The Cerebellum (2020) 19:217–225
https://doi.org/10.1007/s12311-019-01099-1

ORIGINAL PAPER

Cerebellar Volume Is Associated with Cognitive Decline in Mild Cognitive Impairment: Results from ADNI

Chi-Ying Lin[1,2] · Chi-Hua Chen[3] · Sarah E. Tom[1,4] · Sheng-Han Kuo[1,2] · for the Alzheimer's Disease Neuroimaging Initiative

Published online: 4 January 2020

Abstract

Alzheimer's disease (AD) is a disease with dysfunctional brain network. Previous studies found the cerebellar volume changes over the course of AD disease progression; however, whether cerebellar volume change contributes to the cognitive decline in AD, or its earlier disease stage (i.e., mild cognitive impairment [MCI]) remains unclear. In ADNI, cognitive function was assessed using Alzheimer's Disease Assessment Scale-Cognitive Behavior section (ADAS-Cog). We used linear regression and linear mixed effects models to examine whether cerebellar volume is associated with either baseline cognition or with cognitive changes over time in MCI or in AD. We used logistic regression to assess the relationship between cerebellar volume and disease progression to MCI and AD. We found that cerebellar volume is associated with cognition in patients with MCI, after adjusting for age, gender, education, hippocampal volume, and *APOE4* status. Consistently, cerebellar volume is associated with increased odds of the disease stages of MCI and AD when compared to controls. However, cerebellar volume is not associated with cognitive changes over time in either MCI or AD. In summary, cerebellar volume may contribute to cognition level in MCI, but not in AD, indicating that the cerebellar network might modulate the cognitive function in the early stage of the disease. The cerebellum may be a potential target for neuromodulation in treating MCI.

Keywords Cerebellum · MRI · Volumetric MRI · Mild cognitive impairment · Alzheimer's disease

Introduction

The cognitive function is a complex neural process, requiring collaborative effects of different brain regions to operate as a functional brain network [1, 2]. In the neurodegenerative diseases, primary pathology could involve defined brain regions with compensatory effects from other regions within the network [3] to collectively influence the cognitive function. For instance, tau- and beta-amyloid pathologies are primarily observed in hippocampus and other associated brain regions in Alzheimer's disease (AD), yet other brain regions not involved by these primary pathologies can also contribute to clinical presentations [3].

Traditionally, the cerebellum is thought to be relatively spared in AD [2]. However, a number of histopathological studies have recently shown that the cerebellum might undergo neurodegenerative and neuropathological changes in AD [4], including amyloid plaques deposition in the cerebellar cortex [5–7], Purkinje cellular density loss [8, 9], and the atrophic change in the molecular and granular cell layers [9, 10]. In addition, microscopic changes have also been observed in synaptic, dendritic, and axonal levels in the cerebellar neurons of AD patients [11, 12].

The cerebellum has dense connections with other brain regions involved in AD brain networks critical to cognitive functions, such as dorsolateral prefrontal cortex and amygdala complex [4, 13, 14]. The evidence of the cerebellar

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12311-019-01099-1) contains supplementary material, which is available to authorized users.

✉ Sheng-Han Kuo
sk3295@cumc.columbia.edu

[1] Department of Neurology, Columbia University Medical Center, 650 West 168th Street, Room 305, New York, NY 10032, USA

[2] Initiative for Columbia Ataxia and Tremor, Columbia University Medical Center, New York, NY, USA

[3] Center for Multimodal Imaging and Genetics, Department of Radiology, University of California, San Diego, La Jolla, CA, USA

[4] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

contribution to higher cognitive function was also recently identified by positron emission tomography and functional magnetic resonance imaging (fMRI) studies [15, 16]. In addition, patients with cerebellar damages may suffer from a variety of cognitive dysfunction, termed cerebellar cognitive affective syndrome (CCAS)/Schmahmann syndrome, for which patients might have dysfunction of execution, visual–spatial function, linguistic processing abilities, and affect regulation resulting from the disruption of the cerebellar modulation of neural circuits linking to prefrontal, posterior parietal, superior temporal, and limbic cortices [14, 17–25]. Structural or functional lesions in the posterior cerebellum are usually identified [14, 17–25].

Along these lines, the role of the cerebellum in AD has just begun to be understood. The cerebellar volume was found to be smaller in AD patients than controls on structural MRI [4]. And the rate of cerebellar atrophy was faster in AD when compared to age-matched controls [26]. These findings are consistent with the network degeneration hypothesis that the clinical manifestation of neurodegenerative diseases could be an overall result of the neuropathological spreading along the disease-specific neuronal brain networks and the compensatory effects of other brain regions [1, 2, 26]. However, how the cerebellum could contribute to the cognitive function in AD has not been extensively investigated. Therefore, our overarching goal is to identify the relationship between cerebellum volume and cognition in AD and its earlier stage of the disease, mild cognitive impairment (MCI).

Methods

Study Design and Participants

The data of the present study are from AD Neuroimaging Initiative (ADNI; http://adni.loni.usc.edu/). ADNI was launched in 2003 with the primary goal of combining serial neuropsychological assessment and neuroimaging to monitor the disease progression of MCI and AD. Our research is thus a cohort study comprises of 822 participants in total (230 cognitive normal controls (NC), 399 MCI cases, and 193 AD cases) recruited at 57 sites in the United States and Canada. All participants were between 55 and 90 years old, had at least 6 years of education, had a study partner able to provide an independent evaluation of functioning, and spoke either English or Spanish. Participants' age, gender, and years of formal education were recorded at enrollment. *APOE* genotyping was carried out at the University of Pennsylvania ADNI Biomarker Core Laboratory. *APOE*4 carriers refer to the participants who had at least 1 *APOE*4 allele. Specifically, NC or MCI were followed up for 3 years while AD for 2 years at maximum. Full inclusion and exclusion criteria and detailed schedules of assessment for NC, MCI, and AD are available in the general procedure manual on the ADNI website.

