Cascade process mediated by left hippocampus and left superior frontal gyrus affects relationship between aging and cognitive dysfunction

Yumika Kokudai
Showa University School of Medicine
Motoyasu Honma (mhonma@med.showa-u.ac.jp)
Showa University School of Medicine
Yuri Masaoka
Showa University School of Medicine
Masaki Yoshida
Jikei University School of Medicine
Haruko Sugiyama
Kao Corporation
Akira Yoshikawa
Showa University School of Medicine
Nobuyoshi Koiwa
University of Human Arts and Sciences
Satomi Kubota
Showa University School of Medicine
Natsuko Iizuka
Showa University School of Medicine
Sayaka Wada
Showa University School of Medicine
Shotaro Kamijo
Showa University School of Medicine
Yuki Uchida
Showa University School of Medicine
Satoshi Yano
Showa University School of Medicine
Masahiro Ida
Ebara Tokyo Hospital
Kenjiro Ono
Showa University School of Medicine
Masahiko Izumizaki

Showa University School of Medicine

Research Article

Keywords: Cognitive dysfunction, Wisconsin card sorting test, Aging, Hippocampus, Superior frontal gyrus

Posted Date: October 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-844058/v1

Version of Record: A version of this preprint was published at BMC Neuroscience on December 1st, 2021. See the published version at https://doi.org/10.1186/s12868-021-00680-x.

Abstract

Background: Cognitive function declines with age and has been shown to be associated with atrophy in some brain regions, including the prefrontal cortex. However, the details of the relationship between aging and cognitive dysfunction are not well understood.

Methods: Across a wide range of ages (24- to 85-years-old), this research measured the gray matter volume of structural magnetic resonance imaging data in 39 participants, while some brain regions were set as mediator variables to assess the cascade process between aging and cognitive dysfunction in a path analysis.

Results: Path analysis showed that age affected the left hippocampus, thereby directly affecting the left superior frontal gyrus. Furthermore, the gyrus directly affected higher order flexibility and maintenance abilities calculated as assessed in the Wisconsin card sorting test, and the two abilities affected an assessment of general cognitive function.

Conclusion: Our finding suggests that a cascade process mediated by the left hippocampus and left superior frontal gyrus is involved in the relationship between aging and cognitive dysfunction.

Introduction

Higher brain functions related to thinking, judgment, and behavior are highly human-specific characteristics. In particular, executive functioning to abstract reasoning or to adapt strategies to situations, as assessed by the Wisconsin card sorting test (WCST) [1] and Montreal Cognitive Assessment (MoCA) [2], which measures overall cognitive function, plays an important role in daily life [3-5]. Although the executive functioning declines with age [6], this is also affected by years of education and illness [7-9], and individual differences as such are known to be quite pronounced [10].

Executive functioning is associated with the hippocampal-frontal network [11-13], and some studies suggest that the volume and thickness of the frontal lobe and hippocampus are involved in performance in the WCST [14, 15]. In addition, positron emission tomography and electroencephalography patterns during the WCST are also affected by aging [16, 17]. It is thought that the atrophy of specific regions is an intervening variable in the relationship between aging and the decline in executive functioning; however, the details of the cascade process among relevant variables have not been elucidated yet to date.

The current study measured the gray matter volume from structural magnetic resonance imaging (MRI) data, and the frontal lobe and hippocampus were set as regions of interest (ROIs) (12 locations on the left and right sides of the ROIs: the opercular part of the inferior frontal gyrus, orbital part of the inferior frontal gyrus, triangular part of inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, and hippocampus). First, we assessed the decline in executive functioning (WCST and MoCA) and region atrophy due to aging by comparing younger and older groups. Next, we assessed the relationship between age, years of education, region atrophy, WCST performance, and MoCA by a path analysis to verify the cascade process leading to cognitive dysfunction.

As a rough preliminary model, we assumed that individual profile characteristics would affect the volume of specific brain regions within the frontal lobe-related and hippocampal regions, and then some regions would affect cognitive function. Therefore, three phases were established in the path analysis (Supplementary Figure 1). Phase 1 was set for individual profile characteristics (age and years of education), Phase 2 for brain region volume (12 regions), and Phase 3 for assessments of cognitive function (three indices calculated by WCST and MoCA).

