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Original article

Right-lateralized cerebellar cortical thickening is associated with mild behavioral impairment in mild cognitive impairment

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ABSTRACT

Background: Mild Behavioral Impairment (MBI) reflects later-life emergence of persistent neuropsychiatric symptoms and is increasingly recognized as an early manifestation of neurodegenerative disease, yet cerebellar correlates remain underexplored. We tested whether cerebellar morphometry is associated with incident MBI in mild cognitive impairment (MCI).

Methods: Using longitudinal Alzheimer's Disease Neuroimaging Initiative data, MBI was derived from Neuropsychiatric Inventory/ Neuropsychiatric Inventory-Questionnaire items mapped to five diagnostic domains and defined as new symptoms persisting for ≥2 consecutive visits after a symptom-free baseline. Of 530 MCI participants without baseline symptoms, 181 who developed MBI were matched 1:1 to controls by age, sex, and education. DeepCERES quantified lobular cerebellar cortical thickness and asymmetry from 3T T1-weighted MRI. We used logistic regression with false discovery rate correction and conducted domain-specific analyses (affective dysregulation, impulse dyscontrol, decreased motivation).

Results: MBI cases had lower Mini Mental State Examination scores and higher dementia conversion than controls. Greater thickness in right cerebellar lobules IV (OR 1.215), V (OR 1.122), and VIIIB (OR 1.169), and greater asymmetry in right lobule V (OR 1.035), were associated with incident MBI. Affective dysregulation showed the strongest, largely right-lateralized associations and greater interhemispheric asymmetry. Main results were unchanged after separate sensitivity adjustments for Mini Mental State Examination scores and for index-visit psychiatric medication use.

Conclusion: Incident MBI in MCI is linked to right-lateralized cerebellar cortical thickening and asymmetry, most prominently for affective dysregulation. These patterns may reflect early compensatory and/or neuroinflammatory processes within cerebello–cortical circuits relevant to affect regulation.

Abbreviation

AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
CI	confidence interval
FDR	false discovery rate
FTD	frontotemporal dementia;
ISTAART-AA	International Society To Advance Alzheimer's Research and Treatment–Alzheimer's Association
MRI	magnetic resonance imaging
MBI	mild behavioral impairment
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
NPI	Neuropsychiatric Inventory

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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NPI-Q Neuropsychiatric Inventory-Questionnaire
OR odds ratio

Background

The later-life onset of neuropsychiatric symptoms is increasingly recognized as an early manifestation of neurodegenerative disease and a predictor of future cognitive decline [1,2]. To capture these persistent (≥6 months) behavioral or affective changes occurring in later-life that fall outside traditional psychiatric diagnoses, the International Society to Advance Alzheimer's Research and Treatment–Alzheimer's Association (ISTAART-AA) introduced the concept of mild behavioral impairment (MBI) in 2016 [3]. MBI comprises five domains—affective dysregulation, decreased motivation, impulse dyscontrol, social inappropriateness, and abnormal perception/thought content—and reflects a clinically meaningful change from one's longstanding personality patterns. As a validated risk state for incident mild cognitive impairment (MCI) and dementia [4–7], MBI offers a framework for identifying individuals at increased risk for neurodegenerative disease. Its precise position within the neurodegenerative continuum, however, remains uncertain. The neurobiological basis of MBI needs to be investigated to understand and validate the MBI-to-dementia framework.

Prior studies of MBI have focused primarily on cerebral cortical and limbic structures [8], with structural imaging revealing atrophy in the hippocampus [9–11], parahippocampal gyrus [12], entorhinal cortex [7,10] and temporal lobe [7]. In contrast, the cerebellum has received relatively limited attention. This omission stands in contrast to a growing body of evidence indicating that the cerebellum contributes to a wide range of non-motor functions. Through its extensive reciprocal connections with cerebral regions, the cerebellum plays an established role in affect regulation, executive control, reward processing, and social cognition [13–15]. Structural and functional alterations of the cerebellum have been implicated in neuropsychiatric conditions such as autism spectrum disorder [16,17], schizophrenia [18], frontotemporal dementia (FTD) [19,20], and Alzheimer's disease (AD) [20–22]. However, whether cerebellar structural changes contribute to the emergence of MBI symptoms remains largely unknown. Importantly, the cerebellum is functionally heterogeneous, with lobules topographically connected to specific cortical networks [23,24]. Accordingly, a lobule-specific approach may provide greater anatomical specificity than whole-cerebellum measures when interrogating neurobehavioral phenotypes.

In this study, we examined whether lobule-specific cerebellar morphometric alterations are associated with the onset of MBI symptoms in individuals with MCI. Using a lobule-specific approach, we quantified cortical thickness and asymmetry across cerebellar subregions and compared MCI participants with and without MBI symptoms in a matched sample to identify cerebellar structural markers linked to behavioral changes.

Methods

Study participants

This study utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI; http://adni.loni.usc.edu) [25], a large, longitudinal, multicenter cohort designed to investigate the progression of AD through clinical, imaging, genetic, and biochemical biomarkers. Data from all phases of the ADNI project (ADNI-1, ADNIGO, ADNI-2, and ADNI-3) were included in this analysis.