Standard Protocol Approvals, Registrations, and Patient Consents

The study procedures were approved by the institutional review boards of all participating institutions. Written informed consents of neuropsychological assessment and neuroimaging were obtained from all study participants or their representatives.

MRI and Brain Volume Standardization

The 1.5-T MRI was used with a standardized protocol across all sites [27]. FreeSurfer software was used to obtain cerebellar and hippocampal volumes in mm^3 using volumetric analyses. Cerebellar raw volume is the sum of bilateral cerebellar gray and white matter volume. Hippocampal raw volume is the sum of bilateral hippocampus volume. As gender and ethnicity affects the size of the brain, cerebellar and hippocampal raw volume of each study subject were both divided by the subject's intracranial volume (ICV) as the adjusted cerebellar and hippocampal volume [28, 29]. We then applied standardization (i.e., mean = 0, standard deviation = 1) for each variable and use the standardized values for analyses.

Cognitive Measures

AD Assessment Scale-Cognitive Behavior section (ADAS-Cog) is the subscale of ADAS and has been widely used in clinical trials of AD [30]. It was designed to elaborate ADAS by including several cognitive measures, including attention, concentration, nonverbal memory, and praxis, to reliably assess the cognitive domains of AD with a higher score indicating greater cognitive impairment [31, 32]. A higher score denotes greater impairment. The ADAS-Cog from ADNI uses two versions, ADAS-Cog11 and ADAS-Cog13 to represent two different total scores of this neuropsychological measures [33]: ADAS-Cog11 refers to the original 11 items of ADAS-Cog with 70 points in total; ADAS-Cog13 refers to the modified ADAS-Cog 13-item scale, which was developed to increase the sensitivity of detecting the cognitive change in early stages of AD [32, 34] by adding question 4 (i.e., delayed word recall task) and question 14 (i.e., number cancelation task) with 85 points in total [33]. The ADAS-Cog was administered at baseline and at 6-month follow-up visits.

In addition, we further performed the exploratory analysis assessing the association between the cerebellar volume and domain-specific cognition. We first focused on executive function, a cognitive domain commonly impaired in CCAS/Schmahmann syndrome [14, 17–25]. The executive function was measured by the timing difference of completing trail

making test A and B (TMTB - TMTA), and a higher TMTB-TMTA score represents worse executive function [35]. Second, the cerebellum has recently been found to be the location for "p factor," an index for comorbidity of diverse psychiatric symptoms [36]; therefore, we chose to use neuropsychiatric inventory (NPI) to assess the neuropsychiatric symptoms [37]. The NPI score is divided into binary variables, with a score of 4–36 indicative of psychiatric symptoms, and score 0–3 representing no psychiatric symptoms [38]. Both TMT and NPI were administered at baseline and 6-month follow-up visits.

Statistical Analysis

Shapiro-Wilk test was used to examine the normality of the data distribution and one-way analysis of variance (ANOVA) or Kruskal-Wallis one- way ANOVA were used to compare between normally and non-normally distributed variables across groups (NC vs. MCI vs. AD), respectively, with post hoc analysis. Chi-square tests were used to compare categorical variables, such as *APOE*4 status and sex. The *APOE4* carrier status was divided into individuals with at least one copy of the ε4 allele of *APOE* vs. individuals with no copies of the ε4 allele of *APOE* [39–41]. In models, we centered age and divided by 10, as appropriate for the entire sample of by diagnosis category; the interpretation for age is for a change in decade. For the ADAS-Cog outcomes, we created a z-score [41] as appropriate for the entire sample or by diagnosis category.

We used linear regression models to examine the overall association and the diagnosis category-specific association between baseline cerebellar volume and baseline ADAS-Cog. To understand disease progression, we used logistic regression models to examine the association between baseline cerebellar volume with MCI versus NC, and separately with AD versus MCI. We used linear mixed effects models to investigate the relationship of baseline cerebellar volume with cognition at baseline (coefficient for cerebellar volume) and change in cognition over follow-up (coefficient for interaction between baseline cerebellar volume and follow-up time). Models are accounted for individual variation in the estimated baseline cognition level and the change in cognition over time by specifying a random intercept and slope, respectively. To assess the relationship between the cerebellum and psychiatric symptoms, we used logistic regression. In the aforementioned models, age is centered at the mean and divided by 10 to interpret coefficient as change in decade and education is a continuous variable. We used IBM SPSS statistics software version 25 and Stata/MP version 15.1 for statistical analyses.

Data Availability Statement

Data on participant demographics are listed in Table 1. Summary data of the statistical analyses are available in Table 2 to Table 5. ADNI data are accessible and retrieved from adni.loni.usc.edu/data-samples/ access-data/.