Methods And Materials

Participants

This research was approved by the Ethics Committee of Showa University Hospital, and was conducted in accordance with the principles of the Declaration of Helsinki (clinical trial identifier number: 2561). This study was registered for University hospital Medical Information Network (UMIN)-CTR (ID: UMIN000033776, 20/08/2018). The participants included in this study consisted of a subset of subjects from a previously published study [18], for whom both facial expression and structural MRI data were available. Participants were aged 23 to 59 years in the younger group and 60 to 85 years in the elderly group. All participants provided written informed consent. Twenty elderly participants (10 men and 10 women) and 20 younger adults (11 women and 9 men) participated in this study (Table 1). The average age of all participants was 56.95 (SD = 18.95). Cerebral infarction was diagnosed in one man in the elderly group; his data were excluded from the analysis. Nineteen elderly and 18 younger participants were right-hand dominant, and all had normal visual acuity. The average age of the elderly group (mean age: 74.1) was higher than that in the younger group (mean age: 40.7; t_{37} =11.970, $p < 0.0001$). The average number of years of education in the elderly group was lower than that in the younger group (t_{37} = 4.610, $p < 0.0001$). The average MoCA score in the elderly group was lower than that in the younger group (t_{37} = 3.012, p = 0.005).

Wisconsin card sorting test

We used a modified and computerized version of the Keio Version WCST [19]. The WCST is a test that uses cards with printed figures consisting of one to four triangles, stars, crosses, and circles in red, green, yellow, and blue. Participants were required to place the response cards one by one under the four stimulus cards according to one of the three classification categories: color, shape, or number. The outcome measures were the number of categories achieved (CA), perseverative errors of Nelson (PEN), and difficulties in maintaining set (DMS). The CA is the number of categories for which six consecutive correct responses are achieved (eight is the maximum number of categories that can be achieved), and reflects the sum measure of the level of conceptual shifts. The index reflects the degree of concept formation and transformation. PEN reflects the number of incorrect responses in the same category as

Table 1. Participants characteristics

	Younger group		Elderly group		
	Average	S.D.	Average	S.D.	*p* value
Age	40.7	11.5	74.1	4.3	< 0.0001
MoCA	27.9	2.1	25.8	2.2	0.005
Years of education	17.1	2.4	13.4	2.6	< 0.0001
Region volume					
ICV	1568011	135892	1460717	164837	
Left opercular part of inferior frontal gyrus	3202	522	2810	493	0.492
Left orbital part of inferior frontal gyrus	1099	169	994	203	0.122
Left triangular part of inferior frontal gyrus	2474	485	2167	320	0.020
Left middle frontal gyrus	10348	1699	8239	1301	0.003
Left superior frontal gyrus	17598	1647	14854	1780	0.005
Left hippocampus	4172	359	3440	358	< 0.0001
Right opercular part of inferior frontal gyrus	3347	479	2856	452	0.040
Right orbital part of inferior frontal gyrus	1031	199	866	208	0.323
Right triangular part of inferior frontal gyrus	2127	396	1966	420	0.124

Right middle frontal gyrus	9044	1047	7517	1183	0.003
Right superior frontal gyrus	16644	1573	13646	2005	< 0.0001
Right hippocampus	4389	332	3609	439	< 0.0001

MoCA: Montreal Cognitive Assessment. Years of Education: Years of education since entering elementary school. The standard deviations are shown in parentheses. Unpaired t test was used to age, MoCA, and years of education. RM-ANCOVA with MoCA and years of education as covariate was used to Wisconsin card sorting test. ICV: Intracranial volume. ANCOVA with intracranial volumes, MoCA, and years of education as covariate was used to brain volume. The unit of region volume is mm^3.

the immediately preceding incorrect response. The index indicates a tendency for false reactions to persist and a failure to suppress the previous reaction. DMS reflects the number of false responses after consecutive correct answers. The index refers to the degree to which the subject loses track of the classification category to which the participant is conforming.

MRI acquisition

MRI data were obtained at Ebara Hospital (Tokyo, Japan) using a Siemens Avanto 3 T Magnetom TIM Trio scanner. T1-weighted anatomical scan was measured following parameters (repetition time, 2250 ms; echo time, 3.06 ms; flip angle, 9 °; inversion time, 1000 ms; field of view, 256 × 256 mm; matrix size, 256 × 256; voxel size, 1 × 1 × 1 mm). The acquisition of high-resolution anatomical images

Were optimized with magnetization-prepared rapid gradient echo sequence.

