

Long-term memory and microstructural changes after chemotherapy and low-dose radiotherapy covering the whole ventricle in patients with germinoma

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Abstract

Purpose

This study assessed memory impairment and underlying microstructural changes in patients with germinoma treated long-term with 24 Gy radiation, which covered the whole ventricle, with chemotherapy (low-dose WVI with chemotherapy).

Methods

This prospective observational study included patients treated with low-dose WVI with chemotherapy at our departments from 1999 to 2021. Their intelligence and memory were assessed using the Wechsler Adult Intelligence Scale, 3rd Edition, and the Wechsler Memory Scale, Revised Edition (WMS-R). Diffusion tensor images (DTI) and neurite orientation dispersion and density imaging (NODDI) metrics were calculated in white and gray matter and compared to the mean values from 11 age-matched healthy individuals. Associations between DTI and NODDI metrics and WMS-R memory scores were also examined.

Results

Among 68 patients treated with low-dose WVI with chemotherapy, 32 provided consent for evaluation. The median ages at treatment and evaluation were 17.1 and 24.9 years, respectively. Sixteen (50%) patients had WMS-R index scores below 85 (-1 standard deviation). Memory was more severely impaired than intelligence or attention. DTI and NODDI metrics showed alterations in extensive gray and white matter regions associated with memory. DTI and NODDI metrics in the fornix, cingulum, cingulate cortex, orbital cortex, and thalamus correlated with memory scores.

Conclusion

Memory impairment is common in these patients, with microstructural changes in extensive memory-related regions associated with impaired memory function.

Background

Germinomas are highly sensitive to radiation and chemotherapy, and effective tumor control can be achieved with radiation therapy alone [1]. However, late effects of radiation therapy, including neurocognitive function, can cause significant long-term morbidity in survivors [1–3]. To reduce late complications, “low-dose irradiation, covering the whole ventricle, combined with chemotherapy (low-dose WVI with chemotherapy),” which reduces the radiation dose while covering the entire ventricular system, has achieved excellent tumor control [4–6]. We reported that full-scale intelligence quotient

(FSIQ) was maintained following low-dose WVI with chemotherapy in a longitudinal study [2]. Although memory was preserved after an average follow-up of 3.0 years in 20 patients treated with low-dose WVI with chemotherapy [7], evidence regarding long-term memory preservation after low-dose WVI with chemotherapy for germinomas remains limited.

Two key neural circuits are involved in memory. The Papez circuit is a major limbic system pathway involved in controlling both memory and emotion [8]. These components include the hippocampus, fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nuclei, thalamocingulate tract, cingulate gyrus, cingulum, and parahippocampal gyrus/hippocampus. Another is the Yakovlev circuit, which consists of the amygdala, stria terminalis, dorsomedial thalamic nuclei, prefrontal and orbitofrontal gyri, uncinate fasciculus, and hippocampus/temporal pole [9]. Although the anatomical mechanisms underlying memory impairment remain unclear, we reported a correlation between the rate of cerebral atrophy and memory impairment in patients with germinomas treated with high-dose radiation therapy to the primary site or low-dose WVI with chemotherapy [10].

Recent advances in MRI have enabled detailed assessment of white and gray matter microstructures and their changes under various pathological conditions. Among these techniques, diffusion-weighted imaging (DWI), which assesses water-molecule mobility, is effective for evaluating white and gray matter damage by detecting restricted water-molecule mobility. Diffusion tensor imaging (DTI) is a mathematical model that assumes water diffusion within a single compartment follows a three-dimensional Gaussian distribution [11]. This model calculates mean diffusivity (MD) and fractional anisotropy (FA). MD is useful for assessing diffusion restrictions, such as in acute cerebral infarction. In contrast, FA quantitatively indicates the directional dependence of water molecule diffusion and is useful for evaluating axonal and myelin sheath integrity. In patients treated with radiation therapy, FA and MD in the fornix, dorsal cingulum, parahippocampal cingulum, and medial temporal lobe white matter, rather than the hippocampus volume, were correlated with memory scores [12]. However, FA values may be inaccurate in regions with crossing white matter fibers or pathological changes, where water distribution may not necessarily follow a Gaussian distribution [11, 13]. To address these limitations, high-angular-resolution diffusion imaging techniques, such as neurite orientation dispersion and density imaging (NODDI), have been developed. NODDI provides physiological characteristics by assessing axonal and dendritic density, morphology, and dispersion using a three-compartment model comprising intracellular, extracellular, and cerebrospinal fluid (CSF) compartments, thereby characterizing gray and white matter microstructure [14]. The neurite density index (NDI) reflects the neurite volume fraction, indicating axonal and dendritic density. The orientation dispersion index (ODI) reflects neurite orientation coherence, indicating fiber-orientation dispersion in white matter and dendritic complexity in the gray matter. Isotropic volume fraction (FISO) reflects the volume fraction of CSF-like freely diffusing water [14].