Table 1 Demographics and baseline imaging features of the participants

	NC (SD) (n = 230)	MCI (SD) (n = 399)	AD (SD) (n = 193)	p value			
				NC vs. MCI vs. AD	NC vs. MCI	NC vs. AD	MCI vs. AD
Age (years)	76.12 ± 5.02	74.94 ± 7.48	75.53 ± 7.48	0.470[a]			
Female (%)	48	35	47	0.003[b]	< 0.001	0.760	0.001
Education (years)	16.03 ± 2.85	15.67 ± 3.04	14.71 ± 3.13	< 0.001[a]	0.523	< 0.001	0.001
Follow-up (months)	34.36 ± 12.04	24.78 ± 12.50	17.56 ± 8.95				
*APOE4** (%)	2.6%	11.8%	18.7%	< 0.001[b]	< 0.001	< 0.001	0.001
ADAS-Cog13	9.49 ± 4.23	18.65 ± 6.27	28.90 ± 7.64	<0.001[a]	< 0.001	< 0.001	< 0.001
ASAS-Cog11	6.19 ± 2.94	11.52 ± 4.43	18.62 ± 6.31	< 0.001[a]	< 0.001	< 0.001	< 0.001
Intracranial volume**	152.04 ± 17.83	156.35 ± 19.71	155.17 ± 21.65	0.049[a]	0.046	1.000	0.655
Raw cerebellar volume**	12.11 ± 1.22	12.22 ± 1.36	11.93 ± 1.29	0.052[a]			
Cerebellar volume#***	8.02 ± 0.82	7.87 ± 0.83	7.77 ± 0.93	0.007[c]	0.081	0.005	0.450
Raw hippocampal volume**	0.73 ± 0.09	0.65 ± 0.11	0.58 ± 0.10	< 0.001[a]	< 0.001	< 0.001	< 0.001
Hippocampal volume##***	0.48 ± 0.06	0.42 ± 0.07	0.38 ± 0.07	< 0.001[a]	< 0.001	< 0.001	< 0.001

APOE apolipoprotein E gene; *ADAS-Cog* Alzheimer's Disease Assessment Scale-cognitive subscale; *MMSE* mini-mental stats examination; *ICV* intracranial cerebral volume; *NC* normal cognition, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

*One or two copies of E4; **Units: 10^{-4} mm^3 # cerebellar volume/intracranial volume; ## hippocampal volume/intracranial volume; ***original value × 10^2, representing as the percentage of the intracranial volume [a] Kruskal-Wallis one-way ANOVA, [b] Chi-square test, [c] One-way ANOVA

Results

Baseline Demographics and MRI Features

Table 1 showed the age, gender, education, *APOE*4 positivity (defined as 1 or 2 copies of *APOE*4 alleles), baseline scores of ADAS-Cog13, ADAS-Cog11, ICV, cerebellar volume, and hippocampal volume in each diagnostic group. As expected, the mean hippocampal volume was significantly decreased in a step-wise fashion in the three categories (NC vs. MCI vs. AD = 0.48 ± 0.06 vs. 0.42 ± 0.07 vs. 0.38 ± 0.07, $p < 0.001$). Interestingly, There was also a step-wise decrease in the mean cerebellar volume across from NC to MCI and to AD (NC vs. MCI vs. AD = 8.02 ± 0.82 vs. 7.87 ± 0.83 vs. 7.77 ± 0.93, $p = 0.007$), although the statistical significance only exists between cerebellar volume of NC and that of AD ($p = 0.005$).

Cerebellar Volume and Cognition

Since the cerebellum seems to be undergoing volume changes during AD disease process, we next asked whether the cerebellar volume is associated with cognition by constructing linear regression models to study the effect of the cerebellar volume on ADAS-cog scores in all participants at the baseline visit, taking into consideration of age, gender, *APOE*4 status [39], and hippocampal volume [40] which are known factors that might affect cognitive performance. Surprisingly, we found that greater cerebellum volume is associated with worse cognition, measured by ADAS-Cog13 ($\beta = 0.05$, $p = 0.04$, Table 2), and there is a similar trend of association between cerebellum volume and ADAS-Cog11, though not statistically significant ($\beta = 0.04$, $p = 0.09$, Table 2). The effect of cerebellar volume on cognition is independent of hippocampal volume, which also showed a strong negative effect on the cognition in these models ($\beta = -0.22$, $p < 0.001$ on ADAS-Cog13, $\beta = -0.20$, $p < 0.001$ on ADAS-Cog11) (Table 2).

We next explored whether the contribution of the cerebellar volume to cognition differ in different disease stages by constructed linear regression models in each diagnostic group. We found that greater cerebellum volume is associated with worse baseline cognition in MCI (ADAS-Cog13, $\beta = 0.13$, $p = 0.003$; ADAS-Cog11, $\beta = 0.12$, $p = 0.003$, Table 3) but not in NC (ADAS-Cog13, $\beta = -0.09$, $p = 0.26$; ADAS-Cog11, $\beta = -0.05$, $p = 0.53$,) or in AD (ADAS-Cog13, $\beta = 0.01$, $p = 0.80$; ADAS-Cog11, $\beta = -0.01$, $p = 0.64$). On the other hand, hippocampus volume was negatively associated with cognition in both MCI ($\beta = -0.36$, $p < 0.001$ on ADAS-Cog13, $\beta = -0.30$, $p < 0.001$ on ADAS-Cog11) and AD ($\beta = -0.34$, $p < 0.001$ on ADAS-Cog13, $\beta = -0.29$, $p < 0.001$ on ADAS-Cog11) (Table 3).