Image processing

Image processing were performed with FreeSurfer version 6 [20, 21] including motion correction, removing nonbrain tissue, normalization with non-uniform intensity, affine registration to Montreal Neurological Institute (MNI) space, and Talairach transformation [22]. Volumetric segmentation [23], cortical surface reconstruction [24-26], and parcellation [27, 28] were automatically performed with the recon-all script on FreeSurfer after the image processing. Detailed descriptions have been provided elsewhere [29]. The 70 gray matter volumes determined by Desikan-Killiany brain atlas [28] were used in this study. All gray matter boundaries were confirmed by visual inspections of two trained neurologists with a graphic tool of Freeview after affine registration to MNI space. The two neurologists performed manual editing within the range of removing non-brain tissue included within the cortical boundary. Intracranial volume (ICV) was estimated using FreeSurfer version 6 [20, 21] for using as a covariate for statistical analysis.

Statistical analysis

An unpaired *t*-test was used to compare the age, years of education, and MoCA scores between the two groups. A one-way repeated measures analysis of covariance (RM-ANCOVA) was used to assess the age effect in the younger and elderly groups, with years of education and MoCA scores as covariates. Twelve regions were selected as the ROIs. An ANCOVA was used to compare the regional volumes between groups, with ICVs, years of education, and MoCA scores as covariates. Post-hoc *t*-tests with Bonferroni correction were performed for multiple comparisons for both the ANCOVA and RM-ANCOVA analyses. All tests were two-tailed. Results are presented as the mean ± standard error of the mean. SPSS version 26 was used for all statistical analyses. Relationships among age, years of education, 12 ROIs, 3 indices in WCST, and MoCA scores were determined using path analysis. The goodness of fit of index (GFI), root mean square error of approximation (RMSEA), comparative fit index (CFI), and Bollen-Stine bootstrap were calculated to check the model fitting. AMOS 27.0, was used for path analysis. Statistical significance was defined as an adjusted *p-value of* < 0.05.

Results

Group comparison in the Wisconsin card sorting test

For the WCST, a one-way RM-ANCOVA with years of education and MoCA as covariates showed that the CA score of the elderly group was lower than that of the younger group (Fig. 1A: $F_{1,35} = 5.058$, $p = 0.031$), while there were no group differences in the PEN (Fig. 1B: $F_{1,35} = 3.375$, $p = 0.075$) or DMS scores (Fig. 1C: $F_{1,35} = 0.887$, $p = 0.353$).

Group comparisons of region volumes

For the ROIs, the ANCOVA with ICV, years of education, and MoCA as covariates showed that eight of the 12 regions differed significantly between the two age groups (Table 1). The elderly group had smaller volumes in the left triangular part of the inferior frontal gyrus ($p = 0.020$), left middle frontal gyrus ($p = 0.003$), left superior frontal gyrus ($p = 0.005$), left hippocampus ($p < 0.0001$), right opercular part of inferior frontal gyrus ($p = 0.040$), right middle frontal gyrus ($p = 0.003$), right superior frontal gyrus ($p < 0.0001$), and right hippocampus ($p < 0.0001$) than the younger group.

Path analysis

We conducted a path analysis to assess the cascade process from age to overall cognitive function. Age, years of education, 12 region volumes corrected by ICV, 3 WCST scores, and MoCA scores were set as the observed variables. The most suitable model was the path in which age affected the left hippocampus (standardized path coefficient: -0.712), left hippocampus affected the left superior frontal gyrus (0.811), left superior frontal gyrus affected PEN (-0.464) and DMS (-0.321), and PEN (-0.526) and DMS (-0.254) affected the MoCA (Fig. 2: chi- square (9) = 16.473, p = 0.058; GFI = 0.892; RMSEA = 0.148; CFI = 0.927; Bollen-Stine bootstrap = 0.174).

Discussion

The WCST performance revealed a difference in CA, while no difference was observed in PEN and DMS between the aged groups. This may have reflected the large variance in the PEN and DMS data, suggesting that the aged-group comparison had no direct impact on the PEN and DMS. The CA is meant to be an overall assessment of the WCST, while the PEN reflects a response inhibition and DMS reflects attention maintenance [30]. In our results, these response inhibition and attention maintenance functions are likely to be independent of age.

