Associations of demyelination in the right middle temporal gyrus and right praecuneus with visuospatial cognitive dysfunction in Alzheimer's disease

Running Title: Demyelination and visuospatial deficits

Hiroki Ohnishi, MD[1], Kiwamu Matsuoka, MD, PhD[1], Masato Takahashi, MD, PhD[1], Hiroaki Yoshikawa, MD, PhD[1], Akihiro Minami, MD[1], Kazuya Ueda, MD[1], Yuka Fujimoto, MD[1], Kuniaki Kiuchi, MD, PhD[2], Tomoko Ochi, MD, PhD[3], Toshiteru Miyasaka, MD, PhD[3], Toshihiro Tanaka, MD, PhD[3], Ryohei Matsumoto, MD, PhD[4], Manabu Makinodan, MD, PhD[1], Takashi Okada, MD, PhD[1]

[1]Department of Psychiatry, Nara Medical University, Nara, Japan

[2]Department of Psychiatry, Higashiosaka City Medical Center, Osaka, Japan

[3]Department of Radiology, Nara Medical University, Nara, Japan

[4]Department of Psychiatry, Kyoto Prefectural University of Medicine, Kyoto, Japan

Corresponding Author: Kiwamu Matsuoka, MD, PhD

Department of Psychiatry, Nara Medical University

840 Shijocho, Kashihara, Nara, 634-8522, Japan.

Tel.: +81-744-22-3051

Fax: +81-744-22-3854

E-mail:kiwamu@naramed-u.ac.jp

ABSTRACT

Background: Alzheimer's disease (AD) is associated with impairments in not only memory but also visuospatial cognitive function. Despite its adverse effects on the quality of life, patients with early-stage AD are often neglected. Emerging evidence suggests that patients with AD exhibit increased vulnerability of myelin, a crucial component for neuronal conduction and survival. To test our hypothesis that myelin damage was associated with cognitive deficits in AD, we examined correlations of myelin integrity, quantified by T1-weighted/T2-weighted (T1w/T2w) ratios, with visuospatial cognitive abilities and compared them between patients with AD and cognitively normal (CN) individuals.

Methods: Fifty-seven patients with AD and 22 CN subjects were enrolled in this study. To assess subjects' visuo-constructive abilities, we employed the Rey–Osterrieth Complex Figure Copy Test (ROCFT-c) paired with analysis of T1- and T2-weighted magnetic resonance imaging brain images. Voxel-based associations between T1w/T2w ratios and ROCFT-c scores in the AD group were assessed, controlling for age and handedness (voxel threshold uncorrected $P < 0.001$, cluster threshold uncorrected $P < 0.05$). Additionally, we compared the T1w/T2w ratios of these identified brain regions between the AD and CN groups.

Results: The voxel-based analysis demonstrated positive correlations between T1w/T2w ratios and ROCFT-c scores in the right middle temporal gyrus and right praecuneus in patients with AD who exhibited significantly lower T1w/T2w ratios in the right middle temporal gyrus ($P = 0.038$) and a trend towards lower T1w/T2w ratios in the right praecuneus ($P = 0.055$).

Conclusions: Our results demonstrated a strong association between reduced myelin integrity in the right middle temporal gyrus and right praecuneus and visuospatial cognitive dysfunction in patients with AD. These findings are believed to shed light on the neural basis of visuospatial processing in patients with AD, underlining the necessity for developing objective biomarkers for assessing patients' visuospatial cognitive function.

Keywords (4/3-6): Alzheimer's disease, T1-weighted/T2-weighted ratios, myelin, visuospatial cognition

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by progressive cognitive dysfunction involving not only memory but also visuospatial cognition.[1] Visuospatial cognitive dysfunction in patients with AD has been reportedly associated with impaired activities of daily living and instrumental activities of daily living,[2-4] consequently deteriorating quality of life[5-7] and caregiver burden.[8, 9] Although crucial, visuospatial cognitive dysfunction often goes undetected in early clinical stages of AD (reviewed in [10]). A deeper understanding of the neural underpinnings of visuospatial cognition is essential for developing objective biomarkers.