ADNI participants were between 55 and 90 years of age at enrollment and met standardized inclusion criteria, including minimal depressive symptoms (Geriatric Depression Scale score <6), low vascular burden (Hachinski Ischemic Score ≤4), stable medication use, and no significant sensory impairments. Individuals with major neurological or psychiatric conditions, brain magnetic resonance imaging (MRI) contraindications, or structural brain abnormalities were excluded. Full eligibility criteria are available on the ADNI website https://adni.loni.usc.edu/help-faqs/adni-documentation, where details can be found in the documents listed under Clinical Protocols.

Although MBI can be diagnosed across the cognitive spectrum, we focused on participants with MCI to align with the conceptualization of MBI as a prodromal state of dementia. This approach also reduced clinical heterogeneity and improved statistical power by limiting the analysis to a more homogeneous at-risk group. MCI diagnosis in ADNI was based on (i) subjective memory complaint, (ii) objective memory impairment (typically measured by delayed recall on the Wechsler Memory Scale-Revised Logical Memory II), (iii) largely preserved general cognition and functional independence, and (iv) absence of dementia [25].

Assessment of MBI

MBI symptoms were evaluated using items from Neuropsychiatric Inventory (NPI) [26] or its brief version, the NPI-Questionnaire (NPI-Q) [27]. Based on the ISTAART–AA mapping framework [3,28–30], 10 of the 12 NPI/NPI-Q domains were mapped to five MBI domains as follows: decreased motivation to NPI/NPI-Q apathy/indifference; affective dysregulation to NPI/NPI-Q depression/dysphoria, anxiety, and elation/euphoria; impulse dyscontrol to NPI/NPI-Q agitation/aggression, aberrant motor control, and irritability/lability; social inappropriateness to NPI/NPI-Q disinhibition; and abnormal perception or thought content to NPI/NPI-Q delusions and hallucinations (Fig. 1). Criteria for MBI require that symptoms represent a distinct change from an individual's usual behavior or personality and persist for at least six months within one or more of the five MBI domains. Because the NPI/NPI-Q in ADNI dataset assesses symptoms occurring over the preceding month, it does not confirm the ≥6-month persistence required for MBI diagnosis. To approximate this criterion, we operationalized persistence by requiring that symptoms within the same MBI domain be observed at ≥2 consecutive assessments, typically 6–12 months apart.

To examine the emergence of MBI, we first identified a subsample of 530 MCI participants who were free of neuropsychiatric symptoms at baseline (Fig. 1). Absence of symptoms was defined as a score of zero on all NPI/NPI-Q items corresponding to the MBI domain mapping criteria. Emergence of MBI symptoms was defined as the appearance of non-zero scores on any MBI-mapped NPI/NPI-Q item after a baseline score of zero, reflecting new onset of behavioral symptoms within the corresponding diagnostic domain. Among the 530 eligible participants, 181 developed MBI symptoms during follow-ups. To reduce confounding, we conducted 1:1 Propensity Score Matching (PSM) using age, sex, and education years as covariates, resulting in a final matched sample of 362 participants—181 with newly developed MBI symptoms ("MBI+") and 181 without MBI symptoms ("MBI-"). The adequacy of matching was evaluated by comparing standardized mean differences (SMD) before and after matching.

Structural MRI data acquisition

Raw T1w images (MP-RAGE, IR-SPGR) were obtained from 3T MRI scans across all ADNI phases, downloaded via the ADNI data repository (http://www.loni.ucla.edu/ADNI) [31]. MRI acquisition used standardized 3D T1-weighted protocols implemented uniformly across sites and scanner platforms. Details of the ADNI design, recruitment procedures, clinical assessments, and MRI methodology are available at www.adni-info.org.

For the MBI+ group, we selected the first MRI scan acquired after the initial emergence of symptoms. For the MBI- group, the baseline MRI scan was used. By using the age at these respective MRI time points for matching, we aimed to minimize potential confounding due to age differences at the time of imaging.