In the aged-group comparison of ROIs, most regions were smaller in the elderly than in the younger group. However, in a path analysis, the left superior frontal gyrus was found to be the key intervening variable affecting WCST performance, while many ROIs were not used as the influencing variable. Furthermore, the left hippocampus, which influences the left superior frontal gyrus, was more strongly affected by age. This path analysis, which deals with the volume of brain regions, is limited in its ability to shed light on the relationship between regions. However, the hippocampus is known to be the first region associated with cognitive decline and is associated with early symptoms of Alzheimer's disease [31]. As such, the model whereby age has the strongest and most direct effect on the hippocampus seems to be supported by previous findings. Furthermore, the model of the hippocampus influencing the WCST via the superior frontal gyrus was more suitable than the model of the hippocampus directly influencing the WCST. A reduction in the superior frontal gyrus has been associated with WCST performance in patients with schizophrenia and psychopathy patients [32-34], and these findings may support the current model.

Executive functioning is associated with the hippocampal-frontal network [11-13], and may require the functioning of both the hippocampus and prefrontal cortex. The results of the path analysis suggest that the left superior frontal gyrus is directly responsible for the response inhibition and attention maintenance functions shown by PEN and DMS, and that the function of the left hippocampus may be important in supporting the left superior frontal gyrus. The left hippocampus is associated with working memory, which is related to attention maintenance [35], and with bilingual language ability, requiring inhibitory functions [36]. It is possible that the hemispheric features in relation to executive functioning are reflected in the current model.

Since MoCA is an indicator of overall cognitive function, it was perhaps not surprising that PEN and DMS had a direct effect on MoCA. However, since CA did not lead to MoCA, it could be due to small variations in CA; as such, the variation may not be suitable for variations in MoCA. In fact, in the path analysis, the model fit index increased when the CA was removed.

This study found that a specific brain region mediates the relationship between age and cognitive dysfunction, which offers valuable insights into the individual differences in aging. Some people maintain their executive functioning even when they age, while others have low executive functioning even when they are young. In light of this individual difference, in the path of the relationship between age and cognitive dysfunction, we provide one explanation for the cascade process, whereby the lack of any signs of atrophy of specific brain regions may help maintain cognitive function.

Declarations

Acknowledgments

We thank Katsutoshi Murata (Siemens Healthcare, Japan) for providing the MRI sequence prototype used in this study, and Terumi Tabei, Ken Yashiro, and Toshiyuki Onodera (Department of Radiology, Ebara Tokyo Hospital, Japan) for assistance with scanning.

Authors' contributions

Y.M. designed the experiments. M.I. supervised the project. Y.K., S.K., N.I., S.W., A.Y., S.K., and Y.U. conducted the behavioral experiments. Y.M., M.Y., N.K., H.S., M.I., R.K., S.Y., and K.O. measured the MRI. M.H. and M.Y. analyzed the data. All authors discussed the results. M.H. wrote the manuscript. All authors approved the final manuscript.

Funding

This study was supported by a JSPS KAKENHI Grant (JP15K00210, JP18K03185) and the Kao Corporation.

Availability of data and materials

The data analyzed for the current study are not publicly available because we did not obtain the consent of participants to provide them to third parties, but the data is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethical Committees of the Showa University School of Medicine. All methods were carried out in accordance with the relevant

guidelines and regulations expressed in the Declaration of Helsinki. All participants provided written informed consent to participate in the study. Author H.S. is employed by Kao Corporation. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. H.S. was involved in MRI measurements and was not involved in the subsequent data analysis or interpretation of the results.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Milner B. Effects of different brain lesions on card sorting: The role of the frontal lobes. Arch Neurol. 1963;9(1):90-100.
2. Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. Neurology. 2011;77(13):1272-5.
3. Dehaene S, Changeux JP. The Wisconsin Card Sorting Test: theoretical analysis and modeling in a neuronal network. Cereb Cortex. 1991;1(1):62-79.
4. Koechlin E, Summerfield C. An information theoretical approach to prefrontal executive function. Trends Cogn Sci. 2007;11(6):229-35.
5. Miles S, Howlett CA, Berryman C, Nedeljkovic M, Moseley GL, Phillipou A. Considerations for using the Wisconsin Card Sorting Test to assess cognitive flexibility. Behav Res Methods. 2021.
6. Rhodes MG. Age-related differences in performance on the Wisconsin card sorting test: a meta-analytic review. Psychol Aging. 2004;19(3):482-94.
7. Miranda AR, Franchetto Sierra J, Martínez Roulet A, Rivadero L, Serra SV, Soria EA. Age, education and gender effects on Wisconsin card sorting test: standardization, reliability and validity in healthy Argentinian adults. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2020;27(6):807-25.
8. Steinke A, Kopp B. Toward a computational neuropsychology of cognitive flexibility. Brain Sci. 2020;10(12).
9. Lange F, Seer C, Kopp B. Cognitive flexibility in neurological disorders: Cognitive components and event-related potentials. Neurosci Biobehav Rev. 2017;83:496-507.
10. Boone KB, Ghaffarian S, Lesser IM, Hill-Gutierrez E, Berman NG. Wisconsin Card Sorting Test performance in healthy, older adults: relationship to age, sex, education, and IQ. J Clin Psychol. 1993;49(1):54-60.
11. Mizumori SJY, Baker PM. The lateral habenula and adaptive behaviors. Trends Neurosci. 2017;40(8):481-93.
12. Avigan PD, Cammack K, Shapiro ML. Flexible spatial learning requires both the dorsal and ventral hippocampus and their functional interactions with the prefrontal cortex. Hippocampus. 2020;30(7):733-44.
13. Park AJ, Harris AZ, Martyniuk KM, Chang CY, Abbas AI, Lowes DC et al. Reset of hippocampal-prefrontal circuitry facilitates learning. Nature. 2021;591(7851):615-9.
14. Yuan P, Raz N. Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. Neurosci Biobehav Rev. 2014;42:180-92.
15. Burzynska AZ, Nagel IE, Preuschhof C, Gluth S, Bäckman L, Li SC et al. Cortical thickness is linked to executive functioning in adulthood and aging. Hum Brain Mapp. 2012;33(7):1607-20.