Research suggests that myelin content plays a vital role in cognitive function.[11] The myelin sheath enwraps axons, creating gaps of uninsulated segments known as nodes of Ranvier. This structure facilitates rapid saltatory conduction of the action potential.[12] Myelin also supports neuronal survival by releasing trophic factors.[13-15] Consequently, myelin damage can lead to conduction impairments and axonal degeneration, contributing to cognitive decline.[16] Previous studies have utilised T1-weighted/T2-weighted (T1w/T2w) ratio images derived from feasible magnetic resonance imaging (MRI) data to evaluate myelin integrity within the brain.[17, 18] Several clinical studies have reported associations between cognitive function and myelin integrity in patients with multiple system atrophy, as assessed using T1w/T2w ratio images.[19, 20]

Accumulated evidence indicates that patients with AD exhibit myelin vulnerability concurrent with the development of amyloid-β (Aβ) plaques and neurofibrillary tangles, two pathological hallmarks of AD.[21] The Aβ peptides and phosphorylated tau are toxic to oligodendrocytes, the cells responsible for myeline sheath formation (reviewed in [22]). Conversely, a recent study using mouse models of AD suggested that structural defects of myelin can promote Aβ plaque formation.[23] Aligning with these studies, an in vivo imaging study utilising the T1w/T2w ratios demonstrated an association between aggregated Aβ with myelin structural changes in patients with AD.[24]

We hypothesised that myelin damage is associated with visuospatial cognitive dysfunction in patients with AD. To test this hypothesis, we investigated the correlations between T1w/T2w ratios and visuospatial cognitive performance in patients with AD, evaluated using the Rey–Osterrieth Complex Figure Copy Test (ROCFT-c). Additionally, we compared regional T1w/T2w ratios between patients with AD and cognitively normal (CN) subjects.

METHODS

Subjects

MRI data were obtained from 57 patients with AD and 22 CN subjects. All patients with AD had been recruited from the outpatient psychiatry clinic at Nara Medical University Hospital and were diagnosed with probable AD in accordance with the criteria of The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[25] Exclusion criteria included any non-AD neurodegenerative disease (e.g., dementia with Lewy bodies, Parkinson's disease, or frontotemporal dementia), visual or hearing disorders, or a history of substantial brain injury. CN subjects had no dementia or history of any neurological or psychiatric disorders. This study was approved by the institutional review board of Nara Medical University and performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Measures

Subjects' visuo-constructional abilities were assessed using the ROCFT-c, a widely used measure of visuospatial cognitive function.[26] Subjects were instructed to replicate a complex figure composed of 18 items, with each item scored up to 2 points (1 point for copying accuracy and 1 point for drawing location accuracy), yielding a maximum total score of 36. General cognitive function was evaluated using the Mini-Mental State Examination (MMSE), which consists of 11 items (0–30 points).[18]

MRI data acquisition

MRI scans were acquired using a 3.0-T clinical scanner (Magnetom Verio; Siemens, Erlangen, Germany) equipped with a 32-channel phased-array brain coil. High-resolution three-dimensional T1-weighted images were obtained using a magnetisation-prepared rapid gradient-echo sequence (TR, 1,800 ms; TE, 2.4 ms; flip angle, 10°; FOV, 256 mm; acquisition matrix, 256 × 256; acquired resolution, 1 × 1 × 1 mm; 208 sagittal slices). T2-weighted images were obtained using a fast-spin echo sequence (TR, 4800 ms; TE, 90ms; echo train length [ETL], 8; FOV, 256 mm; acquisition matrix, 256× 256; acquired resolution, 1 × 1 × 3 mm; 37 transverse slices).

MRI data analysis of T1w/T2w ratio images

T1- and T2-weighted images were processed based on the workflow described in previous papers.[27, 28] This standardised pipeline involved bias correction and intensity calibration on both T1- and T2-weighted images and the subsequent computation of the ratio between pre-processed T1- and T2-weighted images. The processing of the T1w/T2w ratio images was conducted using the MRTool-Multimodal Mapping function (https://www.nitrc.org/projects/mrtool/) implemented in the Statistical Parametric Mapping software, version 12 (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK) running on the MATLAB R2021a platform (MathWorks, Natick, MA, USA). First, original T2-weighted images were co-registered onto their respective T1-weighted images through a rigid-body transformation. Next, the T1- and T2-weighted images were separately bias-corrected using default input parameters. Both images were processed for intensity standardisation using a linear scaling procedure. Following the calibration of the T1- and T2-weighted images, their ratio was calculated to produce calibrated T1w/T2w ratio images. These ratio images were subsequently spatially normalised from individual subject space to the Montreal Neurological Institute space to enable statistical comparisons.

Voxel-based morphometry

We conducted an exploratory voxel-based analysis using the SPM12 software to examine the correlations between the T1w/T2w ratios and the ROCFT-c scores for patients with AD. The T1w/T2w ratio images were smoothed with a 6-mm full-width at half-maximum Gaussian kernel. To prevent potential edge effects between tissue types, we excluded all voxels outside the grey and white matter through absolute threshold masking. After controlling for the effects of age and handedness, a liberal significance threshold of $P < 0.001$ was utilised to produce clusters with an uncorrected threshold of $P < 0.05$. Regions of interest (ROIs) were defined from clusters where significant correlations were observed. Subsequently, we calculated regional T1w/T2w ratios within these regions for CN subjects for comparisons.

