 0.008$), and right cerebellum ($r = 0.515$ $p = 0.017$). Additionally, positive correlations were found with the whole cerebellum ($r = 0.484$, $p = 0.022$) and left Crus II ($r = 0.442$, $p = 0.045$), whereas these associations were not present in the ADD group. In contrast, in the ADD group, sMMSE scores correlated positively with the grey matter volume ($r = 0.285$ $p = 0.041$), posterior cerebellum ($r = 0.300$, $p = 0.031$), left cerebellum ($r = 0.295$, $p = 0.034$), and right cerebellum ($r = 0.285$, $p = 0.040$), similar to the MCI group. However, additional significant correlations were observed with the right VIIb ($r = 0.299$, $p = 0.031$) and left X regions ($r = 0.387$, $p = 0.005$), which were not present in MCI. No significant correlations were found in the SCD group.

The partial correlation analysis of total ACE-R scores revealed a significant positive association with multiple cerebellar volumes exclusively in the MCI group. Specifically, significant correlations were observed with the whole cerebellum ($r = 0.641$, $p = 0.004$), grey matter ($p = 0.655$, $p = 0.003$), left Crus II ($r = 0.550$, $p = 0.018$), posterior cerebellum ($r = 0.684$,$p = 0.002$), and both left and right cerebellum ($r = 0.684$, $p = 0.001$ and $r = 0.691$, $p = 0.001$). In contrast, in the ADD group, only the right X region showed a significant positive correlation with ACE-R scores ($r = 0.210$, $p = 0.007$). No correlations were found between ACE-R scores and the different cerebellar volumes in the SCD group.

Further analysis of ACE-R subscale scores reinforced these findings by identifying specific cerebellar regions associated with different cognitive domains in MCI. Significant positive correlations were observed between whole cerebellar volume and attention ($r = 0.487$, $p = 0.034$), word fluency ($r = 0.609$, $p = 0.006$), language ($r = 0.650$, $p = 0.003$), and visuoperceptual function ($r = 0.455$, $p = 0.050$), while grey matter volume correlated with memory ($r = 0.489$, $p = 0.033$), word fluency ($r = 0.589$, $p = 0.008$), and language ($r = 0.635$, $p = 0.003$). At the lobular level, left Crus II correlated strongly with memory ($r = 0.527$, $p = 0.010$) and language ($r = 0.541$, $p = 0.017$), right VIIB with visuoperceptual function ($r = 0.503$, $p = 0.028$), and left VIIIa/VIIIb with word fluency ($r = 0.497$, $p = 0.030$ and $r = 0.578$, $p = 0.010$).

In contrast, and in line with the findings for total ACE-R scores, the ADD group exhibited fewer significant correlations. Different cerebellar lobules showed varying degrees of association with orientation. Left Crus II and VIIB demonstrated moderate correlations ($r = 0.346$, $p = 0.045$; $r = 0.445$, $p = 0.008$, respectively). Stronger associations were observed for right VIIB ($r = 0.512$, $p = 0.002$) and right VIIIa ($r = 0.543$, $p < 0.001$). Additionally, left lobule X was significantly correlated with orientation ($r = 0.493$, $p = 0.003$), memory ($r = 0.499$, $p = 0.003$), and language ($r = 0.541$, $p < 0.001$). However, diverging from the total ACE-R score results, two significant correlations were observed in the SCD group. The volume of the left VIIb region was positively correlated with memory ($r = 0.609$, $p = 0.035$), while the right VIIb region exhibited a negative correlation with language ($r = -0.784$, $p = 0.003$).

Linear regression analysis

Building on the findings from the partial correlation analyses, multiple linear regression models were conducted to investigate whether specific cerebellar regions, in combination with age, could better explain variance in

cognitive performance compared to models that included age alone. Cerebellar regions were selected based on their significant associations with cognitive performance in the partial correlation analyses.