No studies have reported cerebral and hippocampal atrophy, microstructural changes, or functional outcomes in patients with germinoma treated with low-dose WVI with chemotherapy. This study aimed to characterize memory impairment following low-dose WVI with chemotherapy, identify volume

changes in the cerebrum and hippocampus and microstructure changes in white and gray matter, and determine the regions associated with memory impairment.

Methods

Patients

This prospective observational study included patients with germinoma treated at our department between April 2000 and March 2021.

Treatments

Patients received platinum-based chemotherapy followed by radiation therapy, covering the whole ventricle, at 24 Gy in 12 fractions, without a primary-site boost [2, 4, 15, 16]. The details of radiation therapy, chemotherapy, and follow-up were shown in the Supplementary data.

Assessment of social status, memory, and intelligence

At evaluation, social status was classified as students, regular or part-time employment, sheltered workshop participation, and unemployment.

Memory was assessed using the revised Wechsler Memory Scale, revised edition (WMS-R) [17], and intelligence was evaluated using the Wechsler Adult Intelligence Scale, third edition (WAIS-III) [18].

Measurement of the cerebral and hippocampal volume

Cerebral, intracranial, and hippocampal volumes on T1-weighted images (T1WI) were automatically segmented using the Brainlab Elements software (Brainlab, Munich, Germany), as previously described [10]. Cerebral-to-intracranial and hippocampal-to-intracranial volume ratios were calculated to estimate cerebral and hippocampal atrophy.

DTI and NODDI

MRI was performed using a 3.0-T Philips Ingenia scanner (Philips Healthcare, Amsterdam, The Netherlands). The details of the acquisition, the fitting, and the spatial normalization of DWI for NODDI were performed as described in the Supplementary data. Region-of-interest analyses were performed using the JHU ICBM-DTI-81 white matter atlas (48 regions) [19] and the Automated Anatomical Labeling 3 (AAL3) atlas (170 regions) [20], respectively. Mean FA, MD, NDI, ODI, and FISO values were extracted from each atlas-defined region for subsequent group comparisons and correlation analyses. The JHU and AAL3 atlases were used to assess white and gray matter microstructural alterations, respectively.

Statistical analysis

Statistical analyses were performed using JMP Student Edition version 18.2 (SAS Institute, Tokyo, Japan). The details were described in the Supplementary data. A p-value < 0.05 indicated statistical significance.

Results

Patients

A total of 88 patients with germinoma were treated at our department, of whom 68 received low-dose WVI with chemotherapy. The analysis included 32 patients aged ≥ 16 years who were evaluated using the WMS-R (Fig. 1). Participant characteristics are summarized in Table 1 and Supplementary data. The mean interval from treatment initiation to evaluation was 91.6 months. At evaluation, nineteen patients (59%) were employed full- or part-time, eight (25%) were students, and five (16%) were in sheltered workshops or unemployed. A total of 11 age-matched healthy individuals served as controls as described in the Supplementary data.

WAIS-III and WMS-R results

The WAIS-III and WMS-R scores are shown in Supplementary Table 1 and Supplementary Fig. 1. On WAIS-III, no difference was observed between indices. On the WMS-R, verbal memory, general memory, and delayed recall scores were lower than visual memory and attention scores (Supplementary Fig. 1). Sixteen (50%) patients had low scores (< 85, - 1 standard deviation (SD) below the mean) on at least one verbal or visual memory or delayed recall index. Verbal memory scores were significantly lower than VC and verbal IQ scores ($p = 0.0015$ and $p = 0.0011$, respectively), while general memory tended to be lower than that of FSIQ ($p = 0.068$). These results suggested that memory scores tended to be lower than intelligence scores. In addition, memory impairment was not attributed to disturbed attention.

Relationship between clinical characteristics and memory

We examined the associations between WMS-R scores and clinical characteristics (Supplementary Table 2). No statistically significant differences were observed according to various clinical characteristics as described in the Supplementary data.