Statistical analyses

Statistical analyses were performed using the IBM SPSS software (version 29.0; IBM Japan Inc., Tokyo, Japan). Independent samples t-tests and Pearson chi-square tests were used to compare baseline demographic and clinical characteristics between patients with AD and CN subjects. Spearman's partial correlations were used to evaluate the correlation between T1w/T2w ratios in the ROIs and ROCFT-c scores, adjusted for age and handedness. An analysis of covariance with age, sex, and handedness as covariates was performed to compare the T1w/T2w ratios of the ROIs between the two groups. All statistical tests were two-tailed, and $P < 0.05$ indicated statistical significance.

RESULTS

Demographic and clinical data

Demographic and clinical characteristics of the patients with AD and CN subjects are summarised in Table 1. No significant differences were observed in age or handedness between both groups; however, the AD group included a significantly higher proportion of female participants than the CN group. Compared to CN subjects, patients with AD had significantly lower education levels ($P = 0.024$), MMSE scores ($P < 0.001$), and ROCFT-c scores ($P = 0.001$). The mean duration of illness in the AD group was 2.1 ± 2.1 years.

– Please insert Table 1 here –

Correlation between ROCFT-c scores and regional T1w/T2w ratios in patients with AD

Voxel-based analysis for patients with AD revealed significant positive correlations between ROCFT-c scores and T1w/T2w ratios in the right middle temporal gyrus (MTG) ([x, y, z] = [63, -22, -10]; cluster voxel size, 652; T, 4.98) and the right praecuneus (PreC) ([x, y, z] = [10, -76, 48]; cluster voxel size, 746; T, 4.25). No significant negative correlations were observed, nor were there any significant correlations within the white matter. Partial correlation analysis confirmed these positive correlations (right MTG: r = 0.28, P = 0.038; right PreC: r = 0.44, P = 0.001) in patients with AD, adjusted for age and handedness (Figure 1). The positive correlations remained statistically significant (right MTG: r = 0.30, P = 0.028; right PreC: r = 0.44, P = 0.001) even when the duration of illness was included as an additional covariate. No significant correlations were found between ROCFT-c scores and T1w/T2w ratios in the right MTG and right PreC in CN subjects.

– Please insert Figure 1 here –

Comparison of T1w/T2w ratios between patients with AD and CN subjects

Patients with AD demonstrated significantly lower T1w/T2w ratios than CN subjects in the right MTG (F = 4.47, P = 0.038) after adjusting for age, sex, and handedness (Table 2; Figure 2). A similar trend towards lower T1w/T2w ratios was observed in the right PreC (F = 3.81, P = 0.055) (Table 2; Supplementary Figure 1).

– Please insert Table 2 here –

– Please insert Figure 2 here –

DISCUSSION

In the present study, we tested the hypotheses that visuospatial cognitive function was associated with demyelination in patients with AD, using T1w/T2w ratios for evaluating myelin densities. We found that patients with AD exhibited impaired visuospatial cognitive functions compared with CN subjects, which is consistent with previous studies (review in [10]). Voxel-based morphometry revealed positive correlations between visuospatial function and T1w/T2w ratios in the right MTG and right PreC in patients with AD. These correlations remained significant when the duration of disease was included as a covariate, controlling for the influence of AD progression. These findings suggest that structural changes in these brain regions may be associated with visuospatial cognitive decline in patients with AD.

It has been proposed that the visuospatial processing model in the brain incorporates two distinct visual streams: ventral and dorsal;[29, 30] the MTG and PreC have been identified as components of the ventral[31] and dorsal[32] visual streams, respectively. In this hypothesised model, the dorsal visual stream has been characterised as the “where” pathway, responsible for spatial vision, whereas the ventral visual stream has been identified as the “what” pathway, associated with object recognition.[33] This model was found to be consistent with our findings; the T1w/T2w ratios in the ventral and dorsal visual streams correlated positively with ROCFT-c scores, which required both spatial processing and object recognition.[26] Previous studies have also reported correlations between ROCFT-c scores and brain metabolism within the MTG and PreC in patients with AD.[34, 35] In this study, we found that ROCFT-c scores were associated with T1w/T2w ratios predominantly in the right hemisphere; this aligns with the established lateralisation of visuospatial cognition to this cerebral hemisphere, which has been reported in prior literature.[36, 37]

The T1w/T2w mapping technique has been established as a reliable method for evaluating in vivo myelin integrity by effectively cancelling the signal intensity bias and increasing the contrast related to myelin content.[17, 18] Post-mortem studies have corroborated this method, confirming the correlation between T1w/T2w ratios and myelin distribution.[18, 38] Furthermore, age-related changes in T1w/T2w ratios have been linked to myelination processes during childhood development,[19, 39] and reductions in these ratios have been observed in demyelinating diseases such as multiple sclerosis, suggesting demyelination within the brain.[40, 41] This study revealed significantly lower T1w/T2w ratios in the right MTG for patients with AD than for CN subjects. Although a similar trend was observed in the right PreC, the difference did not reach statistical significance. Our findings were interpreted as myelin damage within these brain regions in patients with AD.