16. Dias NS, Ferreira D, Reis J, Jacinto LR, Fernandes L, Pinho F et al. Age effects on EEG correlates of the Wisconsin Card Sorting Test. Physiol Rep. 2015;3(7).
17. Takahashi H, Kato M, Takano H, Arakawa R, Okumura M, Otsuka T et al. Differential contributions of prefrontal and hippocampal dopamine D(1) and D(2) receptors in human cognitive functions. J Neurosci. 2008;28(46):12032-8.
18. Kubota S, Masaoka Y, Sugiyama H, Yoshida M, Yoshikawa A, Koiwa N et al. Hippocampus and parahippocampus volume reduction associated with impaired olfactory abilities in subjects without evidence of cognitive decline. Front Hum Neurosci. 2020;14:556519.
19. Banno M, Koide T, Aleksic B, Okada T, Kikuchi T, Kohmura K et al. Wisconsin Card Sorting Test scores and clinical and sociodemographic correlates in Schizophrenia: multiple logistic regression analysis. BMJ Open. 2012;2(6).
20. Fischl B. FreeSurfer. Neuroimage. 2012;62(2):774-81.
21. Wannan CMJ, Cropley VL, Chakravarty MM, Van Rheenen TE, Mancuso S, Bousman C et al. Hippocampal subfields and visuospatial associative memory across stages of schizophrenia-spectrum disorder. Psychol Med. 2019;49(14):2452-62.
22. Malone IB, Leung KK, Clegg S, Barnes J, Whitwell JL, Ashburner J et al. Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. Neuroimage. 2015;104:366-72.
23. Fischl. B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A.M. (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron, 33, 341–355.
24. Dale, A.M., Fischl, B., Sereno M.I. (1999) Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage, 9, 179-194.
25. Fischl, B., Sereno, M.I., &Dale, A.M. (1999) Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage, 9, 195–207.
26. Fischl, B., Dale, A.M. (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. PNAS, 97, 11050–11055.
27. Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., & Dale, A.M. (2004) Automatically parcellating the human cerebral cortex. Cerebral Cortex. 14, 11–22.
28. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31(3):968-80.
29. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. Neuroimage. 2010;53(1):1-15.
30. Grant DA, Berg EA. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol. 1948;38(4):404-11.

31. Koychev I, Gunn RN, Firouzian A, Lawson J, Zamboni G, Ridha B et al. PET tau and amyloid-β burden in mild Alzheimer's disease: divergent relationship with age, cognition, and cerebrospinal fluid biomarkers. J Alzheimers Dis. 2017;60(1):283-93.
32. Bonilha L, Molnar C, Horner MD, Anderson B, Forster L, George MS et al. Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. Schizophr Res. 2008;101(1-3):142-51.
33. Kim YY, Jung YS. Reduced frontal activity during response inhibition in individuals with psychopathic traits: an sLORETA study. Biol Psychol. 2014;97:49-59.
34. Zhang X, Yao J, Lv Y, Zhao X, Li Y, Sui Y et al. An association study on the cognitive function and the cerebral grey matter volume of patients with first-episode Schizophrenia. Shanghai Arch Psychiatry. 2018;30(3):154-67.
35. Tesche CD, Karhu J. Theta oscillations index human hippocampal activation during a working memory task. Proc Natl Acad Sci U S A. 2000;97(2):919-24.
36. Rosselli M, Loewenstein DA, Curiel RE, Penate A, Torres VL, Lang M et al. Effects of bilingualism on verbal and nonverbal memory measures in mild cognitive impairment. J Int Neuropsychol Soc. 2019;25(1):15-28.