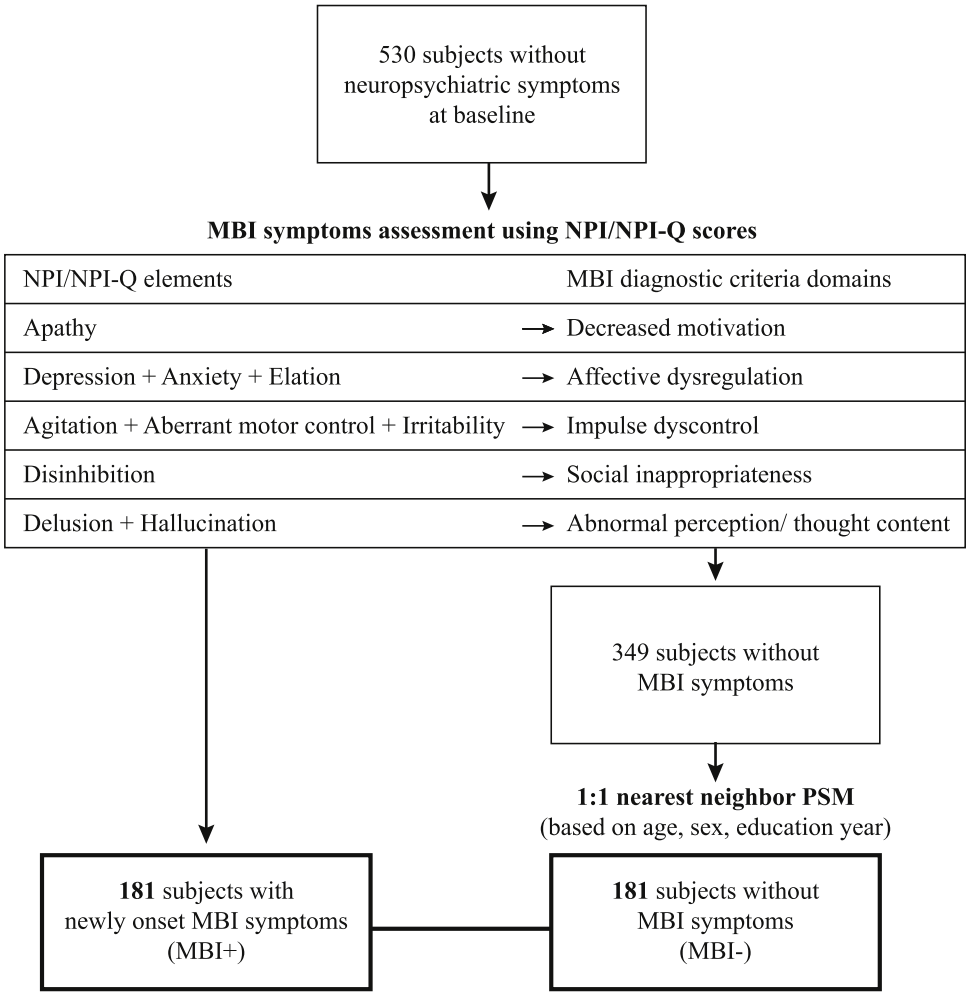
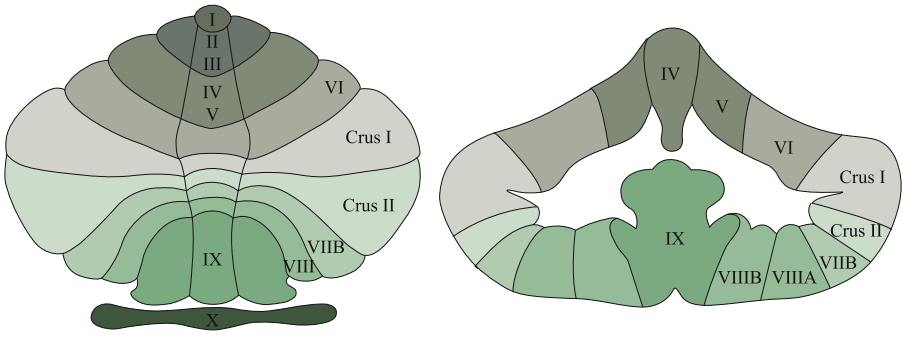


Fig. 1. Flowchart for Study Subject Selection.
Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; MCI, Mild cognitive impairment; MBI, Mild behavioral impairment; NPI/NPI-Q, Neuropsychiatric Inventory/ Neuropsychiatric Inventory Questionnaire; PSM: propensity score matching.

Cerebellar MRI imaging analysis

Structural cerebellar analysis was performed using DeepCERES, a deep learning-based automated segmentation tool implemented in the VolBrain platform (https://volbrain.net/services/DeepCERES)[32,33]. DeepCERES employs a 3D convolutional neural network trained on manually labeled cerebellar MRI scans to achieve accurate parcellation of cerebellar lobules. The method segments the cerebellum into 12 anatomically defined lobules per hemisphere, following the SUIT atlas convention, and provides quantitative metrics including lobule-specific cortical thickness, volume, and asymmetry indices. T1-weighted MRI images were processed to extract cerebellar lobular boundaries, generating cortical thickness measures for each lobule. For all primary analyses, we used cortical thickness values normalized to the cube root of intracranial volume. We chose the normalized metric to mitigate residual head size and global scaling effects that can differ by site, scanner platform, sex, and age. T1-weighted images were processed to extract cerebellar lobular boundaries, yielding left and right cortical thickness



(A) Superior view of an unfolded cerebellum **(B) Coronal view of the cerebellum**

Fig. 2. Illustrative Representation of Cerebellar Lobules.

measures for each of the 12 predefined lobules (lobules I–X and Crus I–II; Fig. 2). Interhemispheric asymmetry indices were computed from the normalized left/right thickness values using:

$$\text{Asymmetry Index (AI)} = \frac{|\text{Right} - \text{Left}|}{\text{Right} + \text{Left}} \times 100,$$

so that higher AI reflects greater left–right deviation independent of head size.