Although neuronal degeneration is the primary hallmark of AD, accumulated evidence suggests a concomitant role for myelin damage.[11] Post-mortem[42] and in vivo[43] studies have demonstrated demyelination in neocortical regions; in line with their findings, our results suggest that patients with AD exhibited myelin damage in the right MTG and right PreC. Myelin damage in AD appears to involve a bidirectional relationship between oligodendrocytes and the abnormal proteins that are the hallmark of AD pathology (reviewed in [22]). Several studies involving animal models and patients with AD have demonstrated that Aβ peptides[44-49] and phosphorylated tau[50, 51] can induce myelin damage. Demyelination has also been linked to increased Aβ plaque formation and phosphorylated tau accumulation.[23, 52] Given that patients with AD present with accumulations of Aβ peptides and phosphorylated tau in the MTG and PreC in early stages of the disease,[53-55] these brain regions are particularly vulnerable to myelin damage.

This study had some limitations. First, the small sample size may have introduced bias, potentially influencing the results. For instance, although previous studies have reported visual perception processing in the left MTG,[56] no significant correlation was observed in this brain region in the current study. Additionally, the correlation between visuospatial function and T1w/T2w ratios in the right PreC in patients with AD did not remain significant after Bonferroni correction for multiple comparisons. Second, despite being included as a covariate in the analysis of covariance, the significant difference in sex between the AD and CN groups may have affected the findings. Third, we did not measure Aβ peptide and phosphorylated tau levels in the brain to investigate their association with myelin damage. Further studies should employ large sample sizes and evaluate Aβ peptide and phosphorylated tau levels to further elucidate the complex interplay among these factors in AD.

In conclusion, this study provides evidence of demyelination in the right MTG and right PreC in patients with AD, as assessed using T1w/T2w ratio imaging. Given the involvement of these regions in visuospatial processing, our findings suggest a potential link between reduced myelin integrity and visuospatial cognitive impairment in AD. These results are believed to contribute to our understanding of the neural basis of visuospatial dysfunction in patients with AD, laying the groundwork for the development of objective biomarkers.

Acknowledgements: We thank the MRI staff at the Department of Radiology, Nara Medical University, Japan, for their dedicated care of the patients and for collecting the MRI data.

Disclosure statement: Authors declare no conflict of interest for this article.

Data availability statement: The data that support the findings of the present study are available from the corresponding author upon reasonable request.

REFERENCES

1 Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol*. 2018; **25**: 59-70.

2 Farias ST, Harrell E, Neumann C, Houtz A. The relationship between neuropsychological performance and daily functioning in individuals with alzheimer's disease: Ecological validity of neuropsychological tests. *Arch Clin Neuropsychol*. 2003; **18**: 655-672.

3 Glosser G, Gallo J, Duda N, de Vries JJ, Clark CM, Grossman M. Visual perceptual functions predict instrumental activities of daily living in patients with dementia. *Neuropsychiatry Neuropsychol Behav Neurol*. 2002; **15**: 198-206.

4 Jefferson AL, Barakat LP, Giovannetti T, Paul RH, Glosser G. Object perception impairments predict instrumental activities of daily living dependence in alzheimer's disease. *J Clin Exp Neuropsychol*. 2006; **28**: 884-897.

5 Akpınar Söylemez B, Küçükgüçlü Ö, Akyol MA, Işık AT. Quality of life and factors affecting it in patients with alzheimer's disease: A cross-sectional study. *Health Qual Life Outcomes*. 2020; **18**: 304.

6 Ballard C, O'Brien J, James I *et al.* Quality of life for people with dementia living in residential and nursing home care: The impact of performance on activities of

daily living, behavioral and psychological symptoms, language skills, and psychotropic drugs. *Int Psychogeriatr*. 2001; **13**: 93-106.

7 Henskens M, Nauta IM, Drost KT, Scherder EJ. The effects of movement stimulation on activities of daily living performance and quality of life in nursing home residents with dementia: A randomized controlled trial. *Clin Interv Aging*. 2018; **13**: 805-817.

8 Aneshensel CS, Pearlin LI, Schuler RH. Stress, role captivity, and the cessation of caregiving. *J Health Soc Behav*. 1993; **34**: 54-70.