When examining all participants, a model including age and left Crus II volume explained 18.7% of the variance in sMMSE scores ($R^2 = 0.187$, $p < 0.001$). The inclusion of left Crus II volume accounted for an additional 4.1% of the variance, representing a significant improvement over the model with age alone ($p < 0.001$). In this model, both age (B = -0.215, $p < 0.001$) and left Crus II volume (B = 0.721, $p = 0.030$) emerged as significant predictors. Similarly, a model including age and right VIIb volume explained 18.3% of the variance in sMMSE scores ($R^2 = 0.183$, $p < 0.001$). The addition of right VIIb volume contributed an extra 3.7% of the variance, a statistically significant improvement ($p = 0.042$). Both age (B = -0.208, $p < 0.001$) and right VIIb volume (B = 1.457, $p = 0.042$) were significant predictors.

In the ADD group specifically, the model including age and right VIIb volume explained 15.6% of the variance in sMMSE scores ($R^2 = 0.156$, $p = 0.008$). While age remained significant (B = -0.153, $p = 0.049$), right VIIb volume approached significance (B = 1.690, $p = 0.055$) and accounted for an additional 2.9% of the variance.

When examining all participants, a model including age and left Crus II volume explained 14.9% of the variance in ACE-R scores ($R^2 = 0.149$, $p = 0.004$). The inclusion of left Crus II volume added 4.0% of the variance, representing a significant improvement over the model with age alone. Both age (B = -0.791, $p = 0.013$) and left Crus II volume (B = 1.230, $p = 0.040$) were significant predictors. In the ADD group, a model including age and right X region volume explained 12.7% of the variance in ACE-R scores ($R^2 = 0.127$, $p = 0.010$). The inclusion of right X region volume accounted for an additional 1.8% of the variance, a statistically significant improvement ($p = 0.035$). Both age (B = -0.801, $p < 0.05$) and right X region volume (B = 0.870, $p = 0.035$) were significant predictors.

Discussion

Based on existing literature, we hypothesized that individuals with MCI and/or ADD would exhibit significant reductions in whole cerebellar volume and grey matter compared to those with SCD. We specifically expected these differences to be most pronounced in the posterior, cognition-related lobules of the cerebellum, particularly in Crus I/II, and that these volumetric changes would correlate with cognitive performance across the AD continuum. Consistent with our hypotheses, this study revealed clinically meaningful differences in global cerebellar and grey matter volumes, with a particularly pronounced reduction in the posterior cerebellum especially between SCD and ADD. Furthermore, these volumetric differences were found to correlate with cognitive performance, reinforcing the clinical relevance of our findings. As hypothesised, significant volume reductions were found in the (left) Crus II. Additionally, reductions were also observed in the bilateral VIIb, VIIIa, VIIIb, and lobule X. These findings align with the triple spatial representation of non-motor functions proposed by Buckner et al.[7] and Guell et al.[8]. Furthermore, previous studies have observed a lateralization pattern of cerebellar atrophy, with prominent atrophy in the right hemisphere during AD[19,21,22,32]as well as a reduction in WM in the later stages of the disease[23,33]. Our study did not replicate these results. However, additional analysis of percentage volume loss revealed a trend towards greater volume reduction in the right cerebellar regions.

Despite the significant findings from the ANOVA analysis, further investigation into the robustness of these results was conducted through ANCOVA, controlling for age. This analysis revealed that diagnosis was no longer a statistically significant predictor of cerebellar volume, suggesting that age plays a more prominent role in determining cerebellar volume in our sample. Although diagnostic category was not a significant predictor in the ANCOVA analyses, this does not entirely rule out its importance. The correlation analysis revealed a significant association between age (covariate) and cerebellar volume (independent variable), suggesting that age is intimately related to cerebellar volume. This is not unexpected, as aging is well-documented to influence brain volume, affecting both cortical and cerebellar structures[34]. As Miller & Chapman[35] have noted, adjusting for age in ANCOVA may not be ideal in this context. Their argument highlights that such adjustments can remove shared variance critical for understanding the relationship between the independent and dependent variables, potentially leading to an underestimation of the true effect of diagnosis. An alternative explanation could be that the differences in cerebellar volume are subtle compared to the more pronounced effects of age, which may obscure the impact of diagnostic category. The small to medium effect sizes observed in both multivariate and between-subject analyses suggest that, while age remains the dominant factor influencing cerebellar volume, diagnostic category plays a meaningful, though more subtle, role in explaining the variation observed in cerebellar volume. Furthermore, the hippocampus, which was used as a control region, showed the expected significant volume reductions across groups[36] further supporting the validity of our results and suggesting that the lack of significant cerebellar findings might point to a more complex and potentially indirect role for the cerebellum in AD. Finally, the linear regression models demonstrated that for both sMMSE and ACE-R scores, incorporating cerebellar volumes (from Crus II, lobule VIIb, and X) accounted for additional variance, highlighting the important role of these regions in cognitive function, independent of age.