Statistical analysis

To compare baseline demographic and clinical characteristics between MBI+ and MBI- groups, we used Student's *t*-tests for continuous variables (age, education years, and Mini-Mental State Examination [MMSE] scores) and chi-square tests for categorical variables (sex and race). Logistic regression models were then fitted for each cerebellar lobule, with cortical thickness and asymmetry indices as independent variables and MBI status as the binary outcome. To account for multiple comparisons across lobular regions, false discovery rate (FDR) correction was applied, and associations with FDR-corrected $p < 0.05$ were considered statistically significant.

As a subanalysis, we ran separate logistic regressions for each MBI diagnostic domain. Within the MBI+ group, we created domain-positive subgroups—affective dysregulation, impulse dyscontrol, and decreased motivation—and compared each subgroup with the MBI- group using the same models (cerebellar cortical thickness and asymmetry as independent variables; adjusted for age, sex, and education). Because individuals could meet criteria for multiple domains at onset, these subgroups were not mutually exclusive. Domains with small samples (social inappropriateness and abnormal perception/thought content) were not analyzed.

As sensitivity analyses within the PSM cohort, we re-estimated the lobule-wise logistic regression models with additional adjustment for (i) MMSE score and (ii) psychiatric medication use, respectively. MMSE and medication exposure were defined at the index MRI visit (MBI+: symptom-emergence; MBI-: baseline/screening). Psychiatric medication use was operationalized as binary indicators (use vs. no use) derived from ADNI's key medication reporting, capturing two broad categories: antidepressant medication and other behavioral medication. In all models, MBI status was the binary dependent variable and cerebellar lobule cortical thickness (left and right modeled separately) and interhemispheric asymmetry indices were the independent variables; FDR correction was applied across lobules.

All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute, Cary, NC, USA), with a significance threshold set at a p of 0.05.

Results

Baseline characteristics

Baseline characteristics of the matched sample (n= 362) are presented in Table 1. After PSM, all baseline covariates achieved acceptable balance (all SMDs < 0.1). After matching, no significant between-group differences were observed in demographic variables or APOE ε4 carrier status, whereas the MBI+ group showed significantly lower MMSE scores and a higher likelihood of conversion to dementia compared with the MBI- group. During follow-up, 77 participants in the MBI+ group converted to dementia: 71 to AD, 4 to FTD, 1 to vascular dementia, and 1 to other dementia. In the MBI- group, 40 participants converted to dementia and all were classified as AD at conversion.

Association between cerebellar thickness and the presence of MBI symptoms

Logistic regression analyses revealed significant associations between regional cerebellar cortical thickness and the presence of MBI symptoms. As summarized in Fig. 3, three right-sided cerebellar lobules—lobule IV (Odds Ratio [OR] = 1.215, 95 % Confidence Interval [CI] 1.067–1.389, FDR-corrected $p = 0.039$), lobule V (OR = 1.122, 95 %, CI 1.027–1.230, FDR-corrected $p = 0.049$), and lobule VIIIB (OR = 1.169, 95 % CI 1.046–1.311, FDR-corrected $p = 0.039$)—were significantly associated with increased odds of MBI. Importantly, these associations

Table 1
Characteristics of the participants before and after PSM.

	Unmatched cohort (N = 512)				Matched cohort after PSM (n = 362)			
	MBI-(n = 331)	MBI+(n = 181)	p	SMD	MBI-(n = 181)	MBI+ (n = 181)	p	SMD
Age (year)	73.18 ± 7.81	75.35 ± 7.54	**0.002**	0.283	75.30 ± 7.86	75.35 ± 7.54	0.953	0.004
Sex			0.293	0.097			0.916	0.022
Male	177 (53.47 %)	88 (48.62 %)			90 (49.72 %)	88 (48.62 %)		
Female	154 (46.53 %)	93 (51.38 %)			91 (50.28 %)	93 (51.38 %)		
Education (year)	16.17 ± 2.72	15.67 ± 2.87	0.055	0.179	15.76 ± 2.80	15.67 ± 2.87	0.753	0.033
Race			0.053				0.073	
White	284 (85.80 %)	168 (92.82 %)			158 (87.29 %)	168 (92.82 %)		
Black or African American	30 (9.06 %)	7 (3.87 %)			18 (9.42 %)	7 (3.87 %)		
Others	17 (5.14 %)	6 (3.31 %)			5 (2.76 %)	6 (3.31 %)		
MMSE	27.64 ± 1.78	26.83 ± 2.71	**<0.001**		27.66 ± 1.76	26.86 ± 2.64	**<0.001**	
APOE ε4 status			0.239				0.108	
Non-carrier	178 (53.78 %)	91 (50.28 %)			104 (57.46 %)	91 (50.28 %)		
Carrier								
Heterozygote	98 (29.61 %)	69 (38.12 %)			56 (30.94 %)	69 (38.12 %)		
Homozygote	30 (9.06 %)	21 (11.60 %)			12 (6.63 %)	21 (11.60 %)		
Unknown	25 (7.55 %)	0 (0.00 %)			9 (4.97 %)	0 (0.00 %)		
Conversion to Dementia			**<0.001**				**<0.001**	
Yes	60 (18.13 %)	77 (42.54 %)			40 (22.10 %)	77 (42.54 %)		
Dementia subtype at conversion								
AD	59 (17.82 %)	71 (92.20 %)			40 (100 %)	71 (92.20 %)		
FTD	0 (0 %)	4 (5.20 %)			0 (0 %)	4 (5.20 %)		
Others	1 (0.30 %)	2 (2.60 %)			0 (0 %)	2 (2.60 %)		
Psychiatric medication use	59 (17.82 %)	39 (21.55 %)	0.306		26 (14.36 %)	39 (21.55 %)	0.075	