We next asked whether the association of the cerebellar volume to cognition is primarily driven by the gray matter or white matter. Our results exhibit that greater cerebellar gray matter volume is associated with worse baseline cognition in MCI (ADAS-Cog13, $\beta = 0.14$, $p = 0.001$, Supplemental Table 1); however, the cerebellar white matter is not associated with baseline cognition in MCI ($\beta = 0.03$, $p = 0.49$; Supplemental Table 1). These results demonstrated that the subregion of the cerebellum (i.e., gray matter) is the main contributor to the cognition in MCI.

We next assessed whether executive function is linked to the cerebellar volume. Interestingly, we found that smaller cerebellar volume was associated with worse executive dysfunction in AD ($\beta = -11.45$, $p = 0.045$) but not in MCI ($\beta = 4.17$, $p = 0.29$), and this association in AD is primarily driven

Table 2 Linear regression models to study the associations between baseline cerebellar volume and covariates with baseline cognition

	ADAS-Cog13		ADAS-Cog11	
	NC + MCI + AD ($n = 802$)		NC + MCI + AD ($n = 802$)	
Characteristics	β	*p* value	β	*p* value
Education (years)	− 0.02	0.001	− 0.02	0.005
Female	0.001	0.97	0.007	0.87
Age (decades)	− 0.07	0.02	− 0.06	0.03
APOE4 positivity [a]	0.004	0.94	0.003	0.97
MCI (vs. Normal)	0.62	< 0.001	0.46	< 0.001
AD (vs. Normal)	1.41	< 0.001	1.18	< 0.001
Cerebellar volume [b]	0.05	0.04	0.04	0.09
Hippocampal volume [c]	− 0.22	< 0.001	− 0.20	< 0.001

APOE apolipoprotein E gene, *ADAS-Cog* Alzheimer's Disease Assessment Scale-cognitive subscale, *NC* normal cognition, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

Zero copy of E4 = 0, One or two copies of E4 = 1; [b] Standardized ratio of bilateral cerebellum/intracranial volume; [c] Standardized ratio of bilateral hippocampal volume/intracranial volume

Age is lefted at the sample mean. Cognitive measures were transformed into z-scores

Table 3 Linear regression models to study the associations between baseline cerebellar volume and covariates with baseline cognition by diagnostic category

	ADAS-Cog13					
	NC (n = 226)		MCI (n = 389)		AD (n = 187)	
Characteristics	β	p value	β	p value	β	p value
Education (years)	− 0.03	0.16	− 0.05	< 0.001	0.02	0.34
Female	0.38	0.004	− 0.07	0.32	− 0.07	0.52
Age (decades)	0.10	0.44	− 0.05	0.29	− 0.22	0.007
APOE4 positivity [a]	− 0.49	0.24	0.13	0.21	− 0.18	0.18
Cerebellar volume [b]	− 0.09	0.26	0.13	0.003	0.01	0.80
Hippocampal volume [c]	− 0.01	0.94	− 0.36	< 0.001	− 0.34	< 0.001
	ADAS-Cog11					
	NC (n = 226)		MCI (n = 392)		AD (n = 191)	
Characteristics	β	p value	β	p value	β	p value
Education (years)	− 0.02	0.33	− 0.05	< 0.001	0.01	0.46
Female	0.24	0.09	− 0.02	0.77	− 0.04	0.70
Age (decades)	0.01	0.93	− 0.04	0.41	− 0.17	0.02
APOE4 positivity [a]	− 0.32	0.47	0.13	0.19	− 0.15	0.22
Cerebellar volume [b]	− 0.05	0.53	0.12	0.003	− 0.01	0.87
Hippocampal volume [c]	− 0.05	0.64	− 0.30	< 0.001	− 0.29	< 0.001

APOE apolipoprotein E gene, *ADAS-Cog* Alzheimer's Disease Assessment Scale-cognitive subscale, *NC* normal cognition, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

[a] Zero copy of E4 = 0, One or two copies of E4 = 1; [b] Standardized ratio of bilateral cerebellum/intracranial volume; [c] Standardized ratio of bilateral hippocampal volume/intracranial volume

Results are from separate linear regression models per diagnostic category. For disease classification, normal control is the reference. Age is lefted at the diagnostic category mean. Cognitive measures were transformed into z-scores

by the cerebellar gray matter, rather than white matter (Supplemental Table 2). On the other hand, neuropsychiatric symptoms were not associated with cerebellar volume (Supplemental Table 3), demonstrating the specificity.

Cerebellar Volume and Disease Evolution

We next investigated whether cerebellar volume could be associated with the disease evolution by comparing the odds between MCI and NC and also between AD and MCI. To this end, we constructed logistic regression models to study whether baseline cerebellar volume is associated with the odds between diagnostic groups, taking into account for age, gender, *APOE*4 positivity, and hippocampal volume. Consistently, we found that higher cerebellar volume is associated with greater odds of MCI compared to NC (odds ratio = 1.36, p = 0.01, Table 4), adjusting for age, sex, *APOE4* status, and baseline hippocampal volume. Cerebellar volume is not associated with the odds of AD compared to MCI. In these models, hippocampal volume was associated with increased odds of both AD compared to MCI (odds ratio = 0.45, p < 0.001, Table 4) and MCI compared to NC (odds ratio = 0.23, p < 0.001, Table 4), which reflects that it still remains an important factor to determine cognitive function. Our results showed that cerebellar volume is associated with different odds in the different diagnostic groups and thus might contribute to cognitive function, particularly in the early stage of the disease.