The observation that crus II showed significantly lower volumes among patients with ADD compared to those with SCD supports previous studies that have linked Crus II to memory issues in AD and highlighted its role in the DMN, which is affected in AD[10,12,13,37]. Furthermore, our correlation analyses further support this association, revealing a strong positive correlation between Crus II volume and memory performance, as well as language. Moreover, we observed a significant difference in volume for lobule VIIb and VIIIa. Lobule VIIb has been linked to the precuneus[13]a core region of the DMN, and is associated with multiple cognitive domains, including executive functioning, attention, language, and working memory[38]. Consistent with this, in our study, lobule VIIb in the MCI group was also found to correlate with language. Similarly, lobule VIIIa, traditionally recognized for its role in motor coordination, has also been implicated in these cognitive processes, reflecting a dual role in motor-cognitive integration[39,40]. This dual role is reflected in our correlation analyses, where in

the MCI group, VIIIa volume was associated with word fluency, constructional praxis, and visuoperceptual function—tasks that demand not only cognitive processing but also motor integration.

In this study, significant differences were also observed in lobule X, a cerebellar region traditionally associated with sensorimotor functions such as processing vestibular and visual inputs for maintaining balance, vestibular reflexes, and eye movements. While its primary role lies in sensorimotor processing, recent research suggests a potential connection between lobule X and the hippocampus which plays a crucial role in spatial representation and navigation[42,43]. According to these studies, lobule X transforms head-centred vestibular signals into self-motion and spatial orientation signals relative to the external world, a process crucial for spatial awareness and navigation. Interestingly, this transformation also appears to have implications for the hippocampus, a brain region heavily implicated in AD pathology[42–44]. Indeed, AD individuals may experience difficulties with spatial orientation, getting lost in familiar surroundings, and navigating through both familiar and unfamiliar environments[44]. Thus, changes in lobule X may influence hippocampal functions related to spatial representation and navigation, potentially contributing to the observed deficits in spatial cognition in AD. Our findings suggest that lobule X may be involved in cognitive functions such as memory, orientation, and visuospatial abilities, all of which are closely related to spatial navigation. These results point to a potential connection, but further research is needed to directly assess the impact of lobule X atrophy on spatial navigation deficits.

The lack of significant differences between MCI and ADD aligns with the concept of cerebellar cognitive reserve (CCR)[24]which proposes that a preserved or functionally adaptable cerebellum may help buffer the effects of cortical damage. In this context, our findings suggest that during the early stages of neurodegeneration, particularly in the MCI stage, cerebellar volumes may remain relatively preserved, potentially contributing to cognitive reserve and providing resilience against cognitive decline driven by cortical pathology. However, as AD progresses, the protective role of the cerebellum may become insufficient, potentially contributing to the transition to more severe stages. While CCR is still an emerging concept with limited direct evidence, it provides a promising framework for therapeutic strategies aimed at enhancing resilience through cerebellar (neuro) stimulation or cognitive enrichment activities. Supporting this idea, a study has shown that repetitive transcranial magnetic stimulation (rTMS) targeting Crus II can modulate cortico-cerebellar connectivity and improve cognitive function in AD patients[45]. Additionally, a meta-analysis examining the effects of TMS across various target sites in AD found that, among these regions, the left DLPFC and cerebellum were the most effective for cognitive enhancement in individuals with MCI and ADD[46]. This highlights the cerebellum as a promising target deserving further investigation.

Factors like education may enhance CCR by fostering structural and functional plasticity within the cerebellum[26]. In this study, educational level did not appear to significantly influence cerebellar volumes, which aligns with prior research suggesting that factors such as work-related activity or physical exercise (which were not included in this study) may have a more direct impact on preserving cerebellar structure than education[26]. While education does enhance overall cognitive reserve[29]its effects may be more pronounced in cortical regions responsible for higher-order cognitive functions, rather than in the cerebellum. It is also possible that education contributes to cognitive reserve by enhancing functional networks, rather than directly preserving cerebellar structure, which could explain the lack of a significant contribution in our study.

