Changes in resting-state Functional Connectivity of Cerebellum in amnestic Mild Cognitive Impairment and Alzheimer's disease: a case-control study

Zhi Zhou

Heilongjiang Provincial Hospital

Rui Zhu

Beijing Geriatric Hospital

Wen Shao

China-Japan Friendship Hospital

Shujuan Zhang

Heilongjiang Provincial Hospital

Lei Wang

China-Japan Friendship Hospital

Xuejiao Ding

China-Japan Friendship Hospital

Dantao Peng (✉ dantao.peng@outlook.com)

China-Japan Friendship Hospital

Research

Keywords: Alzheimer's disease, Amnestic mild cognitive impairment, Cerebellum, resting-state functional MRI, Functional connectivity

Posted Date: August 12th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-55425/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Frontiers in Systems Neuroscience on March 10th, 2021. See the published version at <https://doi.org/10.3389/fnsys.2021.596221>.

Abstract

Background This case-control study is aimed to investigate the correlation of altered functional connectivity (FC) in cerebellum with cognitive impairment in amnesic mild cognitive impairment (aMCI) and Alzheimer's disease (AD).

Methods The morphometric and resting-state FC MRI analysis including 47 participants with AD, 32 with aMCI and 43 age-matched normal controls (NCs) were conducted. We compared the cerebellar gray matter volume and cerebellar FC with cerebral cortical regions among three groups. To investigate the relationship of cerebellar FC with cognition, we measure the correlation of significant altered FC and individual cognitive domain.

Results No significant morphometric differences of cerebellum was observed across three groups. The patients with AD had weaker cerebral cortical FCs in bilateral Crus I, left VIIb and IX compared to NCs, and in bilateral Crus I compared to patients with aMCI. For patients with aMCI, the weaker FC were found between right Crus I, left VIIb and IX and cerebral cortical regions compared to NCs. The strength of left cerebellar FC positively correlated with specific cognitive subdomains, including executive function, attention, visuospatial function, and global cognition in AD and aMCI.

Conclusions These findings demonstrated the alteration of cerebellar FC with cerebral cortical regions, and the correlation of cerebellar FC and cognitive impairment in AD and aMCI.

Background

Alzheimer's disease (AD) is the most common form of dementia, leading to a heavy burden on patients, family and society. Recent strategies of diagnosis and treatment for AD are based on identification and quantification of the pathological biomarkers. Molecular neuroimaging study with selective radioligands, including amyloid β ($A\beta$) and phosphorylated tau, is an important method for the quantification of these biomarkers[1]. The most used parameter is the standardized uptake value ratio (SUVR) between a target region and a reference region[2]. The selection of reference region directly affects the value of SUVR, which therefore is important for the diagnosis and the inclusion of participants in clinical therapeutic trials. The cerebellum has traditionally been recognized as essential only for the motor control, and is most widely used reference region in AD due to being free of $A\beta$ deposition[3–5].

However, increasing evidences demonstrate that the cerebellum is also associated with the regulation of cognition by way of the cerebrocerebellar circuits[6]. Pathological studies also found the deposition of $A\beta$ and other pathological changes on cerebellar cortex in AD[7].

These findings raise the opportunity that the cerebellum is not a “silent bystander” in AD, and the cerebellum may not be an optimal choice for the reference region. With the development of neuroimaging, growing studies reported the cerebellar atrophy and functional alteration in AD[8–13]. However, till now, the studies about the changes of cerebellum in AD patients are still limited, and results are not consistent.

This inconsistency may be due to the poor overlap of cerebellar subregions in parcellation by conventional whole-brain methods. Moreover, most previous studies focused on the relation between cerebellum and global cognitive function, the specific cognitive domain correlates with the alteration of cerebellum remains uncertain. More evidence is needed to illustrate the role of cerebellum in AD.