Cerebellar Volume and Cognitive Changes during Follow-Up

We next asked whether the baseline cerebellar volume could be predictive of cognitive progression in MCI cases or in AD cases in the longitudinal analyses. Therefore, we constructed linear mixed models to determine whether cerebellar volume is associated with the rate of cognitive decline, taking into account for age, gender, baseline hippocampal volume, *APOE4* status, and the rate of cognitive decline associated with baseline hippocampal volume. We found that baseline cerebellar volume is not associated with disease progression over 2 years in either MCI (ADAS-Cog13, β = 0.02, p = 0.29; ADAS-Cog11, β = 0.01, p = 0.59, Table 5) or AD (ADAS-Cog13, β = 0.02, p = 0.22, ADAS-Cog11, β = 0.02, p = 0.42, Table 5). These results indicate that while cerebellar volume may contribute to cognition in MCI, one snapshot of baseline cerebellar volume is not associated with prospective disease progression.

Table 4 Logistic regression models to study the associations between baseline cerebellar volume and covariates with different diagnostic categories

	MCI (n = 393) vs. NC (n = 228)[a]		AD (n = 193) vs. MCI (n = 393)[b]	
Characteristics	Odds Ratio	p value	Odds Ratio	p value
Education (years)	0.90	0.001	0.90	0.001
Female [c]	1.35	0.15	0.53	0.002
Age (decades)	0.47	< 0.001	0.87	0.33
APOE4 positivity[d]	3.84	0.009	1.46	0.15
Cerebellar volume[e]	1.36	0.01	1.06	0.50
Hippocampal volume[f]	0.23	< 0.001	0.45	< 0.001

Results from separate logistic regression models. Age is lefted at the sample mean

APOE apolipoprotein E gene, *NC* normal cognition, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

[a] NC = 0, MCI = 1; [b] MCI = 0, AD = 1; [c] Men = 0, Women = 1, [d] Zero copy of E4 = 0, One or two copies of E4 = 1

[e] Standardized ratio of bilateral cerebellum/intracranial volume; [f] Standardized ratio of bilateral hippocampal volume/intracranial volume

Discussion

The present study suggests cerebellar volume contributes to cognitive function in the early stage of the disease (i.e., MCI) but does not play an important role when the disease evolves into AD. On the other hand, the hippocampal volume can determine the cognitive function throughout the disease process. These data suggest that cognitive function is determined by the multiple regions within the brain network and could change as the disease evolves.

We found that cerebellar volume decreases in a stepwise fashion in three diagnostic groups: NC, MCI cases, and AD cases, consistent with degenerative pathology of the cerebellum observed in AD cases [4]. Interestingly, cerebellum volume is negatively associated with the cognitive function in MCI, different from the association between hippocampal volume and cognitive function. In other words, our finding suggests that larger cerebellar volume is associated with worse cognitive outcome in MCI, and this association is specifically prominent in the cerebellar gray matter. The cerebellar gray matter constitutes mainly Purkinje cell dendritic trees, which form excitatory synaptic connections with parallel fibers and climbing fibers. Purkinje cell synapses are highly plastic and can undergo tremendous reorganization in responses to adaptive learning [42, 43], various cerebellar injuries, and other neurodegenerative diseases such as Parkinson's disease [44]. On the other hand, the cerebellar volume seems to play a role in executive function in AD, but not in MCI, demonstrating the dynamic adaptation of the cerebellum during the dementia process and might play roles in different clinical symptoms. Our findings may imply that maladaptive reorganization [45–49] of the cerebellum can lead to further dysfunctional brain networks. The loss of the association between cerebellar volume and cognitive function in AD might suggest that further degenerative changes in the cerebellum lead to a dampened maladaptive mechanism and/or disconnection of the cerebellum within the dysfunctional network. The structural neuroplasticity of the cerebellum, reflected on the cerebellar volume change, has been shown in subjects who receive long-term motor skill training [50]. Likewise, the plasticity-related cerebellar volume change also occurs in subjects who have different experiences in environmental deprivation leading to different cognitive development [51]. It is plausible that our study finding might be the result of neuroplasticity of the cerebellum, in response to the more aggressive primary insults of the cerebral cortex and hippocampus in the disease process. The detailed neuropathological alterations of the cerebellum in MCI and AD will need to be further investigated.

The cerebellum is known to modulate cognitive function [52]. In particular, patients with ataxia can exhibit a variety of cognitive symptoms, called CCAS/Schmahmann syndrome [14, 17–19, 21–25]. Recently, a scale has been developed to objectively measure CCAS/Schmahmann syndrome [23], and many of the clinical symptoms may overlap with MCI, including executive dysfunction, work memory deficit, language processing, and neuropsychiatric features as well as behavioral changes [14, 17–19, 21–25]. Therefore, it is possible that some of the core cognitive symptoms of MCI can also be modulated by the cerebellar pathology.