Finally, the results revealed significant correlations between cerebellar volumes and cognitive performance across all groups, with distinct patterns emerging at each stage of cognitive decline. These findings suggest a dynamic and evolving role for the cerebellum in cognition as the disease progresses, particularly in the early stages. In the SCD group, strong correlations were observed between cerebellar lobule VIIb and memory and language functions. Given that SCD may include individuals in the preclinical phase of AD, this could reflect early compensatory mechanisms aimed at maintaining cognitive function despite subtle underlying pathology. In the MCI group, we observed a broader distribution of correlations across multiple cerebellar lobules, rather than localization to specific regions. This pattern may suggest that, as pathology progresses, the cerebellum recruits additional regions to counteract increasing cognitive deficits, reflecting a shift from a targeted to a more widespread compensatory mechanism. By contrast, in the dementia group, only lobule X exhibited significant correlations with cognitive performance, particularly in memory and language, suggesting that lobule X becomes increasingly relevant for cognitive function as the disease progresses. These findings align with the work of Zhou et al.[13], who examined cerebellar functional connectivity patterns across different stages of cognitive impairment using ADNI data. Their study demonstrated connectivity between several cerebellar regions (left IX, left Crus I, bilateral Crus II) and cortical areas, including the precuneus, in individuals with MCI. However, during the dementia stage, connectivity patterns shifted, with right lobule X showing later involvement—a pattern absent in aMCI.

It is important to interpret these findings carefully as we must acknowledge certain limitations. Firstly, the sample size of the MCI group was relatively small (< 30), which may have affected the study's ability to detect smaller or more nuanced effects and likely contributed to the wide confidence intervals around the effect sizes. Additionally, the unequal sample sizes across the diagnostic groups, may have introduced a potential bias, which may impact the generalizability of our findings. Furthermore, the absence of a HC group represents a significant limitation. Indeed, subjects with SCD are not HC, as they may display AD pathology. Therefore, future studies should have a prospective, longitudinal study design, aiming for larger, balanced sample sizes with the inclusion of HC to provide a comparative baseline for cerebellar volumes and cognitive function. Additionally, future research could benefit from incorporating additional proxies of cognitive reserve, such as working activity, physical activity, and other lifestyle factors. A more causal approach could also be valuable, exploring how specific interventions—such as physical activity and neurostimulation techniques (e.g., rTMS or tDCS)—might impact both the structural and functional aspects of the cerebellum. Moreover, future interventional studies may benefit from incorporating broader, patient and caregiver-centred outcome measures, including assessments of subjective experience and everyday functional abilities, alongside objective cognitive evaluations to better

capture the real-world impact on patients. These approaches could provide deeper insights into the relationship between the cerebellum, cognitive decline, and cognitive reserve in neurodegenerative conditions.

In conclusion, this study reveals subtle yet clinically significant structural changes in the cerebellum associated with AD. Patients with ADD exhibited reduced cerebellar volumes compared to those with SCD. This reduction was most pronounced in cognition-related lobules (crus II, VIIb, VIIIa, VIIIB and X). Cerebellar atrophy significantly correlated with cognitive performance in the AD continuum. Notably, the affected lobules, implicated in cognitive processes and DMN, suggest that cerebellar pathology may disrupt cerebellar-cortical connectivity, impairing memory and cognition and potentially driving further cognitive decline. This highlights the cerebellum as a potential bridge to key cortical regions involved in memory and cognition, positioning it as a promising target for cognitive, physical, and non-invasive neuromodulation strategies in AD.

Materials and methods

This retrospective study utilised data obtained from routine clinical care at the Bru-BRAIN memory clinic. Due to the retrospective nature of the study, Ethics Committee of the Vrije Universiteit Brussel (VUB)/Universitair Ziekenhuis Brussel, waived the need of obtaining informed consent.