We hypothesized that altered cerebellar volume and functional connectivity (FC) correlated with cognitive dysfunction, and correlated with cognitive impairment in AD continuum. As amnesic mild cognitive impairment (aMCI) has a high incidence of conversion to AD, aMCI also provides a good model to investigate subtle change at the initial stage of the AD continuum[14]. Comparing the change of cerebellum among normal controls (NCs), patients with aMCI and AD, could help us to illustrate the processing of change in different cognitive status. With a cerebellum-specific spatially unbiased infratentorial template (SUIT), we performed voxel-based morphometry (VBM) analysis to compare the cerebellar volume between patients across different cognitively populations, including AD, aMCI and NCs. In addition, we used resting-state functional MRI (rs-fMRI) to investigate the FC between cerebellum and cerebral cortical regions, and the relations between altered FC and specific cognitive domains were calculated.

Methods

Study Design and participants

Participants were recruited in preparation for this study from the memory clinic of China-Japan Friendship Hospital. Participants with structural and rs-fMRI images were enrolled using the inclusion and exclusion criteria below. Patients with AD met the diagnostic criteria of probable AD dementia according to the new National Institute on Aging-Alzheimer's Association criteria of 2011[15]. The inclusion criteria for AD included: 1) significant episodic memory problems reported by the patient, relative or caregiver, which was corroborated by the score of Rey Auditory Verbal Learning Test (AVLT); 2) impaired performance on general cognition test Mini-Mental State Examination (MMSE) score ≥ 24 and activities of daily living (ADL); 3) medial temporal lobe atrophy on visual atrophy rating scale[16]. Patients with aMCI participants satisfied with the Petersen's criteria and the National Institute on Aging-Alzheimer's Association criteria for MCI due to AD[17, 18]. The inclusion criteria were as follows: 1) memory complaint; 2) scoring lower than 1.5 standard deviations of the age- and education-adjusted norm on the score of AVLT; 3) normal performance on general cognition test (MMSE score ≥ 24) and ADL. The NCs included family members of patients, who did not have cognitive complaints or significant decline on the neuropsychological testing, and with MMSE score ≥ 24 . The NCs were matched with AD and aMCI participants in gender and age.

Exclusion criteria for all participants included: 1) current or previous history of significant neurological disorder that could cause cognitive decline, including stroke, epilepsy, head trauma, intracranial mass or normal pressure hydrocephalus; 2) history of addictions or other psychiatric disorders, including

schizophrenia, bipolar disorder or depression; 3) other severe medical problems, including chronic heart failure and chronic respiratory insufficiency.

Clinical and neuropsychological assessment

All participants underwent neurological evaluation and comprehensive neuropsychological assessment. The neuropsychological assessments included general cognitive status and a series of detailed cognitive tests for specific cognitive domains, including memory, language, executive function, attention and visuospatial function (Supplementary Material provide the details). The z score of each cognitive domain and the composite cognitive z score (average of the 5 individual cognitive domains) were computed based on normative data from a database of control participants with similar age, education, and gender distribution in our center. Neuropsychiatric symptoms and functional impairment were assessed by caregiver-based questionnaires: Neuropsychiatric Inventory (NPI) and ADL, respectively[19]. The APOE genotype was determined from genotyping of isolated DNA from blood. The participants who had at least 1 APOE ϵ 4 allele were considered as APOE ϵ 4 carriers.

MRI data acquisition and preprocessing

The rs-fMRI images and T1-weighted MRI images were acquired using a 3.0 T MR imaging system (GE Healthcare, Discovery MR750, Milwaukee, WI, USA) in the Radiology Department of China-Japan Friendship Hospital. The parameters of sagittal three-dimensional T1-weighted images with fast spoiled gradient-echo sequences (FSPGR) were as follows: echo time (TE) = 3.0 ms, repetition time (TR) = 6.9 ms, slice thickness = 1.0 mm, FOV = 256 mm $\times$ 256 mm, acquisition matrix = 256 $\times$ 256, and flip angle = 12°. The parameters of axial resting-state data were as follows: TE = 30 ms, TR = 2,000 ms, slice thickness = 3.0 mm, 33 slices, field of view (FOV) = 240 mm $\times$ 240 mm, in plane matrix = 64 $\times$ 64, flip angle = 90°, and 240 phases.