Of note, the CCAS/Schmahmann syndrome scale was developed in 2018 [23], and ADNI1 data is from 2004 to 2010; therefore, CCAS/Schmahmann syndrome scale was not incorporated as part of the cognitive assessment in this present dataset. Interestingly, CCAS/Schmahmann syndrome is primarily associated with the posterior lobes of the cerebellum, whereas clinical ataxia has been localized predominantly in the anterior lobes of the cerebellum, suggesting that motor and non-motor function of the cerebellum could be anatomically dissociated [14, 17–25]. Multiple imaging studies have demonstrated the structural (e.g., gray matter loss) [53, 54] or functional (e.g., network alteration) [55] across different cerebellar

Table 5 Mixed effect models to study the associations between baseline cerebellar volume and covariates with cognition in longitudinal follow-up

	ADAS-Cog13					
	NC (n = 227)		MCI (n = 393)		AD (n = 191)	
Factors	β	p value	β	p value	β	p value
Education (years)	− 0.06	0.004	− 0.05	< 0.001	0.01	0.73
Female	0.43	< 0.001	− 0.14	0.05	− 0.06	0.56
Age (decades)	0.29	0.009	− 0.02	0.76	− 0.16	0.05
APOE4 positivity [a]	− 0.11	0.76	0.03	0.74	− 0.17	0.2
Cerebellar volume [b]	− 0.10	0.19	0.10	0.01	0.02	0.41
Hippocampal volume [c]	0.002	0.02	− 0.29	< 0.001	− 0.33	*< 0.001*
Visit	0.02	0.26	0.13	< 0.001	0.29	*< 0.001*
Cerebellar volume x visit [d]	0.02	0.23	0.02	0.29	0.01	0.59
Hippocampal volume X visit [e]	− 0.06	0.001	− 0.06	< 0.001	− 0.004	0.89
	ADAS-Cog11					
	NC (n = 227)		MCI (n = 393)		AD (n = 191)	
Factors	β	p value	β	p value	β	p value
Education (years)	−0.04	0.03	− 0.04	< 0.001	0.004	0.81
Female	0.31	0.003	− 0.10	0.12	− 0.04	0.67
Age (decades)	0.20	0.05	0.01	0.81	− 0.1	0.14
APOE4 positivity [a]	− 0.04	0.03	− 0.006	0.95	− 0.18	0.14
Cerebellar volume [b]	− 0.08	0.30	0.08	0.04	− 0.008	0.89
Hippocampal volume [c]	− 0.03	0.73	0.01	0.22	− 0.28	< 0.001
Visit	− 0.01	0.42	0.12	< 0.001	0.27	< 0.001
Cerebellum volume X visit [d]	0.02	0.29	0.02	0.22	0.02	0.42
Hippocampal volume X visit [e]	− 0.04	0.04	− 0.06	< 0.001	− 0.004	0.89

APOE apolipoprotein E gene, *ADAS-Cog* Alzheimer's Disease Assessment Scale-cognitive subscale, *NC* normal cognition, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

[a] Zero copy of E4 = 0, One or two copies of E4 = 1; [b] Standardized ratio of bilateral cerebellum/intracranial volume; [c] Standardized ratio of bilateral hippocampal volume/intracranial volume; [d] Interaction effect between year and the cerebellar volume, [e] Interaction effect between year and the hippocampal volume

Results from linear mixed effects model specifying random intercept and random slope run separately by diagnosis category. Coefficients for variable main effects represent relationship between variable and estimated baseline cognition level; coefficients interaction with time represent relationship between variable and cognition slope. Age is lefted at the sample mean

lobules and regions in MCI and AD. Future studies should focus on the association of topographical volume changes of the cerebellum with cognitive performance in MCI and AD, which will comprehensively help us to understand the cerebellar cognitive affective contribution in the process of dementia. In addition, further studies on the structural changes in the cerebellar gray matter in the postmortem human pathology will enable us to pinpoint the neuropathological substrates of such plastic changes.

The major strength of the current study is that we examined both cross-sectional and longitudinal effects of cerebellar volume in cognitive function in both MCI and AD using well-characterized ADNI dataset. There are limitations of the present study. First, based on our imaging processing pipeline, we do not have the repeated cerebellar volume measures in our dataset to examine the longitudinal, dynamic changes of cerebellar volume during the conversion of NC to MCI (i.e., preclinical phase) [56] and MCI to AD, which will be the important future direction. As the segmentation of the cerebellum is not part of the standard algorithm, the contribution of the anterior and posterior cerebellum to cognition could not be analyzed, either. Second, we did not study the microscopic changes of cerebellar pathology in different diagnostic groups. Third, the sample size of the AD group is smaller than NC and MCI, which might affect the conclusiveness of the study results, and also might contribute to the negative results of longitudinal analyses. A study of a larger sample size with longitudinal imaging analysis focusing on the differentiation of the anterior vs. posterior cerebellum will be required to further determine the contribution of the cerebellum throughout the disease course.

Conclusion

Our study indicates that the cerebellum might contribute to cognitive function in MCI, which suggests its role in early stage of AD disease process. Our findings are consistent with the notion that AD is a dysfunction of brain network [1, 2], and the dynamic interplay of network components will determine the clinical presentations. Consistently, neuromodulation in the cerebellar region has been demonstrated to improve cognitive function in MCI and AD [57–60]. Future studies should focus on the functional neuroimaging and neuropathological studies to delineate the detailed functional and structural alterations in the cerebellum in MCI and AD.

Author Contribution Chi-Ying Lin: study concept, data analysis and interpretation, manuscript draft and revision; Chi-Hua Chen: study concept, data acquisition, analysis and interpretation, and critical revision of the manuscript for important intellectual content; Sarah E. Tom: data analysis and interpretation, critical revision of the manuscript of important intellectual content; Sheng-Han Kuo: study concept, data acquisition, analysis and interpretation, critical revision of the manuscript for important intellectual content, and study supervision.