Diagnostic categories

We selected a subset of a larger dataset that included demographic, medical, neuropsychological, and MRI parameters from patients who attended memory consultations at UZ Brussel between 2020 and 2022. This larger dataset, which included 570 patients, encompassed various underlying causes of memory impairment. From this dataset, we specifically selected three categories of patients based on their diagnosis: 48 SCD, 24 MCI due to AD and 59 ADD (Total $N = 131$). After outlier removal, a total of 46 SCD, 24 MCI due to AD, and 57 ADD patients remained in the analysis (total $N = 127$). The SCD group served as the control group and the minimum age for inclusion in the study was 45[47]. All diagnoses (SCD, MCI and ADD) were made by experienced neurologists following the procedures outlined by Nous et al.[48] and in accordance with the NIA-AA guidelines[49,50].

To capture the spectrum of pathology along the AD continuum, core AD CSF biomarkers were obtained through lumbar puncture (LP). In cases where LP was refused or contraindicated, brain amyloid positron emission tomography (PET) scans were performed instead. Both LP and amyloid PET scans were conducted prior to inclusion in this study as part of routine clinical practice.

The CSF biomarkers measured included Aβ1–42 and the Aβ1–42/Aβ1–40 ratio as indicators of amyloid pathology, along with total tau (T-tau) and phosphorylated tau (P-tau) as markers of neuronal damage. Participants in the AD groups (MCI due to AD and ADD) were either (1) Probable AD cases (total $N = 48$, ADD = 44 and MCI = 4), diagnosed clinically based on objective cognitive impairments identified through neuropsychological testing but without biomarker confirmation of amyloid pathology. These cases met the NIA-AA (2011)[50] criteria for probable AD or (2) Biomarker-confirmed AD cases (total $N = 33$, ADD = 11 and MCI = 22), who also demonstrated objective cognitive impairment as assessed by neuropsychological testing, and additionally exhibited biomarker evidence of amyloid pathology, either through PET amyloid positivity ($N = 3$) or a reduced CSF Aβ1–42/Aβ1–40 ratio, along with neuronal injury indicated by elevated T-tau and P-tau ($N = 30$).

The SCD group consisted of individuals who self-reported concerns about their memory or cognitive function but did not exhibit objective cognitive impairment on standardized neuropsychological testing. While their cognitive performance remained within the normal range for their age, these individuals perceived a decline in cognition. Importantly, they were not routinely tested for AD core biomarkers (e.g., amyloid PET or CSF analysis), meaning some individuals may have been in the preclinical stages of AD. As such, the SCD group was not considered a fully cognitively healthy control group. Additionally, other factors such as depression, anxiety, or other neurological or psychiatric conditions could contribute to their perceived cognitive decline.

CSF biomarkers were analysed at either the UZ Brussel Lab of Neurochemistry or the UAntwerp BIODEM laboratory. At UZ Brussel, an automated enzyme-linked immunosorbent assay (ELISA) or chemiluminescence immunoassay (CLIA)(EUROIMMUN Analyzer I-2P or Lumipulse G600II/Fujirebio) was utilised. At UAntwerp, either an automated EUROIMMUN ELISA or a manual (INNOTEST® -Amyloid1-42, INNOTEST® hTau-Ag, and INNOTEST® Phospho-Tau181P, respectively; Fujirebio Europe, Ghent, Belgium) was used.

Cognitive performance

A comprehensive neuropsychological assessment conducted as part of the diagnostic process was available for all participants. With a diverse range of neuropsychological tests at our disposal, our selection consisted of the sMMSE and the Addenbrooke's Cognitive Examination-Revised (ACE-R). The selection of the sMMSE and ACE-R was based on their well-established credibility, validity, and extensive application in cognitive assessment[51].