Structural three-dimensional (3-D) T1 images were first processed using the SUI toolbox (<http://www.diedrichsenlab.org/imaging/suit.htm>) implemented in the Statistical Parametric Mapping software version 12 (SPM12; <http://www.fil.ion.ucl.ac.uk/spm/>) toolbox[20]. Each cerebellum was separated by a Bayesian algorithm into gray matter (GM) and white matter (WM), normalized to the Montreal Neurological Institute (MNI) space using the high-resolution probability template in SUI, and smoothed with a 4-mm full-width at half-maximum (FWHM) Gaussian kernel.

The rs-fMRIs were preprocessed with the Data Processing Assistant for Resting-State fMRI (DPARSF) and the Resting-State fMRI Data Analysis Toolkit (REST). First, the first 10 volumes were discarded for the signal equilibrium and adaptation of subjects to the scanning noise. The remaining 230 volumes were corrected for timing difference and realigned to the first volume to correct for possible movement. The data of 4 subjects (3 AD and 1 NC) were excluded in this step due to excessive head motion (greater than 3 mm or greater than 3° angular rotation). To normalize the resting images, the T1 images were registered to their corresponding functional images and were then segmented into GM, WM, and cerebrospinal fluid tissue (CSF) probabilistic maps using a unified segmentation algorithm. Second, a GM population template was derived from the whole image data set with the DARTEL technique. Third, nonlinear

warping of the segmented images was then performed to match the MNI space DARTEL template. Spatial smoothing was then performed with an isotropic 4-mm FWHM Gaussian kernel. Next, linear detrending and temporal band-pass filtering (0.01–0.1 Hz) were applied to remove low-frequency drifts and high-frequency noise. Finally, the nuisance variables (including 6 head motion parameters and their derivatives, the WM and CSF signal, and the linear term) were regressed out.

Seed ROIs

Previous studies revealed that the posterior lobe (VI, VIIb, VIII), ansiform lobe (Crus I, Crus II), and flocculonodular lobe (IX, X) of cerebellum are especially associated with cognition[21–24]. Therefore, these lobules were included as seed ROIs. The masks of these ROIs were extracted from the probabilistic cerebellar atlas used in SUIT[20] (Fig. 1). For each participant, the voxel of each seed was extracted to obtain the average seed point time series. A correlation coefficient map for each seed was produced by correlating the coefficients between the reference time series and the time series from all other brain voxels, which was then transformed to Fisher z -values.

– Insert Fig. 1 about here.

Statistical analysis

Data were analyzed using SPSS 22.0 (IBM Corp., Chicago, IL, USA). Demographic and clinical variables were checked for normality of distribution using Kolmogorov–Smirnov tests. Variables revealing normal distribution were compared across groups via ANOVA followed by Bonferroni post-hoc tests if ANOVA was significant ($p < 0.05$). Group comparisons of NPI and ADL between AD and aMCI were performed using Student's t test. Gender and ApoE4 status data were analyzed using a Chi-square test. $p < 0.05$ was regarded as significant.

The resulting images were subsequently entered into a VBM analysis to perform the one-way ANOVAs to identify between-group differences in the cerebellum. Age, gender, and total intracranial volume were included as nuisance covariates.

ANOVA analysis was used to compare the whole-brain FC of each seed among the three different groups. The age, gender, education level, head movement parameters, and total intracranial volume were used as covariates. False discovery rate (FDR) correction was performed with a threshold of 0.05. The z -values of FC were extracted to perform the post-hoc t test in order to identify the inter-group differences between AD and NC, aMCI and NC, and aMCI and AD. Bonferroni correction was performed to adjust for the multiple testing, with a p value of < 0.0167 ($0.05/3$) considered statistically significant for these comparisons.

Due to the small sample size of individual group, we combined the patients with aMCI and AD together to investigate the association between all the significant different FC and the 5 individual cognitive subdomain using the partial correlation, with age, gender, and education level as nuisance covariates. $p < 0.05$ was considered statistically significant.

Results

Demographic and neuropsychological results

From June 2014 to June 2019, we recruited 47 subjects with AD, 32 aMCI, and 43 NCs with the aforementioned procedures (**Fig. 2**). Table 1 shows the clinical and neuropsychological data. No significant differences in age, gender and education level. Regarding the cognitive performance, the AD group had significantly lower scores than both the aMCI and NC groups on general cognitive test and all the cognitive subdomains. aMCI subjects had significantly lower score on memory, language and executive function than NC subjects. The patients with AD scored significantly higher score on the ADL and NPI compared to patients with aMCI.