9 Matsuoka K, Yasuno F, Hashimoto A *et al.* Left dorsolateral prefrontal cortex atrophy is associated with frontal lobe function in alzheimer's disease and contributes to caregiver burden. *Int J Geriatr Psychiatry*. 2018; **33**: 703-709.

10 Coughlan G, Laczó J, Hort J, Minihane AM, Hornberger M. Spatial navigation deficits - overlooked cognitive marker for preclinical alzheimer disease? *Nat Rev Neurol*. 2018; **14**: 496-506.

11 Papuć E, Rejdak K. The role of myelin damage in alzheimer's disease pathology. *Arch Med Sci*. 2020; **16**: 345-351.

12 Arancibia-Carcamo IL, Attwell D. The node of ranvier in cns pathology. *Acta Neuropathol*. 2014; **128**: 161-175.

13 Wilkins A, Majed H, Layfield R, Compston A, Chandran S. Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: A novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J Neurosci*. 2003; **23**: 4967-4974.

14 Wilkins A, Chandran S, Compston A. A role for oligodendrocyte-derived igf-1 in trophic support of cortical neurons. *Glia*. 2001; **36**: 48-57.

15 Shindo A, Liang AC, Maki T *et al.* Subcortical ischemic vascular disease: Roles of oligodendrocyte function in experimental models of subcortical white-matter injury. *J Cereb Blood Flow Metab*. 2016; **36**: 187-198.

16 Kohama SG, Rosene DL, Sherman LS. Age-related changes in human and non-human primate white matter: From myelination disturbances to cognitive decline. *Age (Dordr)*. 2012; **34**: 1093-1110.

17 Glasser MF, Goyal MS, Preuss TM, Raichle ME, Van Essen DC. Trends and properties of human cerebral cortex: Correlations with cortical myelin content. *Neuroimage*. 2014; **93 Pt 2**: 165-175.

18 Glasser MF, Van Essen DC. Mapping human cortical areas in vivo based on myelin content as revealed by t1- and t2-weighted mri. *J Neurosci*. 2011; **31**: 11597-11616.

19 Norbom LB, Rokicki J, Alnaes D *et al.* Maturation of cortical microstructure and cognitive development in childhood and adolescence: A t1w/t2w ratio mri study. *Hum Brain Mapp*. 2020; **41**: 4676-4690.

20 Sugiyama A, Cooper G, Hirano S *et al.* Cognitive impairment in multiple system atrophy is related to white matter damage detected by the t1-weighted/t2-weighted ratio. *Eur Neurol*. 2021; **84**: 435-443.

21 Maitre M, Jeltsch-David H, Okechukwu NG, Klein C, Patte-Mensah C, Mensah-Nyagan AG. Myelin in alzheimer's disease: Culprit or bystander? *Acta Neuropathol Commun*. 2023; **11**: 56.

22 Nasrabady SE, Rizvi B, Goldman JE, Brickman AM. White matter changes in alzheimer's disease: A focus on myelin and oligodendrocytes. *Acta Neuropathol Commun*. 2018; **6**: 22.

23 Depp C, Sun T, Sasmita AO *et al.* Myelin dysfunction drives amyloid-β deposition in models of alzheimer's disease. *Nature*. 2023; **618**: 349-357.

24 Fernandez-Alvarez M, Atienza M, Cantero JL. Cortical amyloid-beta burden is associated with changes in intracortical myelin in cognitively normal older adults. *Transl Psychiatry*. 2023; **13**: 115.

25 American Psychiatric Association D, Association AP. *Diagnostic and statistical*

manual of mental disorders: Dsm-5. Washington, DC: American Psychiatric Association Publishing, 2013.

26 Zhang X, Lv L, Min G, Wang Q, Zhao Y, Li Y. Overview of the complex figure test and its clinical application in neuropsychiatric disorders, including copying and recall. *Front Neurol*. 2021; **12**: 680474.

27 Ganzetti M, Wenderoth N, Mantini D. Whole brain myelin mapping using t1- and t2-weighted mr imaging data. *Front Hum Neurosci*. 2014; **8**: 671.

28 Ganzetti M, Wenderoth N, Mantini D. Mapping pathological changes in brain structure by combining t1- and t2-weighted mr imaging data. *Neuroradiology*. 2015; **57**: 917-928.

29 Xu J, Wang J, Fan L *et al.* Tractography-based parcellation of the human middle temporal gyrus. *Sci Rep*. 2015; **5**: 18883.

30 Cavanna AE, Trimble MR. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*. 2006; **129**: 564-583.

31 Martin CB, Barense MD. Perception and memory in the ventral visual stream and medial temporal lobe. *Annu Rev Vis Sci*. 2023; **9**: 409-434.