The standardized (Dutch) version of the MMSE, developed by Kok and Verhey (2002)[52], is a culturally and linguistically adapted version of the original MMSE[53] for use in Dutch-speaking populations, enhancing its validity and reliability. The MMSE, from which the sMMSE is derived, is a cognitive screening tool, which covers fundamental cognitive areas such as orientation, registration, attention, calculation, recall, language, and visuospatial abilities[53]. With a maximum score of 30, the MMSE typically uses a cutoff score of < 24 to indicate potential cognitive impairment, suggesting the need for further evaluation[52]. However, the MMSE lacks high sensitivity, especially in detecting MCI[51]. To counter this drawback, we incorporated the ACE-R. While the ACE-R includes the MMSE as part of its subscales (e.g., orientation, attention), it also offers a more thorough evaluation by incorporating supplementary aspects like verbal fluency thereby improving its diagnostic precision and sensitivity[51]. The ACE-R has a maximum score of 100 points, and cutoff scores may vary depending on factors such as age and education level[54]. The neuropsychologist conducting the assessments took into account

the participants' educational background during the interpretation of the ACE-R scores, utilizing the established educational norms for the ACE-R. This adjustment addresses one of the limitations of the MMSE, which may not adequately account for educational differences in test performance[55]. Thus, the combined use of the sMMSE and ACE-R allows for a comprehensive comparison of general cognitive screening with a more detailed cognitive profile, offering a nuanced understanding of cognitive status and its correlates.

Out of the 127 participants, 71 had a complete ACE-R assessment, sMMSE scores were available for 99 participants, and 71 participants had both sMMSE and ACE-R total and subscales scores. No participants were excluded due to incomplete neuropsychological assessments.

Neuro-imaging

Brain MRI scans were acquired using four different MRI systems (Philips Ingenia 3T, Philips achieva 1.5T, Siemens Skyra 3T and Siemens Vida 3T) with harmonised scan parameters. The scan parameters were based on the existing clinical routine scans for AD within our institution, primarily those from the 3T Philips scanner, and were adjusted across the various MRI systems to ensure as much consistency as possible. This included standardizing key parameters such as coil type, field of view (FOV), and resolution. Previous research conducted by our research group demonstrated high intraclass correlation coefficients (ICC) (above 90%) and low coefficients of variation (CV) (below 5%) for global, cortical, and subcortical brain structures across scanners, including Philips Ingenia 3T, Philips Achieva 1.5T, and GE systems, indicating a high level of consistency and precision in measurements[56]. In the present study, we included not only the Philips Ingenia 3T and Philips Achieva 1.5T scanners but also the Siemens Skyra 3T and Siemens Vida 3T scanners, which were not part of the study by Wittens and Allemeersch (2021)[56]. Furthermore, while the cerebellum was not specifically tested in that study, it is important to note that the hippocampus, which is much smaller, showed high ICC and low CV values in their study. Given the favourable results for the hippocampus, it is reasonable to assume that similar harmonization would apply to larger brain regions such as the cerebellum.

All four MRI scanners are located at the radiology department of UZ Brussel, Brussels, Belgium. Every MRI scan consisted of a sagittal 3D T1-weighted MR sequence and a sagittal 3D Fluid Attenuated Inversion Recovery (FLAIR) sequence.

Icobrain Dm

Each MRI scan was processed using the automated brain volumetry software Icobrain dm (v. 5.10.2), a CE-labelled and FDA-cleared medical device that provides detailed analysis of global, cortical, and subcortical brain volume structures[57]. For this study, the cerebellar segmentations from Icobrain dm were combined with an atlas-based approach to obtain a finer anatomical parcellation of the cerebellum. More specifically, the cerebellar atlas proposed by Diedrichsen et al.[58] was aligned with the T1-weighted scans of each patient. Image co-registration was done to optimize alignment between the T1 images of the atlas and the patient using the nifty reg toolbox. A two-step approach was used, where first an affine transformation was computed using the Aladin method[59]followed by a non-rigid registration based on the Free-Form Deformation method[60,61]. The computed transformations were then applied to the labels from the atlas. Then, using a nearest-neighbour approach, the cerebellar lobule segmentations of the atlas were transferred to the cerebellar grey matter mask from Icobrain dm. Finally, the volume for different cerebellar regions was determined, including the entire cerebellum, cerebellar grey matter and white matter, as well as the anterior cerebellum (left and right lobules I-IV) and individual lobules such as left and right lobules V, VI, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX, and X.