Cerebellar morphometry

No significant group difference in volume of any cerebellar lobular was found among three groups with predefined threshold.

Seed-based FC

Table 2 and Figure 3 illustrate the significant difference clusters in the FC for each seed among three groups.

The patients with AD had weaker cerebral cortical FCs in bilateral Crus I, left VIIb and IX compared to NCs. The weakened cerebellar FCs with visual cortex (Brodmann area, [BA] 18, 19), including precuneus and cuneus, were found in left VIIb and IX in AD. The left Crus I in AD had weaker correlations with dorsal lateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), and anterior cingulate cortex (ACC) (BA 9, 32, 45, 46). The weakened correlations with associative visual cortex (ASC), fusiform gyrus (FG) and middle temporal gyrus (MTG) (BA19, 21, 37) were found in right Crus I. Among cerebral cortical FCs mentioned above, the weakened FCs in bilateral Crus I still showed significant compared to patients with aMCI. For patients with aMCI, the right Crus I, and Left VIIb and IX was found with significantly weaker cerebral cortical FC compared to NCs.

Cerebral cortical FC in other seeds of cerebellum was not significantly different among three groups.

Cognitive correlations of cerebellar FC

Cognitive correlates of the FC findings in patients with AD and aMCI were investigated for all reported significant cerebellar-cerebral cortical FCs after controlling for age, gender and education (Table 3 and Figure 4). For left Crus I, Both of the strength of FC with left DLPFC and ACC (BA 9, 32), and right DLPFC and IFG (BA 45,46), positively correlated with executive function and visuospatial function, and global

cognition (Figure 4, A-F). The FC of right Crus I with left ASC and FG correlated with memory, language, and global cognition (Figure 4, G-I). No significant correlation with other cognitive subdomain was found. In the cerebral cortical FC with Left VII, IX, no significant correlation was found with individual cognitive domain and global cognition. The correlation for aMCI and AD subgroup is detailed in Supplementary Table 2.

Discussion

This case-control study investigated the cerebellar anatomic and functional changes across three different cognitive status, including the NC, aMCI, and AD group. The strength of cerebellar FC with cerebral cortical areas were different among three groups, and it correlated with cognitive function in AD and aMCI.

The weakened FC was found between the left VIIb and contralateral precuneus and cuneus, and between left IX and bilateral precuneus and cuneus in AD. Precuneus is one of the core regions of default mode network (DMN)[25]. A β accumulation preferentially starts in several of the core regions of the DMN, including the precuneus at the early stage of AD[26]. From the perspective of clinical symptoms, the DMN has been found to be related to episodic memory in AD [25, 27]. Failure to detect the correlation with the cognitive performance, especially with the memory, could be due to the restricted range of this dependent variable in our aMCI cohort. The correlation with memory was found between left IX and contralateral precuneus in AD group (Supplementary Table 2).

Compared to NC, the aMCI and AD group showed weaker FC of the left Crus I correlated with frontal lobe (bilateral DLPFC, left ACC and right IFG), while right Crus I with occipital and temporal lobule (bilateral FG, left ASC and right MTG). The role of Crus I in working memory, planning and organization have been highlighted by functional imaging studies[28]. In addition, the role of DLPFC in executive function had been clearly established. This is consistent with our result that the FC between left Crus I and bilateral DLPFC correlated with execution. Previous fMRI also demonstrated the crossed cerebro-cerebellar projections, language is heavily right lateralized and visuospatial function left lateralized. Interestingly, in this study, we found similar lateralization in Crus I, as the FC of left Crus I connected with the execution and visuospatial function, and right Crus I connected with the memory and language.

Crossed cerebellar diaschisis (CCD) is the remote effect of supratentorial dysfunction in the unilateral hemisphere inducing contralateral cerebellar hypometabolism[29], which could explain the weakened FC between cerebellum and cerebrum. The mechanism of CCD implies the involvement of cortico-ponto-cerebellar fibers. However, whether the focal change in the cerebellum is a form of Wallerian degeneration or the result of accumulation of AD pathological substrates in the cerebellum itself is still unknown. In this study, we did not find morphometric difference in any of the observed cerebral cortical regions across the three groups, also implicating altered FC could be due to the dysfunction of neurotransmitter or network connection, instead of being secondary to the atrophy.