Cerebral and hippocampal atrophy after low-dose WVI with chemotherapy

We compared cerebral and hippocampal atrophy between patients and healthy controls. The details of relative cerebral and hippocampal volume to intracranial volume were shown in the Supplementary data. Analysis of covariance demonstrated that no significant difference in hippocampal atrophy was observed between patients and healthy controls ($p = 0.71$), but that patients tended to have a lower

cerebral-to-intracranial volume ratio after age adjustment ($p = 0.055$) (Supplementary Fig. 2). These findings suggest that low-dose WVI with chemotherapy was not associated with hippocampal-specific atrophy, but was associated with cerebral atrophy.

Differences in FA, MD, NDI, ODI, and FISO values in whole and memory-associated white matter between patients and healthy controls

Figures 2 and Supplementary Table 3 show the JHU regions with statistically significant differences between patients with germinoma and healthy controls. FA and NDI were lower, whereas the other metrics were higher in patients with germinoma.

Differences in certain metrics were observed in memory-associated regions and periventricular structures (Fig. 2, 3, Supplementary Table 3 and Supplementary data). Significant differences in memory-associated regions were more extensive for FA and MD than for NODDI metrics (Figs. 2 and 3). In contrast, ODI and FISO abnormalities were regionally distinct (Fig. 3): FISO was increased in the fornix and left cingulum, whereas ODI was increased in the anterior limb of the internal capsule and right uncinate fascicles. NDI did not differ significantly in memory-associated regions.

These findings suggested microstructural changes in memory-associated white matter in germinoma patients and that the characteristics of these changes differ depending on the anatomical region.

Differences in FA, MD, NDI, ODI, and FISO values in whole and memory-associated gray matter between patients and healthy controls

Figure 4 and Supplementary Table 4 show the regions with statistically significant differences compared with healthy controls in AAL3. FA, most of the NDI, and part of the ODI values decreased, whereas values of other metrics increased in patients with germinoma (Fig. 4).

Certain metrics differed between patients and healthy controls in memory-associated regions (Figs. 3, 4, Supplementary Table 4 and Supplementary data). The region distribution with significant differences in FA, MD, and FISO values was similar and more extensive than that of NDI and ODI (Figs. 3 and 4). Of NODDI metrics, only the FISO value was higher in the hippocampus, dorsomedial thalamic nucleus, anterior cingulate cortex, orbital gyrus, and temporal pole. In contrast, ODI and FISO values were increased in the parahippocampal gyrus and anterior cingulate cortex (Fig. 3). Changes in NDI values were limited in the cingulate gyrus and anterior cingulate cortex.

These findings suggest microstructural changes in memory-associated gray matter in patients with germinoma and that the pattern of these changes in DTI and NODDI metrics in gray matter, as well as white matter, differed by anatomical region.

Relationship of DTI and NODDI metrics in white and gray matter and cerebral atrophy to memory scores

Using linear correlation analysis, we examined correlations between memory scores, including verbal, visual memory, and delayed recall, and DTI and NODDI metrics in memory-associated regions with significant differences from healthy controls (Table 2). FA, NDI, and ODI values were positively correlated with memory scores, whereas MD and FISO were negatively correlated with memory scores. Most regions with significant correlation were correlated with verbal memory and delayed recall.

In DTI metrics, the R-value ranged from 0.36 to 0.46 in FA and from -0.36 to -0.40 in MD. The fornix was a common region in which FA and MD values were correlated with memory scores.

In NODDI metrics, few regions were associated with memory scores, compared with DTI metrics. NDI values of the right middle cingulate gyri and ODI values of the right lateral orbital cortex are positively correlated with delayed recall, with R-values of 0.36 and 0.39, respectively. FISO values of the left medial dorsomedial thalamic nucleus were negatively correlated with verbal memory, with an R-value of -0.39 .

The cerebral-to-intracranial volume ratio was positively correlated with verbal memory, with an R-value of 0.40.

These findings suggest that microstructural changes assessed by both mathematical and physiological models were correlated with memory impairment, with similar correlation coefficients. Compared with NODDI metrics, DTI metrics captured more widespread changes in memory-associated regions. In addition, cerebral atrophy was correlated with memory scores.

Discussion

This study demonstrated memory impairment and underlying structural changes in memory following treatment with low-dose WVI with chemotherapy after a long follow-up interval. About 84% of patients maintain a social life. However, 50% of the patients had low scores of < -1 SD in memory scores. DTI and NODDI metrics indicated that extensive changes had occurred in both gray and white matter related to memory. DTI and NODDI metrics in the components of the Papez and Yakovlev circuit were correlated with memory scores.