32 Sulpizio V, Fattori P, Pitzalis S, Galletti C. Functional organization of the caudal part of the human superior parietal lobule. *Neurosci Biobehav Rev*. 2023; **153**:

105357.

33 Kravitz DJ, Saleem KS, Baker CI, Mishkin M. A new neural framework for visuospatial processing. *Nat Rev Neurosci*. 2011; **12**: 217-230.

34 Melrose RJ, Harwood D, Khoo T, Mandelkern M, Sultzer DL. Association between cerebral metabolism and rey-osterrieth complex figure test performance in alzheimer's disease. *J Clin Exp Neuropsychol*. 2013; **35**: 246-258.

35 Chiaravalloti A, Ricci M, Di Biagio D, Filippi L, Martorana A, Schillaci O. The brain metabolic correlates of the main indices of neuropsychological assessment in alzheimer's disease. *J Pers Med*. 2020; **10**: 25.

36 Boxer AL, Kramer JH, Du AT *et al.* Focal right inferotemporal atrophy in ad with disproportionate visual constructive impairment. *Neurology*. 2003; **61**: 1485-1491.

37 Trojano L, Fragassi NA, Chiacchio L *et al.* Relationships between constructional and visuospatial abilities in normal subjects and in focal brain-damaged patients. *J Clin Exp Neuropsychol*. 2004; **26**: 1103-1112.

38 Sandrone S, Aiello M, Cavaliere C *et al.* Mapping myelin in white matter with t1-weighted/t2-weighted maps: Discrepancy with histology and other myelin mri measures. *Brain Struct Funct*. 2023; **228**: 525-535.

39 Dipnall LM, Yang JYM, Chen J, Fuelscher I, Craig JM, Silk TJ. Childhood

development of brain white matter myelin: A longitudinal t1w/t2w-ratio study. *Brain Struct Funct*. 2024; **229**: 151-159.

40 Granberg T, Fan Q, Treaba CA *et al.* In vivo characterization of cortical and white matter neuroaxonal pathology in early multiple sclerosis. *Brain*. 2017; **140**: 2912-2926.

41 Righart R, Biberacher V, Jonkman LE *et al.* Cortical pathology in multiple sclerosis detected by the t1/t2-weighted ratio from routine magnetic resonance imaging. *Ann Neurol*. 2017; **82**: 519-529.

42 Ihara M, Polvikoski TM, Hall R *et al.* Quantification of myelin loss in frontal lobe white matter in vascular dementia, alzheimer's disease, and dementia with lewy bodies. *Acta Neuropathol*. 2010; **119**: 579-589.

43 Luo X, Li K, Zeng Q *et al.* Application of t1-/t2-weighted ratio mapping to elucidate intracortical demyelination process in the alzheimer's disease continuum. *Front Neurosci*. 2019; **13**: 904.

44 Desai MK, Mastrangelo MA, Ryan DA, Sudol KL, Narrow WC, Bowers WJ. Early oligodendrocyte/myelin pathology in alzheimer's disease mice constitutes a novel therapeutic target. *Am J Pathol*. 2010; **177**: 1422-1435.

45 Desai MK, Guercio BJ, Narrow WC, Bowers WJ. An alzheimer's disease-

relevant presenilin-1 mutation augments amyloid-beta-induced oligodendrocyte dysfunction. *Glia*. 2011; **59**: 627-640.

46 Jantaratnotai N, Ryu JK, Kim SU, McLarnon JG. Amyloid beta peptide-induced corpus callosum damage and glial activation in vivo. *Neuroreport*. 2003; **14**: 1429-1433.

47 Lee JT, Xu J, Lee JM *et al.* Amyloid-beta peptide induces oligodendrocyte death by activating the neutral sphingomyelinase-ceramide pathway. *J Cell Biol*. 2004; **164**: 123-131.

48 Sun SW, Liang HF, Mei J, Xu D, Shi WX. In vivo diffusion tensor imaging of amyloid-β-induced white matter damage in mice. *J Alzheimers Dis*. 2014; **38**: 93-101.

49 Xu J, Chen S, Ahmed SH *et al.* Amyloid-beta peptides are cytotoxic to oligodendrocytes. *J Neurosci*. 2001; **21**: Rc118.

50 McAleese KE, Firbank M, Dey M *et al.* Cortical tau load is associated with white matter hyperintensities. *Acta Neuropathol Commun*. 2015; **3**: 60.

51 McAleese KE, Walker L, Graham S *et al.* Parietal white matter lesions in alzheimer's disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathol*. 2017; **134**: 459-473.

52 Rubinski A, Dewenter A, Zheng L *et al.* Florbetapir pet-assessed demyelination

is associated with faster tau accumulation in an apoe ε4-dependent manner. *Eur J Nucl Med Mol Imaging*. 2023; **51**: 1035-1049.