Note: Values are presented in mean ± standard deviation for continuous variables or n (%) for categorical variables. Continuous variables were assessed by Student t-test, and categorical variables by chi-sq test.

Abbreviations: AD, Alzheimer's disease; APOE, Apolipoprotein E; FTD, frontotemporal dementia; MBI, Mild behavioral impairment; MMSE, Mini-Mental State Examination; PSM, propensity score matching; SMD, standardized mean difference.

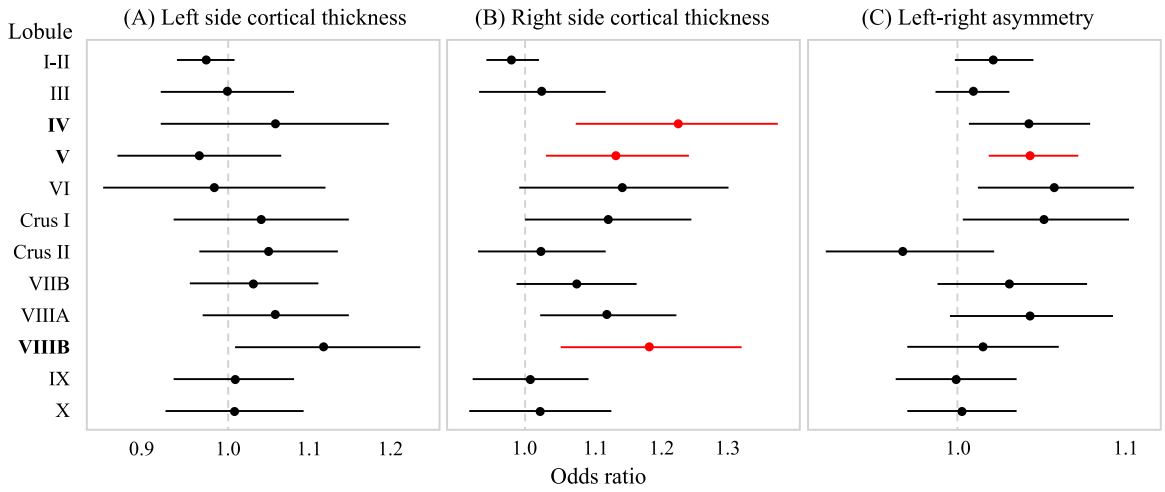


Fig. 3. Associations Between Cerebellar Lobular Cortical Thickness and MBI Status From Logistic Regression Models.
Logistic regression models tested whether lobule-specific cerebellar measures predicted MBI status. Independent variables included (A) left cortical thickness, (B) right cortical thickness, and (C) left–right asymmetry indices for each cerebellar lobule. To control for multiple testing across lobular regions, FDR correction was applied. Points indicate OR for MBI status, and horizontal lines indicate 95 % CI; the vertical dashed line marks OR = 1. Red points/intervals denote results that remained significant after FDR correction ($p < 0.05$), and black denote non-significant findings.
Abbreviations: CI, Confidence interval; FDR, False discovery rate; MBI, Mild behavioral impairment; OR, Odds ratio.

indicated that greater cortical thickness in these lobules was linked to higher likelihood of MBI symptom emergence. Interhemispheric asymmetry in lobule V was also significantly associated with the presence of MBI symptoms (OR = 1.035, 95 % CI 1.015–1.057, FDR-corrected p = 0.010). No left-sided cerebellar regions, however, showed significant associations after correction for multiple comparisons. Full results are shown in Supplementary Table 1.

Domain-specific analysis: associations between cerebellar thickness and the presence of MBI subdomain symptoms

Domain-specific analyses were performed for the three most prevalent MBI diagnostic criteria domains: affective dysregulation (n = 107), impulse dyscontrol (n = 77), and decreased motivation (n = 32) (Table 2). Domains with insufficient sample sizes (social inappropriateness [n = 17] and abnormal thought content [n = 5]) were excluded from subgroup analyses.