No clinical characteristics were associated with memory impairment in this study. This study included patients aged > 16 years at assessment because the memory battery was available only for this age group, and only six patients were treated before age 13 years. Therefore, whether younger patients are more vulnerable to memory impairments remains unclear. Park et al. reported neurocognitive outcomes after proton beam therapy consisting of 19.8 Gy WVI and 10.8–19.8 Gy to the primary site [21]. Patients with basal ganglia had impaired memory function but tended to improve during the early follow-up period (1–2 years), whereas patients with neurohypophyseal lesion showed declining memory function during follow-up. They presume that endocrine dysfunction and irradiation to the primary site and surrounding structures, such as the temporal lobe, contribute to the memory decline. In this study, careful endocrine management and the absence of a primary-site boost may explain the lack of differences in memory impairment between locations.

Zureick et al. reported that the left hippocampal volume receiving ≥ 20 GyE of proton was associated with declines in verbal memory scores in survivors of pediatric brain tumors [22]. In this study, all patients received 24 Gy of radiation to the bilateral hippocampus, and FA values decreased and MD and FISO values increased without hippocampal atrophy, but these metrics did not correlate with memory scores. These findings suggest that hippocampal microstructural changes occurred without volume loss, but their impact on memory was modest.

Previous reports have demonstrated microstructural changes after long-term with DTI in patients with pediatric brain tumors and acute lymphoblastic leukemia (ALL) treated with cranial irradiation [23–26]. There are conflicting data on the changes in FA and MD values after radiation therapy. Consistent with our results, long-term survivors 16–28 years after 18–24 Gy of prophylactic whole brain irradiation (WBI) to ALL had decreased FA in the temporal lobe, hippocampus, and thalamus. They had increased MD in the temporal lobe, compared to age-matched healthy controls [24]. Decreased FA values were also found in normal-appearing white matter in medulloblastoma patients [25]. This decreased FA value at the chronic phase after radiation therapy was attributed to demyelination and changes in gray and white matter integrity [27]. In contrast, some reports suggested an increase in FA and MD values in both gray and white matter in the survivors of pediatric brain tumors treated with radiation therapy compared to healthy controls [23]. This increased FA value was associated with iron deposition, the presence of perivascular space, relative loss of neural stem cells with isotropic properties, and changes in the extracellular matrix [23]. In contrast to DTI, only one study reported microstructure changes assessed by NODDI after radiation therapy. Zhou et al. examined cognitive function and NODDI metric changes over a 1–3-month period following 25–30 Gy of WBI in 26 patients with metastatic brain tumors with a mean age of 60 years [28]. NDI and ODI values decreased in the extensive area, both in white and gray matter, in contrast to this study. Our findings were interpreted as moderate morphological changes. They increased interstitial fluid without a decrease in axonal or neurite density in patients with germinoma long-term after low-dose WBI with chemotherapy. In 169 patients with cerebral small vessel disease (CSVD) and mild cognitive impairment, ODI and FISO values in the hippocampus are elevated, whereas NDI remains unchanged [29]. This is considered to reflect that microvascular damage causes blood leakage before obvious microstructural atrophic changes occur, leading to increased extracellular fluid and complex changes in dendrites [29]. Although CSVD and germinoma differ greatly in patient background and prior treatment, similar phenomena may occur after long-term follow-up.

Although both mathematical and physiological models showed similar correlations with memory impairment, DTI metrics captured more widespread memory-associated changes than NODDI metrics. The model that best predicts cognitive function remains controversial. NODDI metrics have shown stronger associations with cognitive function than DTI metrics in 66 patients with obstructive sleep apnea hypopnea syndrome and 199 and 28 patients with mild cognitive impairment (MCI)/Alzheimer's disease [30–32]. In contrast, MMSE was equally correlated with FA in the fornix, left anterior corona radiata, and right stria terminalis, and with NDI in the splenium of the corpus callosum, and with FISO in the stria terminalis in 43 patients with MCI/Alzheimer's disease [33]. Large-scale longitudinal studies and

disease-specific evaluations are necessary to explain the mechanisms of memory impairment and establish which diffusion models are most useful for predicting cognitive prognosis in each disease.