In this study, we did not find significant differences in volumes of any cerebellar lobular in AD or aMCI group. Though previous VBM studies reported cerebellar gray matter loss, some studies reported no atrophy in AD and aMCI[13, 30–32]. One reason may be the choice of SUIT template in this study, which can improve the alignment of cerebellar structures[20]. Another reason may be the relatively mild degree of cognitive decline in the AD group of this study (MMSE: 18.64 ± 3.39 ; MoCA: 14.11 ± 4.22 ; composite cognitive z score -2.01 ± 1.01), which indicates an earlier stage of disease. Tabatabaei-Jafari et al. also found that cerebellar atrophy happened at the late stage of AD [33].

There are some limitations to this study. First, as a retrospective case-control study, the identification of the aMCI and AD groups was not based on pathological evidence, such as A β PET, which is still expensive for some patients in China. However, in this study, the prevalence of APOE ϵ 4 carriers in AD and aMCI was 61.70% and 59.38%, respectively, which is similar to that of a previous study with large sample of A β biomarker positive individuals (66% in AD and 64% in MCI)[34]. Second, though we included the aMCI group as the prodromal stage of AD, this was still a cross-sectional study. In the future, longitudinal studies are needed to investigate the dynamic changes in the cerebellum throughout disease progression.

Conclusions

In conclusion, these findings suggest the functional changes of the cerebellum indicating the critical role cerebellum in the cognitive impairment in aMCI and AD. This was important because using the cerebellum as the reference region for ligand neuroimaging studies could bring the possible biased results.

Abbreviations

AD

Alzheimer's disease

A β

amyloid β

SUVr

standardized uptake value ratio

FC

functional connectivity

aMCI

amnesic mild cognitive impairment

NCs

normal controls

SUIT

spatially unbiased infratentorial template

VBM

voxel-based morphometry

rs-fMRI

resting-state functional MRI

AVLT

Auditory Verbal Learning Test

MMSE

Mini-Mental State Examination

ADL

activities of daily living

NPI

Neuropsychiatric Inventory

FSPGR

fast spoiled gradient-echo sequences

TE

echo time

TR

repetition time

FoV

field of view

FWHM

full-width at half-maximum ()

ANOVA

Analysis of Variance

FDR

False discovery rate

BA

Brodamann area.

DLPFC

Dorsal lateral prefrontal cortex

IFG

Inferior frontal gyrus

ACC

Anterior cingulate cortex

ASC

Associative visual cortex

FG

Fusiform gyrus

MTG

Middle temporal gyrus

DMN

Default mode network
CCD
Crossed cerebellar diaschisis

Declarations

Ethics approval and consent to participate

The study was approved by the Research Ethics Committees of China-Japan Friendship Hospital. All procedures were performed in accordance with methods approved by the Ethics Committee. Written informed consent for participate was obtained from each participant or his or her relatives.

Consent for publication

Written informed consent for publication was obtained from each participant or his or her relatives.

Availability of data and materials

The dataset is available at <http://dx.doi.org/10.17632/tc7xmjbmfw.1>.

Competing interests

The authors declare no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81571657).

Authors' contributions

Conceptualization: DT. P; Methodology: Z. Z, W. S, L. W; Formal analysis and investigation: Z. Z, R. Z, SJ. Z, L. W, XJ. D; Writing - original draft preparation: Z. Z; Writing - review and editing: R. Z, DT. P; Funding acquisition: DT. P; Supervision: DT. P. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the MRI technologists and operators for their assistance, and thank all the participants for their dedication, time, and effort to this study.

References

1. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's dementia: the journal of the Alzheimer's Association*. 2018;14(4):535–62.

2. Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, Joshi AD, Clark CM, Mintun MA, Pontecorvo MJ, et al. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol*. 2011;68(11):1404–11.
3. Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, Pontecorvo MJ, Hefti F, Carpenter AP, Flitter ML, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. *Jama*. 2011;305(3):275–83.
4. Maass A, Landau S, Baker SL, Horng A, Lockhart SN, La Joie R, Rabinovici GD, Jagust WJ. Alzheimer's Disease Neuroimaging I: **Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease**. *NeuroImage*. 2017;157:448–63.
5. Stern RA, Adler CH, Chen K, Navitsky M, Luo J, Dodick DW, Alosco ML, Tripodis Y, Goradia DD, Martin B, et al. Tau Positron-Emission Tomography in Former National Football League Players. *N Engl J Med*. 2019;380(18):1716–25.
6. Schmahmann JD, Guell X, Stoodley CJ, Halko MA. The Theory and Neuroscience of Cerebellar Cognition. *Annu Rev Neurosci*. 2019;42:337–64.
7. Sepulveda-Falla D, Barrera-Ocampo A, Hagel C, Korwitz A, Vinueza-Veloz MF, Zhou K, Schonewille M, Zhou H, Velazquez-Perez L, Rodriguez-Labrada R, et al. Familial Alzheimer's disease-associated presenilin-1 alters cerebellar activity and calcium homeostasis. *J Clin Investig*. 2014;124(4):1552–67.
8. Mascali D, DiNuzzo M, Gili T, Moraschi M, Fratini M, Maraviglia B, Serra L, Bozzali M, Giove F. Intrinsic patterns of coupling between correlation and amplitude of low-frequency fMRI fluctuations are disrupted in degenerative dementia mainly due to functional disconnection. *PloS one*. 2015;10(4):e0120988.
9. Bai F, Liao W, Watson DR, Shi Y, Yuan Y, Cohen AD, Xie C, Wang Y, Yue C, Teng Y, et al. Mapping the altered patterns of cerebellar resting-state function in longitudinal amnesic mild cognitive impairment patients. *Journal of Alzheimer's disease: JAD*. 2011;23(1):87–99.
10. Wang Z, Yan C, Zhao C, Qi Z, Zhou W, Lu J, He Y, Li K. Spatial patterns of intrinsic brain activity in mild cognitive impairment and Alzheimer's disease: a resting-state functional MRI study. *Hum Brain Mapp*. 2011;32(10):1720–40.
11. Lou W, Shi L, Wang D, Tam CW, Chu WC, Mok VC, Cheng ST, Lam LC. Decreased activity with increased background network efficiency in amnesic MCI during a visuospatial working memory task. *Hum Brain Mapp*. 2015;36(9):3387–403.
12. Jacobs HIL, Hopkins DA, Mayrhofer HC, Bruner E, van Leeuwen FW, Raaijmakers W, Schmahmann JD. The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline. *Brain*. 2018;141(1):37–47.
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(Pt 5):1527–38.

14. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1133–42.
15. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's dementia: the journal of the Alzheimer's Association*. 2011;7(3):263–9.
16. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, Kuiper M, Steinling M, Wolters EC, Valk J. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry*. 1992;55(10):967–72.
17. van den Burg W, Kingma A. Performance of 225 Dutch school children on Rey's Auditory Verbal Learning Test (AVLT): parallel test-retest reliabilities with an interval of 3 months and normative data. *Archives of clinical neuropsychology: the official journal of the National Academy of Neuropsychologists*. 1999;14(6):545–59.
18. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *Journal of internal medicine*. 2014;275(3):214–28.
19. Cummings JL. Changes in neuropsychiatric symptoms as outcome measures in clinical trials with cholinergic therapies for Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1997;11(Suppl 4):1–9.
20. Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N. A probabilistic MR atlas of the human cerebellum. *NeuroImage*. 2009;46(1):39–46.
21. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex*. 2010;46(7):831–44.
22. Barton RA, Harvey PH. Mosaic evolution of brain structure in mammals. *Nature*. 2000;405(6790):1055–8.
23. Whiting BA, Barton RA. The evolution of the cortico-cerebellar complex in primates: anatomical connections predict patterns of correlated evolution. *Journal of human evolution*. 2003;44(1):3–10.
24. Prevosto V, Graf W, Ugolini G. Cerebellar inputs to intraparietal cortex areas LIP and MIP: functional frameworks for adaptive control of eye movements, reaching, and arm/eye/head movement coordination. *Cerebral cortex*. 2010;20(1):214–28.
25. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1–38.
26. Palmqvist S, Scholl M, Strandberg O, Mattsson N, Stomrud E, Zetterberg H, Blennow K, Landau S, Jagust W, Hansson O. Earliest accumulation of beta-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nature communications*. 2017;8(1):1214.