Full regression result of the domain-specific findings is presented in Supplementary Table 2–4 and summarized in Fig. 4. Among the domains, affective dysregulation showed the strongest associations with cerebellar structure. Significant associations were observed in four right-sided lobules, including lobule IV (OR = 1.225, 95 % CI 1.059–1.424, FDR-corrected p = 0.007), Crus I (OR = 1.191, 95 % CI 1.040–1.370, FDR-corrected p = 0.044), lobule VIIIA (OR = 1.147, 95 % CI 1.040–1.370, FDR-corrected p = 0.044), and lobule VIIIB (OR = 1.227, 95 % CI 1.075–1.409, FDR-corrected p = 0.035). In addition, increased left-right thickness asymmetry in lobule IV (OR = 1.054, 95 % CI 1.021–1.090, FDR-corrected p = 0.010) and lobule V (OR = 1.043, 95 % CI 1.018–1.070, FDR-corrected p = 0.010) was also significantly associated with affective dysregulation. By contrast, decreased motivation and impulse dyscontrol domains showed no significant associations with regional cerebellar thickness or asymmetry after FDR correction.

Table 2
Frequency of initial symptoms in MBI diagnosis using NPI/NPI-Q items.

MBI diagnostic domains	NPI/NPI-Q categories used to assess each domain	n (total =181)
Decreased motivation	Apathy	32 (17.7 %)
Affective dysregulation	Depression, Anxiety, Elation	107 (59.1 %)
Impulse dyscontrol	Agitation, Aberrant motor control, Irritability	77 (42.5 %)
Social inappropriateness	Disinhibition	17 (9.4 %)
Abnormal perception/thought content	Delusion, Hallucination	5 (2.8 %)

Frequency and distribution of first-emerging neuropsychiatric symptoms leading to a diagnosis of MBI were investigated using 10 selected NPI/NPI-Q items. Symptoms were categorized into five MBI diagnostic domains according to established criteria. The count (n) and percentage represent the number and proportion of patients (out of n = 181) who exhibited each symptom domain as part of their earliest behavioral presentation. Because multiple symptoms could co-occur at onset, patients may be counted in more than one domain, and the percentages therefore sum to more than 100 %.
Abbreviations: MBI, Mild behavioral impairment; NPI/NPI-Q, Neuropsychiatric Inventory/ Neuropsychiatric Inventory Questionnaire.

Sensitivity analysis

After additional adjustment for MMSE, right lobules IV, V, and VIIIB and lobule V asymmetry remained significant after FDR correction (Supplementary Table 5). Results were unchanged after additional adjustment for index-visit psychiatric medication use, with the same lobules remaining significant (Supplementary Table 6).

Discussion

In this study, we investigated whether cerebellar structural alterations are associated with the emergence of MBI symptoms in participants with MCI. We found that specific right cerebellar lobules—IV, V, and VIIIB—showed increased cortical thickness in the MBI+ group, and that affective dysregulation demonstrated the strongest and most widespread cerebellar associations. These findings suggest that cerebellar morphometry, particularly within right-lateralized regions, may serve as an early structural marker of neurobehavioral vulnerability in the prodromal stages of dementia.

MBI+ participants exhibited lower global cognition and a substantially higher likelihood of converting to dementia compared with MBI- participants. These observations align with prior longitudinal studies demonstrating that MBI predicts accelerated cognitive decline, increased risk of incident dementia, and reflects underlying neurodegenerative change [3,4,34,35]. The identification of cerebellar structural signatures associated with MBI further supports the interpretation