Various regions have been reportedly associated with memory impairment. It is reasonable that candidate regions for memory impairment differed between mathematical and physiological models and patients' backgrounds. In this study, differences in certain DTI or NODDI metric values were found in most memory-associated regions, indicating that Papez's and Yakovlev's circuits were extensively involved in memory impairment. In addition, the profile of NODDI metrics varied among anatomical locations, indicating that the underlying microstructural mechanisms varied depending on memory-associated components. Among them, DTI and NODDI metrics in the components of Papez's circuit, including the fornix, cingulum, and cingulate gyrus, and those of Yakovlev's circuit, including the orbital cortex, dorsomedial thalamic nuclei, and anterior cingulate cortex, correlated with memory scores. In addition, the cerebral-to-intracranial volume ratio was correlated with verbal memory. Collectively, the memory impairment was caused by these local and global changes after low-dose WVI with chemotherapy.

This study has limitations. First, the relatively small sample size limited our ability to clarify associations between memory and clinical factors. Second, the cross-sectional design of this study limits assessment of the relationships between memory profiles and NODDI parameters, as individual differences may have influenced the findings; longitudinal studies are required. Third, this study includes 40% of patients who received WBI or craniospinal irradiation (CSI). Although there were no differences in the score of WMS-R between patients treated by WVI and WBI/CSI, the impact of WBI/CSI might be underestimated. Fourth, this study did not demonstrate the relationship between microstructural changes and radiation fields.

Conclusion

This study characterized memory impairment and microstructural changes during long-term follow-up of patients with germinoma treated with low-dose WVI with chemotherapy. 50% had memory impairment below -1 SD. DTI and NODDI analyses revealed extensive microstructural changes in memory-associated gray and white matter. Some DTI and NODDI metrics in the components of Papez's and Yakovlev's circuit correlated with memory scores. In addition, cerebral atrophy was associated with memory scores. These local and global changes may contribute to memory impairment after low-dose WVI with chemotherapy.

Declarations

Funding

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Data availability

No datasets were generated or analyzed during the current study.

Code availability

Not applicable.

Ethics approval

The current study was approved by the institutional ethical review board of Tohoku University Hospital (2021–1-362).

Consent to participate and consent for publication

Informed consent was obtained from all individual participants included in the study. This study contains no individual person's data.

Competing interests

The authors declare no competing interests.

Author contributions

Concept and design: M.K., S.M., O.I.

Data collection: M.K., S.M., N.M., O.I., Y. Shimoda, Y.O., S.Y., I.S., R.S., Y. Sonoda, and T.K.

Data analysis: M.K. S.M., N.M.

Critical revision of the draft: S.M., N.M., R.U., T.K., and K.S.

Writing the manuscript: M.K. and S.M.

Supervising this study: K.J., K.S., and H.E.

All authors read and approved the final version of the manuscript.

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

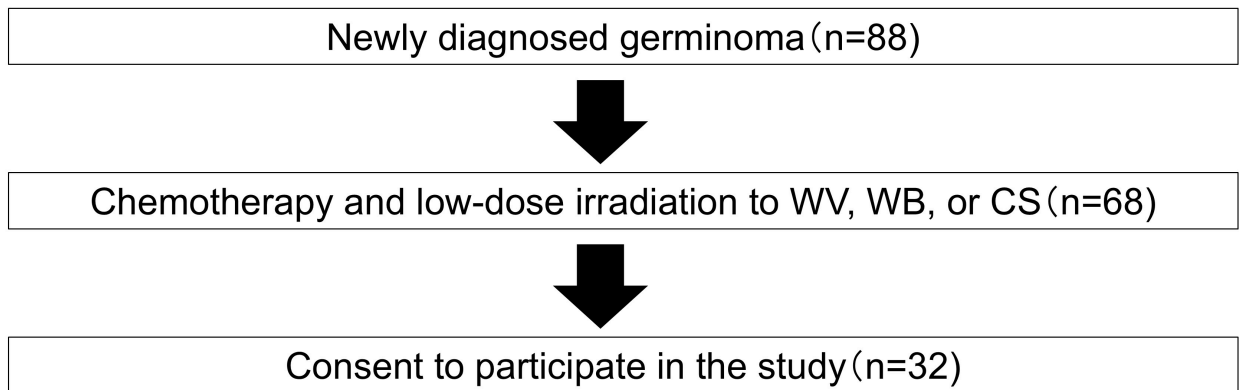


Figure 1

Patient flow in this study.