53 Palmqvist S, Schöll M, Strandberg O *et al.* Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nat Commun*. 2017; **8**: 1214.

54 Cho H, Choi JY, Hwang MS *et al.* In vivo cortical spreading pattern of tau and amyloid in the alzheimer disease spectrum. *Ann Neurol*. 2016; **80**: 247-258.

55 Braak H, Braak E. Neuropathological stageing of alzheimer-related changes. *Acta Neuropathol*. 1991; **82**: 239-259.

56 Martins MJD, Krause C, Neville DA, Pino D, Villringer A, Obrig H. Recursive hierarchical embedding in vision is impaired by posterior middle temporal gyrus lesions. *Brain*. 2019; **142**: 3217-3229.

Figure Legends

Figure 1. Brain regions with positive correlations between ROCFT-c scores and T1w/T2w ratios in patients with AD

a) Brain images from four directions showing voxels with positive correlations between ROCFT-c scores and T1w/T2w ratios in patients with AD after controlling for the effects of age and handedness. The detected areas have an uncorrected P value of 0.001 and were corrected using a cluster-extent threshold combined with a height threshold of 0.001 to produce only clusters exceeding the expected number of voxels per cluster. Scatterplots b and c show the correlations between ROCFT-c scores and regional T1w/T2w ratios in the right MTG and right praecuneus, respectively, adjusted for age and handedness. AD, Alzheimer's disease; MTG, middle temporal gyrus; ROCFT-c, Rey-Osterrieth Complex Figure Copy Test; T1w/T2w, T1-weighted/T2-weighted ratio.

Figure 2. Scatterplot comparing T1w/T2w ratios in the right MTG of both patients with AD and CN subjects

Ratios were adjusted for age, sex, and handedness. Horizontal lines represent the mean T1w/T2w ratios of the two groups. AD, Alzheimer's disease; CN, cognitively normal; MTG, middle temporal gyrus; T1w/T2w, T1-weighted/T2-weighted ratio.

Tables

Table 1. Summary of the demographic and clinical characteristics of the study population

Items	AD	CN	t or χ^2	*P*
	Mean (SD)	Mean (SD)		
Sex, male/female	18/39	14/8	$\chi^2 = 6.77$	0.010*
Age, years	75.8 (6.6)	74.2 (5.4)	$t = 1.01$	0.317
Education, years	12.0 (3.1)	13.7 (2.6)	$t = -2.30$	0.024*
Handedness, right/left	53/4	20/2	$\chi^2 = 0.10$	0.538
MMSE	22.3 (3.2)	29.3 (0.7)	$t = -10.20$	< 0.001***
ROCFT-c	31.5 (7.1)	35.0 (1.7)	$t = -3.62$	0.001**

AD, Alzheimer's disease; CN, cognitively normal; SD, standard deviation; t, independent samples t-test; χ^2, Pearson chi-square test; MMSE, Mini-Mental State Examination; ROCFT-c Rey-Osterrieth Complex Figure Copy Test. *P < 0.05, **P < 0.01, ***P < 0.001.

Table 2. Comparison of the T1w/T2w ratios between AD and CN groups

Items	**AD**	**CN**	***F***	***P***
	Mean (SD)	**Mean (SD)**		
Right MTG T1w/T2w ratio	1.17 (0.16)	1.24 (0.13)	4.47	0.038*
Right PreC T1w/T2w ratio	0.92 (0.15)	0.98 (0.11)	3.81	0.055

AD, Alzheimer's disease; CN, cognitively normal; SD, standard deviation; MTG, middle temporal gyrus; PreC, praecuneus. *$P < 0.05$.