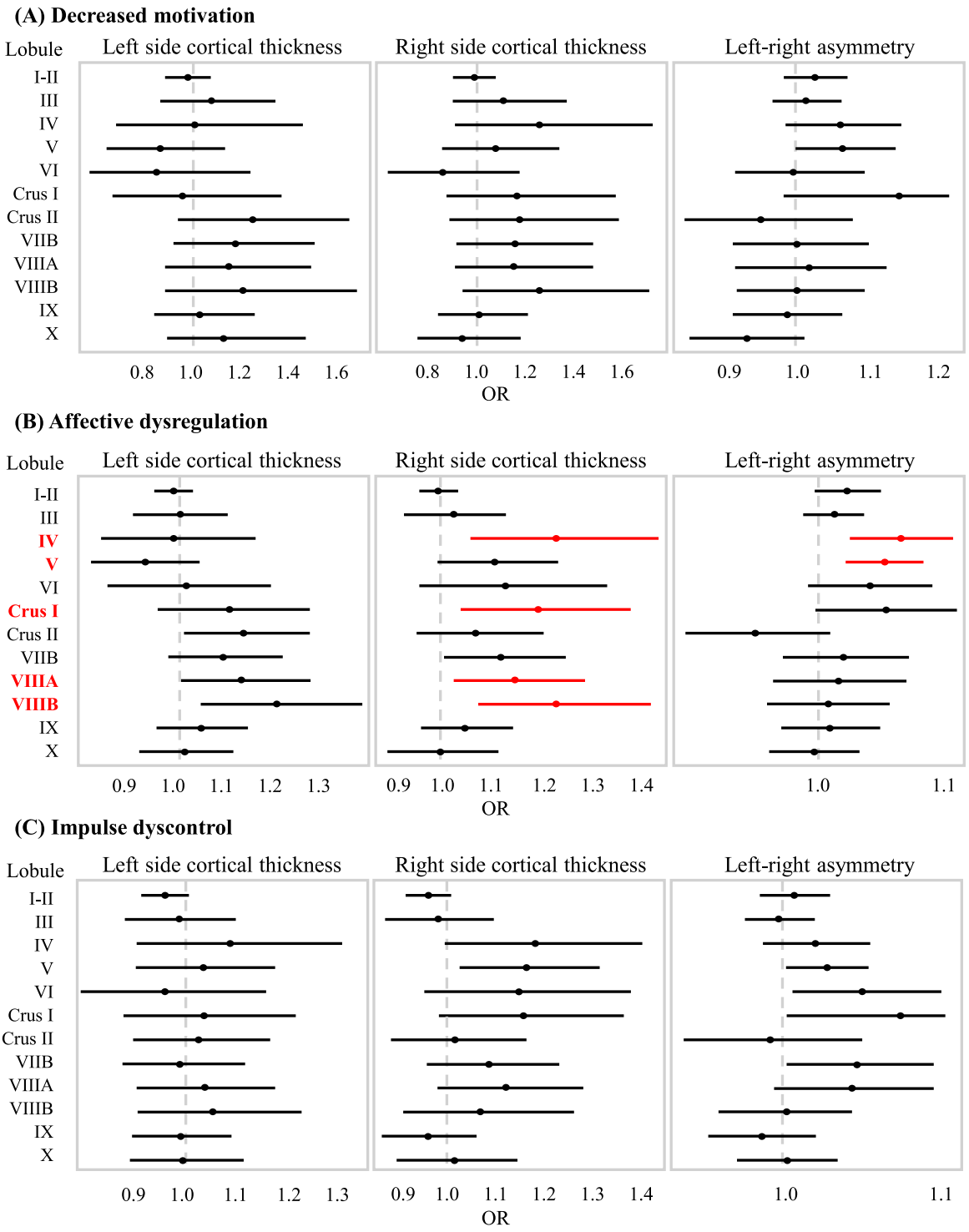


Fig. 4. Subgroup Logistic Regression Analyses of Cerebellar Cortical Thickness Across MBI Diagnostic Domains.
This figure presents domain-specific logistic regression analyses assessing associations between cerebellar lobular thickness and the presence of three diagnostic domains of MBI. For each diagnostic domain—(A) decreased motivation, (B) affective dysregulation, and (C) impulse dyscontrol—separate models were fitted with MBI domain status (present vs. absent) as the dependent variable and lobule-specific cerebellar left/right cortical thickness and left–right asymmetry as independent variables. FDR correction was then applied. Odds ratios (ORs) and 95 % confidence intervals (CIs) are shown; the vertical dashed line denotes OR = 1. Red points/intervals denote results that remained significant after FDR correction ($p < 0.05$), and black denote non-significant findings.
The remaining two MBI diagnostic domains—social inappropriateness and abnormal perception/thought content—were not analyzed due to insufficient sample size.
Abbreviations: CI, Confidence interval; FDR, False discovery rate; MBI, Mild behavioral impairment; OR, Odds ratio.

of MBI as an early neurobiological phenotype, rather than a purely behavioral construct. Although MBI has been linked to multiple dementia etiologies (including AD and FTD), conversion in our cohort was predominantly to AD dementia. This likely reflects the AD-enriched sampling and diagnostic framework of ADNI MCI, rather than etiologic specificity of MBI [5,36,37].

Contrary to our initial expectations, the associations we observed pointed toward increased, rather than decreased, cerebellar cortical

thickness in right cerebellar lobules IV, V, and VIIIB in the MBI+ group. In line with our findings, Lin et al. reported that larger cerebellar volume in MCI was associated with worse cognition and steeper decline [22]. Several mechanisms may account for this pattern.

One possibility is that cerebellar hypertrophy reflects compensatory neuroplastic responses to early cortical or limbic dysfunction. Although cortical thinning is a hallmark of AD pathology [38], regionally increased cortical thickness has been reported in preclinical or very early symptomatic stages and has been interpreted as a marker of compensatory plasticity or dendritic remodeling [39,40]. In MBI, symptom emergence—particularly affective dysregulation—has been linked to altered resting-state connectivity across large-scale control networks (default mode [41–43], salience [41–43], and frontoparietal/executive systems [41,42]). The cerebellum acts as a connector hub that is tightly integrated with these cortical networks [23,44]. Therefore, as these networks undergo early reconfiguration along the AD continuum [45], the changes are likely to extend to cerebello-cortical systems, manifesting as the structural thickening we observed in specific lobules. Future studies integrating connectivity and clinical symptoms are needed to test this hypothesis.

An additional, potentially concurrent possibility is that early cerebellar thickening reflects neuroinflammatory responses, alongside compensatory neuroplastic changes within cerebello-cortical circuits. Microglial activation, reactive astrogliosis, and cytokine-driven glial swelling can transiently increase regional cortical thickness in early AD stages before overt neurodegeneration becomes dominant [39,40,46,47]. Activated microglia and astrocytes can induce local tissue swelling, expand extracellular water content, and remodel microstructural architecture—changes that increase apparent gray matter thickness on structural MRI—even in the absence of true neuronal hypertrophy [48,49]. Future studies incorporating inflammation-specific biomarkers and/or multimodal imaging approaches are needed to investigate this possibility.