Statistical analysis

In this study, an extensive statistical analysis was conducted using IBM SPSS Statistics for Windows, version 29.0.0.0[62]. Initially, descriptive statistics were calculated for each variable to establish a foundational understanding of the dataset. All data were tested for normality and homogeneity of variances as it was crucial for the post hoc analyses following the one-way ANOVA. Outliers were meticulously identified using boxplots, and each outlier was carefully examined. Any outliers deemed to be clear measurement errors were subsequently removed from the analysis. For the neuropsychological test scores, one outlier was identified where a patient scored 16 out of 16 instead of the expected score out of 30. This outlier was excluded from the analysis due to ambiguity surrounding its interpretation. For volumetric data 18 outliers were identified. We sought to understand why these volumes differed significantly from the rest and investigated whether measurement errors could be attributed to mis-segmentation. Measurement errors were identified by employing a quality control overlay approach to detect inaccuracies in cerebellar map overlays. Upon review, we found that only 3 of the outliers were indeed due to segmentation errors. Consequently, we opted to exclude them from the analyses. For the remaining outliers, we couldn't identify any clear measurement errors or alternative explanations, leading us to retain them in the dataset.

For each demographic, medical, neuropsychological and volumetric variable, either an ANOVA (for continuous variables) or a chi-square test (for categorical variables) was performed to assess whether there were significant differences between the diagnostic groups. If the assumption of homogeneity of variances was violated, the Games-Howell post-hoc test was utilised. Conversely, in cases where homogeneity of variances was upheld, the Tukey Honestly Significant Difference (HSD) post-hoc test was applied. Demographic and medical variables that showed significant differences were considered as potential covariates in subsequent ANCOVA analyses. An ANCOVA was performed with age and educational level as a covariate to account for its potential influence on cerebellar volume. Further, the significance of cerebellar volumes differing significantly between groups was investigated using partial correlations with a two-tailed approach. This analysis aimed to determine whether the observed volumetric differences were associated with cognitive performance, as measured by sMMSE and ACE-R scores. The partial correlations controlled for the time interval between MRI scans and

neuropsychological assessments, thereby ensuring that the relationships identified between cerebellar volumes and cognitive function were not confounded by the timing of these measurements. For all analyses, a significance level of $p < 0.05$ was considered statistically significant. To assess the strength of the effects in our analysis, partial eta squared (η^2) was used as a measure of effect size. The interpretation of η^2 followed Cohen's[63] conventional benchmarks, where values of 0.01, 0.06, and 0.14 are typically interpreted as small, medium, and large effects, respectively. However, effect size benchmarks provide a general guideline, but their interpretation can depend on the context of the study, including the specific field of research, sample size, and the practical significance of the findings.

In this cross-sectional study—and in the absence of longitudinal outcomes or patient-reported measures—results were interpreted as clinically meaningful when both of the following criteria were fulfilled:

(1) Effect sizes for diagnostic group differences in cerebellar volume reaching or exceeding $\eta^2 \geq 0.06$, even if not statistically significant. This threshold was selected by comparison with effect sizes observed in the hippocampus ($\eta^2 = 0.277$)—a brain region extensively documented in the literature as exhibiting large, clinically meaningful atrophy in AD[36]. Given the cerebellum's anticipated more modest and complex involvement in AD pathology, the observed effect size for group differences in cerebellar volume ($\eta^2 = 0.123$) suggested clinical meaningfulness.
(2) Volumetric differences were further required to demonstrate significant associations with key disease-related outcomes, such as cognitive symptoms assessed using standardized tools like the MMSE and ACE-R, thereby reinforcing their clinical significance[64].

Data availability

The datasets generated and analysed during this retrospective study are derived from medical records of patients at the memory clinic. Due to the sensitive nature of the data and to protect patient confidentiality, these datasets are not publicly available. However, anonymized datasets may be made available from the corresponding author upon reasonable request.

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Author contributions

D.V.R performed the study and contributed to the conception and design of the work; data analysis; drafting and revising the manuscript. Following authors contributed to data acquisition; G.-J. A. and J. D. M. contributed to the acquisition of MRI data. N. B. and A.R. contributed to the extraction of MRI volumes using icobrain DM. J. T., I. R., and M.D. contributed to the acquisition of demographical and clinical variables and the selection of subjects, V. M. contributed to neuropsychological testing. This study was supervised by S. D. W., S. E., and C. B. who also significantly contributed to the conception, design and final approval of this manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests

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Additional information

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