Funding Information Dr. Chen has received funding from the National Institute of Health: NINDS #R01 MH118281 (principal investigator), NINDS #R01 MH100351 (principal investigator), and NINDS #R56 AG061163 (principal investigator). Dr. Tom has received funding from the National Institutes on Aging: NINDS #K01 AG050723. Dr. Kuo has received funding from the National Institutes of Health: NINDS #R01 NS104423 (principal investigator), NINDS #K08 NS083738 (principal investigator), and the Louis V. Gerstner Jr. Scholar Award, Parkinson's Foundation, and International Essential Tremor Foundation.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Drzezga A. The network degeneration hypothesis: spread of neurodegenerative patterns along neuronal brain networks. J Nucl Med. 2018;59:1645–8.
2. Hoenig MC, Bischof GN, Seemiller J, Hammes J, Kukolja J, Onur ÖA, et al. Networks of tau distribution in Alzheimer's disease. Brain. 2018;141:568–81.
3. Gould RL, Arroyo B, Brown RG, Owen AM, Bullmore ET, Howard RJ. Brain mechanisms of successful compensation during learning in Alzheimer disease. Neurology. 2006;67:1011–7.
4. Thomann PA, Schlafer C, Seidl U, Santos VD, Essig M, Schroder J. The cerebellum in mild cognitive impairment and Alzheimer's disease - a structural MRI study. J Psychiatr Res. 2008;42:1198–202.
5. Braak H, Braak E, Bohl J, Lang W. Alzheimer's disease: amyloid plaques in the cerebellum. J Neurol Sci. 1989;93:277–87.
6. Li YT, Woodruff-Pak DS, Trojanowski JQ. Amyloid plaques in cerebellar cortex and the integrity of Purkinje cell dendrites. Neurobiol Aging. 1994;15:1–9.
7. Wang HY, D'Andrea MR, Nagele RG. Cerebellar diffuse amyloid plaques are derived from dendritic Abeta42 accumulations in Purkinje cells. Neurobiol Aging. 2002;23:213–23.
8. Fukutani Y, Cairns NJ, Rossor MN, Lantos PL. Purkinje cell loss and astrocytosis in the cerebellum in familial and sporadic Alzheimer's disease. Neurosci Lett. 1996;214:33–6.
9. Sjobeck M, Englund E. Alzheimer's disease and the cerebellum: a morphologic study on neuronal and glial changes. Dement Geriatr Cogn Disord. 2001;12:211–8.
10. Wegiel J, Wisniewski HM, Dziewiatkowski J, Badmajew E, Tarnawski M, Reisberg B, et al. Cerebellar atrophy in Alzheimer's disease-clinicopathological correlations. Brain Res. 1999;818:41–50.
11. Baloyannis SJ, Manolidis SL, Manolidis LS. Synaptic alterations in the vestibulocerebellar system in Alzheimer's disease–a Golgi and electron microscope study. Acta Otolaryngol. 2000;120:247–50.
12. Mavroudis I. Cerebellar pathology in Alzheimer's disease. Hell J Nucl Med. 2019;22(Suppl):174–9.
13. Guo CC, Tan R, Hodges JR, Hu X, Sami S, Hornberger M. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. Brain. 2016;139:1527–38.
14. Schmahmann JD. Cerebellum in Alzheimer's disease and frontotemporal dementia: not a silent bystander. Brain. 2016;139:1314–8.
15. KH E, Chen SH, Ho MH, Desmond JE. A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. Hum Brain Mapp. 2014;35:593–615.
16. Stoodley CJ, D'Mello AM, Ellegood J, Jakkamsetti V, Liu P, Nebel MB, et al. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. Nat Neurosci. 2017;20:1744–51.
17. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998;121(Pt 4):561–79.
18. Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci. 2004;16:367–78.
19. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum - insights from the clinic. Cerebellum. 2007;6:254–67.
20. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage. 2009;44:489–501.
21. Schmahmann JD. The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy. Neuropsychol Rev. 2010;20:236–60.
22. Hickey CL, Sherman JC, Goldenberg P, Kritzer A, Caruso P, Schmahmann JD, et al. Cerebellar cognitive affective syndrome: insights from Joubert syndrome. Cerebellum Ataxias. 2018;5:5.
23. Hoche F, Guell X, Vangel MG, Sherman JC, Schmahmann JD. The cerebellar cognitive affective/Schmahmann syndrome scale. Brain. 2018;141:248–70.
24. Schmahmann JD. The cerebellum and cognition. Neurosci Lett. 2019;688:62–75.
25. Schmahmann JD, Guell X, Stoodley CJ, Halko MA. The theory and neuroscience of cerebellar cognition. Annu Rev Neurosci. 2019;42:337–64.
26. Tabatabaei-Jafari H, Walsh E, Shaw ME, Cherbuin N. Alzheimer's disease neuroimaging I. the cerebellum shrinks faster than normal ageing in Alzheimer's disease but not in mild cognitive impairment. Hum Brain Mapp. 2017;38:3141–50.
27. Jack CR Jr, Bernstein MA, Fox NC, Thompson P, Alexander G, Harvey D, et al. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. J Magn Reson Imaging. 2008;27:685–91.