Although lobules IV/V and VIIIB are traditionally categorized as sensorimotor, cerebellar organization is increasingly viewed as a functional gradient with significant overlap across networks, rather than having discrete boundaries [23]. Consistent with our findings, a meta-analysis of emotion processing found that anterior lobules IV-V and right lobule VIII are engaged during implicit emotion processing (i.e., automatic responses to emotional stimuli). This suggests that these lobules may apply their inherent motor-calibration mechanism to emotional states, precisely tuning the magnitude and timing of behavioral responses [50,51]. Accordingly, structural variation in right IV/V/VIIIB may plausibly relate to MBI by modulating behavioral responses to internal affective states.

Notably, this early thickening was predominantly right-lateralized, prompting consideration of cerebellar hemispheric specialization. Our findings of lateralized associations align with a growing body of evidence suggesting hemispheric specialization within the cerebellum. For instance, a recent meta-analysis demonstrated that the right cerebellar hemisphere is more consistently activated during affective and social-cognitive tasks [52]. This functional asymmetry may help explain the right-dominant pattern observed in our study, particularly for emotional behavioral symptoms. Beyond task-based asymmetry, meta-analytic evidence shows that the right cerebellum is more prone to structural degeneration in AD, particularly in regions linked to higher-order cognition [53]. These functional and structural observations may explain the right-dominant pattern observed in our study, especially for emotional and behavioral symptoms.

In this context, our study has several strengths. It is among the earliest neuroimaging investigations to examine cerebellar involvement in MBI, addressing a major gap in a field that has focused predominantly on cerebral markers. The use of sub-lobular analyses allowed anatomically detailed characterization of cerebellar regions, which is rarely implemented in MBI research. High-resolution, lobule-specific morphometry was obtained using DeepCERES, a modern deep learning-based segmentation framework. Moreover, by leveraging longitudinal NPI/NPI-Q assessments and requiring symptom emergence and persistence across follow-up visits, we approximated the ISTAART–AA criteria for MBI and constructed a well-defined MBI+ cohort with an appropriately matched comparison group. Collectively, these strengths enhance the robustness and clinical relevance of our findings in understanding early neurobehavioral change.

However, several limitations should be considered. MBI symptoms were derived from NPI/NPI-Q items, as the MBI Checklist was not available in the ADNI protocol. Although we required symptom persistence across consecutive visits, the NPI and NPI-Q assess neuropsychiatric symptoms only within approximately a one-month reference period, making it difficult to ascertain whether symptoms fulfilled the six-month persistence required for an MBI diagnosis and potentially leading to misclassification of transient symptoms. Additionally, MRI acquisition timing differed slightly between groups, though matching minimized the bias. Because the MRI scan for the MBI+ group was defined as the first scan after MBI onset, we cannot determine whether the observed cerebellar thickening is a preceding risk factor or a consequent result of MBI. Future studies with pre-onset imaging and symptom-anchored longitudinal trajectories will be needed to clarify temporal ordering. Another limitation is that we could not account for medical comorbidities (e.g., hypertension, diabetes), lifestyle factors (alcohol consumption, smoking), or handedness, all of which may affect brain structure or neurobehavioral symptoms and could introduce residual confounding. We also had limited information on specific psychiatric medications (e.g., active ingredients, dosage, and longitudinal changes), precluding drug-specific analyses. However, medication-related bias is likely attenuated because the ADNI protocol emphasizes medication stability and restricts certain medications (see ADNI procedures manual on the ADNI documentation page: https://adni.loni.usc.edu/help-faqs/adni-documentation). Finally, the lack of racial and ethnic diversity in the ADNI cohort limits generalizability, warranting replication in more diverse populations.

Conclusion

In this study, we demonstrated that increased cortical thickness in specific right cerebellar lobules is significantly associated with the emergence of MBI symptoms in older adults with MCI. Domain-specific analyses further highlighted cerebellar correlates of affective dysregulation, supporting the cerebellum's expanding role in emotion regulation beyond motor control. These findings suggest that morphometric changes in the cerebellum may reflect early pathophysiologic processes in pre-dementia states and underscore the need for future longitudinal and multimodal studies to clarify their mechanistic and prognostic significance.

Ethics approval and consent to participate

The study procedures were approved by the institutional review board of all participating centers (https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf), and were conducted after obtaining informed consent from all participants or authorized representatives.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are from the ADNI database (http://adni.loni.usc.edu), which is accessible to interested scientists with the ADNI Data Use Agreement (http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Data_Use_Agreement.pdf).

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CRediT authorship contribution statement

Sohee Kim: Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Young-Chul Jung:** Supervision, Project administration. **Eosu Kim:** Supervision, Project administration. **Keun You Kim:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Keun You Kim reports financial support was provided by Yonsei University College of Medicine. Keun You Kim reports a relationship with Yonsei University College of Medicine that includes: employment and funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100540.

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