27. Sperling RA, Laviolette PS, O'Keefe K, O'Brien J, Rentz DM, Pihlajamaki M, Marshall G, Hyman BT, Selkoe DJ, Hedden T, et al. Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron*. 2009;63(2):178–88.
28. Buckner RL. The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron*. 2013;80(3):807–15.
29. Lin WY. Crossed cerebellar diaschisis: related to lesion location or disease duration? *Journal of nuclear medicine: official publication Society of Nuclear Medicine*. 1997;38(12):2006.
30. Mrzilkova J, Zach P, Bartos A, Tintera J, Ripova D. Volumetric analysis of the pons, cerebellum and hippocampi in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2012;34(3–4):224–34.
31. Bas O, Acer N, Mas N, Karabekir HS, Kusbeci OY, Sahin B. Stereological evaluation of the volume and volume fraction of intracranial structures in magnetic resonance images of patients with Alzheimer's disease. *Annals of anatomy = Anatomischer Anzeiger: official organ of the Anatomische Gesellschaft*. 2009;191(2):186–95.
32. 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 research*. 2014;223(3):187–91.
33. 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(6):3141–50.
34. Mattsson N, Groot C, Jansen WJ, Landau SM, Villemagne VL, Engelborghs S, Mintun MM, Lleo A, Molinuevo JL, Jagust WJ, et al. Prevalence of the apolipoprotein E epsilon4 allele in amyloid beta positive subjects across the spectrum of Alzheimer's disease. *Alzheimer's dementia: the journal of the Alzheimer's Association*. 2018;14(7):913–24.

Tables

Table 1. Demographic and neuropsychological data

	Normal Controls	Amnesic MCI	Alzheimer's disease	<i>p</i> (ANOVA)
N	43	32	47	
Age, years	70.09 ± 6.76	70.84 ± 7.54	73.21 ± 6.42	0.098
Gender (Male, %)⁴	18 (41.86%)	16 (50.0%)	20 (42.55%)	0.747
Education, years	14.47 ± 3.10	13.68 ± 3.43	12.74 ± 4.32	0.091
MMSE	29.30 ± 0.86	26.16 ± 1.65	18.64 ± 3.39	<0.001 ^{1, 2, 3}
MoCA	27.09 ± 1.46	21.72 ± 2.87	14.11 ± 4.22	<0.001 ^{1, 2, 3}
NPI⁵	-	6.41 ± 5.21	12.40 ± 11.97	0.010
ADL⁵	-	23.59 ± 3.43	33.81 ± 8.41	<0.001
APOE ε4 carrier (n, %)⁴	11 (25.58%)	18 (59.38%)	29 (61.70%)	0.001
Composite cognitive z score	0.03 ± 0.43	-1.03 ± 0.73	-1.81 ± 0.71	<0.001 ^{1, 2, 3}
z-memory	0.13 ± 0.70	-2.10 ± 0.49	-2.68 ± 0.68	<0.001 ^{1, 2, 3}
z-language	0.25 ± 0.61	-1.29 ± 1.28	-1.98 ± 1.14	<0.001 ^{1, 2, 3}
z-executive function	-0.06 ± 0.76	-0.62 ± 1.31	-1.44 ± 1.07	<0.001 ^{1,3}
z-attention	-0.08 ± 0.94	-0.30 ± 1.32	-1.05 ± 1.50	0.001 ^{1,3}
z-visuospatial	-0.10 ± 0.85	-0.85 ± 1.12	-1.92 ± 1.80	<0.001 ^{1,3}

Abbreviations: MMSE, mini-mental status examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; ADL, Activity of Daily Living.

1. Post-hoc analysis showed significant group differences between NC and AD.
2. Post-hoc analysis showed significant group differences between NC and aMCI.
3. Post-hoc analysis showed significant group differences between aMCI and AD.
4. Values were mean ± standard deviation. Comparisons using Chi-square test.
5. Values were mean ± standard deviation (sd). Comparisons using Student's t test.