28. O'Brien LM, Ziegler DA, Deutsch CK, Kennedy DN, Goldstein JM, Seidman LJ, et al. Adjustment for whole brain and cranial size in volumetric brain studies: a review of common adjustment factors and statistical methods. Harv Rev Psychiatry. 2006;14:141–51.
29. Voevodskaya O, Simmons A, Nordenskjöld R, Kullberg J, Ahlström H, Lind L, et al. The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. Front Aging Neurosci. 2014;6:264.
30. Vellas B, Andrieu S, Sampaio C, Wilcock G, European Task Force g. Disease-modifying trials in Alzheimer's disease: a European task force consensus. Lancet Neurol 2007;6:56–62.
31. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984;141:1356–64.
32. Mohs RC, Knopman D, Petersen RC, Ferris SH, Ernesto C, Grundman M, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11(Suppl 2):S13–21.
33. Battista P, Salvatore C, Castiglioni I. Optimizing neuropsychological assessments for cognitive, behavioral, and functional impairment classification: a machine learning study. Behav Neurol. 2017;2017:1850909.
34. Podhorna J, Krahnke T, Shear M, Harrison JE. Alzheimer's disease neuroimaging I. Alzheimer's Disease Assessment Scale-Cognitive subscale variants in mild cognitive impairment and mild Alzheimer's disease: change over time and the effect of enrichment strategies. Alzheimers Res Ther. 2016;8:8.
35. Hashimoto R, Meguro K, Lee E, Kasai M, Ishii H, Yamaguchi S. Effect of age and education on the trail making test and determination of normative data for Japanese elderly people: the Tajiri project. Psychiatry Clin Neurosci. 2006;60:422–8.
36. Romer AL, Knodt AR, Houts R, Brigidi BD, Moffitt TE, Caspi A, et al. Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. Mol Psychiatry. 2018;23:1084–90.
37. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44:2308–14.
38. Poulin SP, Bergeron D, Dickerson BC. Alzheimer's disease neuroimaging I. risk factors, neuroanatomical correlates, and outcome of neuropsychiatric symptoms in Alzheimer's disease. J Alzheimers Dis. 2017;60:483–93.
39. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A. 1993;90:1977–81.
40. Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology. 2000;55:484–9.
41. Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, et al. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. Arch Neurol. 2010;67:1370–8.
42. Steuber V, Mittmann W, Hoebeek FE, Silver RA, De Zeeuw CI, Häusser M, et al. Cerebellar LTD and pattern recognition by Purkinje cells. Neuron. 2007;54:121–36.
43. Shim HG, Jang DC, Lee J, Chung G, Lee S, Kim YG, et al. Long-term depression of intrinsic excitability accompanied by synaptic depression in cerebellar Purkinje cells. J Neurosci. 2017;37:5659–69.
44. Kuo SH, Lin CY, Wang J, Sims PA, Pan MK, Liou JY, et al. Climbing fiber-Purkinje cell synaptic pathology in tremor and cerebellar degenerative diseases. Acta Neuropathol. 2017;133:121–38.
45. Wolff JR, Missler M. Synaptic reorganization in developing and adult nervous systems. Ann Anat. 1992;174:393–403.
46. Morara S, Colangelo AM, Provini L. Microglia-induced maladaptive plasticity can be modulated by neuropeptides in vivo. Neural Plast. 2015;2015:135342.
47. Jones TA. Motor compensation and its effects on neural reorganization after stroke. Nat Rev Neurosci. 2017;18:267–80.
48. Mohan A, Vanneste S. Adaptive and maladaptive neural compensatory consequences of sensory deprivation-from a phantom percept perspective. Prog Neurobiol. 2017;153:1–17.
49. Kim R, Healey KL, Sepulveda-Orengo MT, Reissner KJ. Astroglial correlates of neuropsychiatric disease: from astrocytopathy to astrogliosis. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;87:126–46.
50. Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. Neuron. 2011;72:443–54.
51. Bauer PM, Hanson JL, Pierson RK, Davidson RJ, Pollak SD. Cerebellar volume and cognitive functioning in children who experienced early deprivation. Biol Psychiatry. 2009;66:1100–6.
52. Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. Neuron. 2013;80:807–15.
53. Colloby SJ, O'Brien JT, Taylor JP. Patterns of cerebellar volume loss in dementia with Lewy bodies and Alzheimers disease: a VBM-DARTEL study. Psychiatry Res. 2014;223:187–91.
54. Toniolo S, Serra L, Olivito G, Marra C, Bozzali M, Cercignani M. Patterns of cerebellar Gray matter atrophy across Alzheimer's disease progression. Front Cell Neurosci. 2018;12:430.
55. Zheng W, Liu X, Song H, Li K, Wang Z. Altered functional connectivity of cognitive-related cerebellar subregions in Alzheimer's disease. Front Aging Neurosci. 2017;9:143.
56. Budson AE, Solomon PR. New criteria for Alzheimer disease and mild cognitive impairment: implications for the practicing clinician. Neurologist. 2012;18:356–63.
57. Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology. 2008;71:493–8.
58. Cotelli M, Calabria M, Manenti R, Rosini S, Zanetti O, Cappa SF, et al. Improved language performance in Alzheimer disease following brain stimulation. J Neurol Neurosurg Psychiatry. 2011;82:794–7.
59. Turriziani P, Smirni D, Zappala G, Mangano GR, Oliveri M, Cipolotti L. Enhancing memory performance with rTMS in healthy subjects and individuals with mild cognitive impairment: the role of the right dorsolateral prefrontal cortex. Front Hum Neurosci. 2012;6:62.
60. Elder GJ, Taylor JP. Transcranial magnetic stimulation and transcranial direct current stimulation: treatments for cognitive and neuropsychiatric symptoms in the neurodegenerative dementias? Alzheimers Res Ther. 2014;6:74.