Figure 1

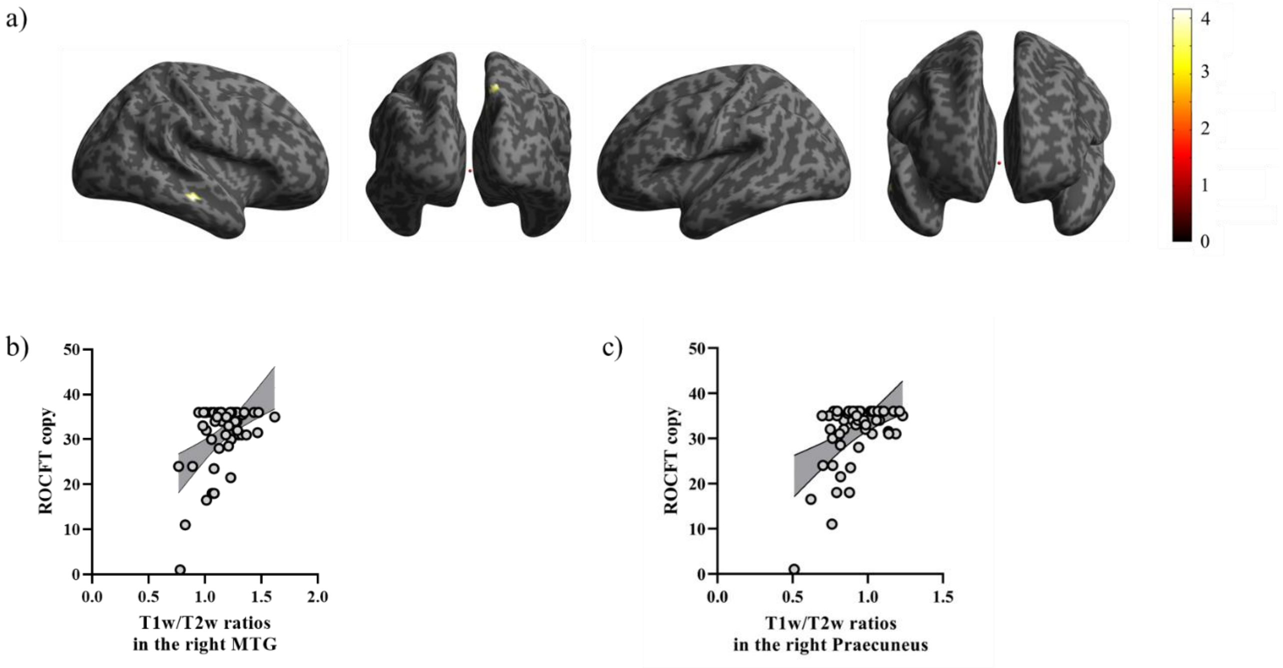
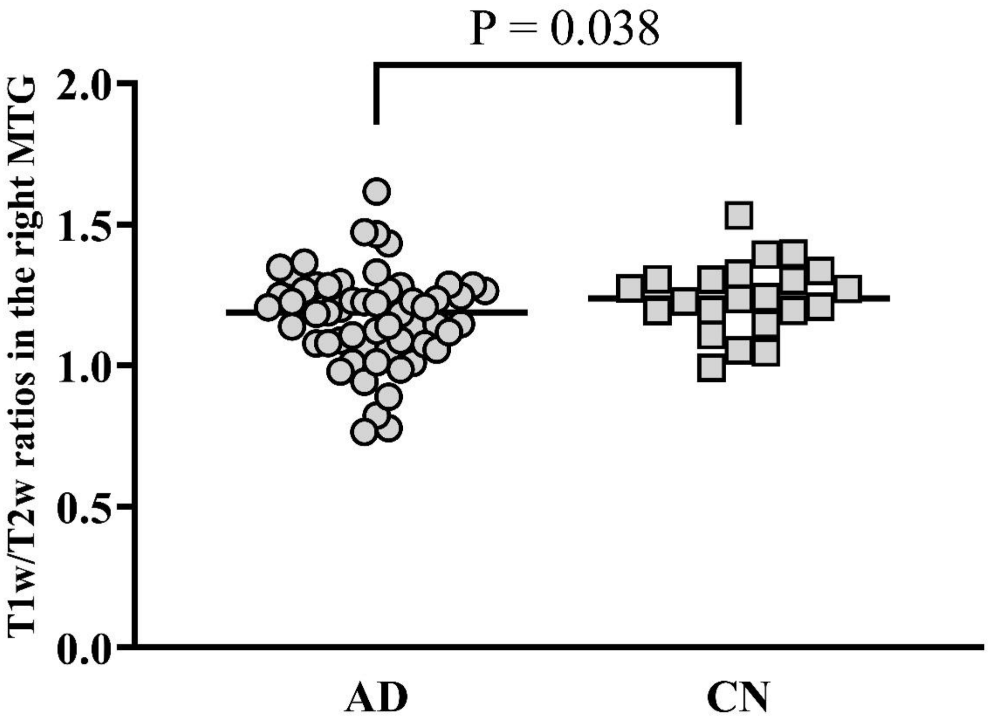

a)
4
3
2
1
0
b)
ROCFT copy
T1w/T2w ratios
in the right MTG
c)
ROCFT copy
T1w/T2w ratios
in the right Praecuneus

Figure 2



Supplementary Figure 1. Scatterplot comparing T1w/T2w ratios in the right praecuneus of both patients with AD and CN subjects

Ratios were adjusted for age, sex and handedness. Horizontal lines represent the mean T1w/T2w ratios of the two groups. AD, Alzheimer's disease; CN, cognitively normal; T1w/T2w, T1-weighted/T2-weighted ratio.