Table 2. Brain regions showing significant differences during one-way ANOVA on z value of functional connectivity maps of NC, aMCI, and AD groups

Seed	Cluster Voxels	Brain regions	Laterality	BA	MNI coordinate			Maximum <i>F</i>
					x	y	z	
Left VIIb	12	Visual cortex (Pcu and Cu)	Right	18, 19	21	78	-24	19.85
Left IX	12	Visual cortex (Pcu and Cu)	Right	18, 19	18	-69	24	14.18
	15	Visual cortex (Pcu and Cu)	Left	18, 19	12	-75	45	16.57
Left Crus I	32	DLPFC and IFG	Right	45, 46	42	42	18	17.12
	20	DLPFC and ACC	Left	9, 32	-6	48	33	16.65
Right Crus I	22	MTG and FG	Right	21, 37	-45	-69	-12	25.28
	17	ASC and FG	Left	19, 37	60	-57	6	24.61

Abbreviations: BA: Brodamann area. PCu: precuneus; Cu: cuneus; DLPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; ACC: anterior cingulate cortex; MTG: middle temporal gyrus; FG: fusiform gyrus. ASC: associative visual cortex.

Table 3. Correlation between cognition and cerebellar FC.

BA			Composite	Memory	Language	Executive	Attention	Visuospatial
			z score	z score	z score	z score	z score	z score
Left VIIb	Right BA 18, 19	<i>r</i>	-0.029	-0.145	-0.103	0.120	-0.092	0.058
		<i>p</i>	0.804	0.211	0.374	0.303	0.428	0.619
Left IX	Left BA 18, 19	<i>r</i>	-0.097	0.044	-0.051	-0.145	0.046	-0.152
		<i>p</i>	0.406	0.708	0.662	0.211	0.692	0.189
	Right BA 18, 19	<i>r</i>	0.024	0.168	0.072	-0.016	-0.073	0.013
		<i>p</i>	0.836	0.147	0.538	0.892	0.531	0.914
Left Crus I	Left BA 9,32	<i>r</i>	0.259	0.178	0.091	0.259	0.036	0.274
		<i>p</i>	0.024*	0.125	0.434	0.024*	0.760	0.017*
	Right BA 45, 46	<i>r</i>	0.334	0.216	0.208	0.283	0.081	0.300
		<i>p</i>	0.003*	0.061	0.071	0.013*	0.487	0.008*
Right Crus I	Left BA 21,37	<i>r</i>	0.256	0.395	0.268	0.181	0.112	0.036
		<i>p</i>	0.026*	0.000*	0.019*	0.118	0.334	0.755
	Right BA 21, 37	<i>r</i>	0.147	0.211	0.100	0.063	0.152	0.021
		<i>p</i>	0.206	0.067	0.392	0.587	0.189	0.857

Abbreviations: BA: Brodamann area. Bold and * means $p < 0.05$.

Figures

Figure 1

The seeds of the cerebellum. The image was transformed into the space of the SUI atlas and was overlapped by the seeds. The different colors show the lobular parcellation.

Figure 2

Diagram showing the number and flow of subjects in this study. Abbreviations: NC: normal control; aMCI: amnestic mild cognitive impairment; naMCI: non-amnestic mild cognitive impairment; rs-fMRI: resting-state functional MRI

Figure 3

Statistical parametric map and the scatterplot of the significant cerebral clusters among three groups and the post-hoc analysis between groups. Each row corresponds to a distinct cerebellar lobular seed region of interest. The difference remained significant after Bonferroni correction at post-hoc analysis. Color bar represents F values. BrainNet Viewer (Beijing Normal University, <http://www.nitrc.org/projects/bnv/>) was used for the visualization of the results. Abbreviations: L: left; R: right; Bi: bilateral; PCu: precuneus; Cu:

cuneus; DLPFC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; ACC: anterior cingulate cortex; ASC: associative visual cortex; MTG: middle temporal gyrus; FG: fusiform gyrus

Figure 4

Scatter plots for the significant cognitive-functional connectivity (FC) correlations.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [AdditionalfileTable2.pdf](#)
- [AdditionalfileTable1.pdf](#)
- [Additionalfile1.pdf](#)