Figures

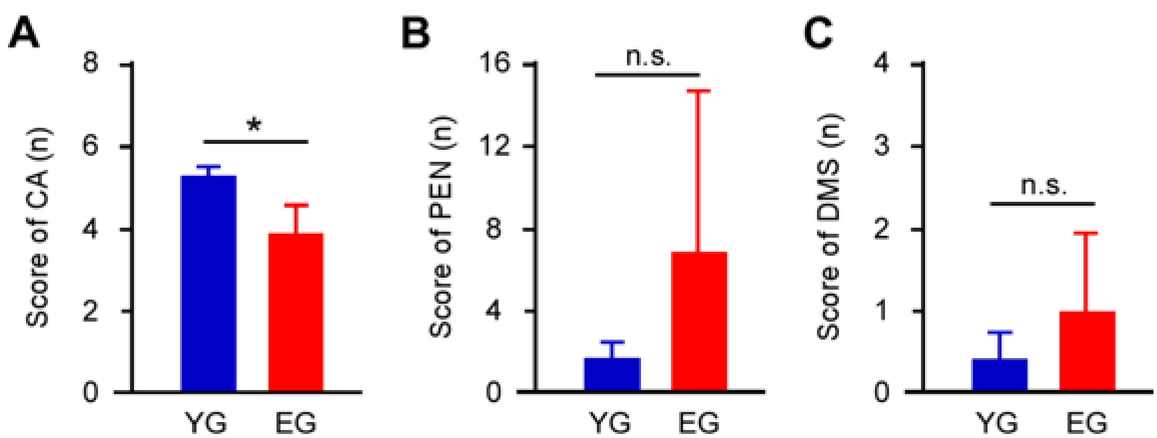

Figure 1

Results of Wisconsin card sorting test. (A) Scores of the categories achieved (CA) in the elderly group (EG) was lower than that in the younger group (YG). (B) Scores of the perseverative errors of Nelson (PEN) revealed no difference between the groups. (C) Scores of the difficulties of maintaining set (DMS) revealed no difference between the groups. Asterisks indicate significant differences ($p < 0.05$). Error bars indicate the standard error of mean.

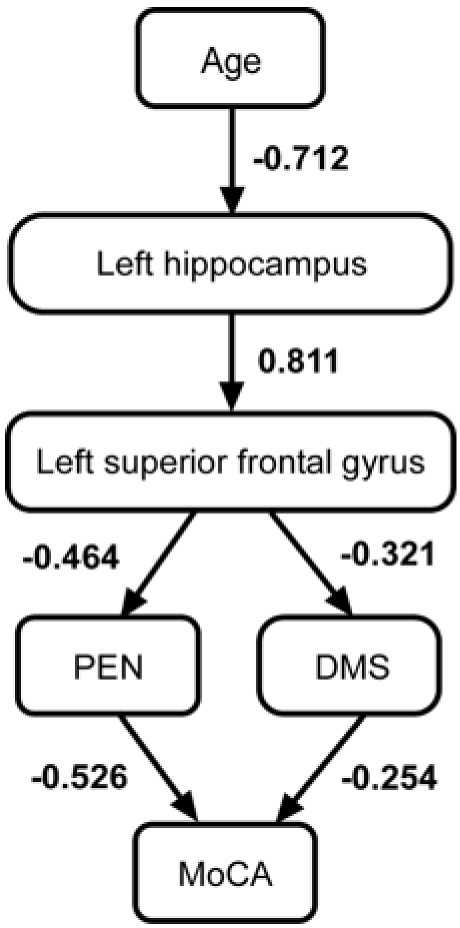

Figure 2

Path diagram. The age, years of education, 12 regions, 3 WCST scores, and MoCA were set as the observed variables (Supplemental Figure 1). Finally, the path diagram reflected the relationship among the six variables. The solid lines indicate a significant direct effect. Numbers indicate the standardized path coefficients.

Supplementary Files

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

- SupplementaryInformationKokudaietal..docx