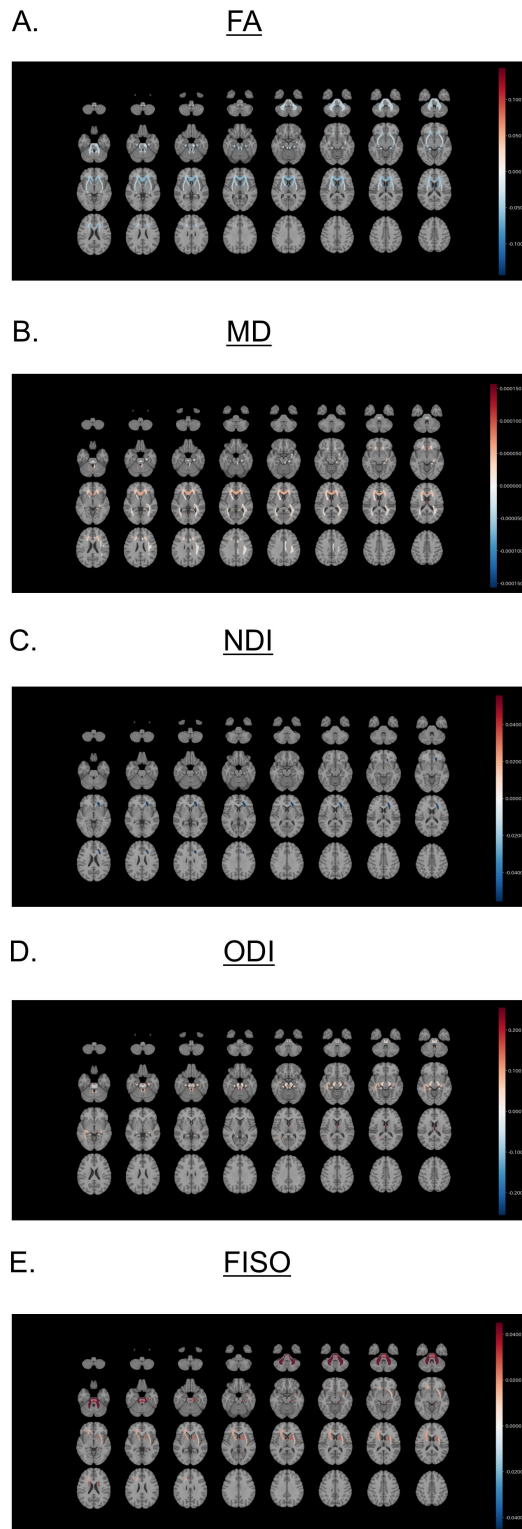


Figure 2

Heat map of differences in fractional anisotropy (FA) (A), mean diffusivity (MD) (B), neurite density index (NDI) (C), orientation dispersion index (ODI) (D), and isotropic volume fraction (FISO) (E) values between patients and healthy controls in white matter regions with significant differences examined using the Benjamini and Hochberg method with a false discovery rate of 0.1. Red and blue indicate increased and decreased values in patients, respectively.

	Regions	FA	MD	NDI	ODI	FISO
White matter	Fornix (column and body of fornix)	-0.14	0.000157			0.256
	Fornix (cres) / Stria terminalis L	-0.047				0.074
	Fornix (cres) / Stria terminalis R	-0.048	0.0000359			0.087
	Anterior limb of internal capsule L	-0.047	0.000015		0.0186	
	Anterior limb of internal capsule R	-0.055			0.0289	
	Cingulum (cingulate gyrus) L					
	Cingulum (cingulate gyrus) R		0.000015			
	Cingulum (hippocampus) L	-0.032				
	Cingulum (hippocampus) R	-0.045	0.000023		0.0342	
	Uncinate fasciculus L					
	Uncinate fasciculus R		0.00003		0.0239	
	Hippocampus L	-0.0131	0.00003			0.138
	Hippocampus R	-0.0152	0.000032			0.156
	Thal AV L	-0.0245				
Gray matter	Thal AV R	-0.0352			0.0401	
	Thal MDm L	-0.0399	0.000052			0.144
	Thal MDm R	-0.0608	0.000063			0.233
	Cingulate Ant L					
	Cingulate Ant R					
	Cingulate Mid L	-0.0324	0.000049			
	Cingulate Mid R	-0.06	0.000047	-0.0521	0.0456	
	Cingulate Post L					
	Cingulate Post R					
	ParaHippocampal L	-0.0108			0.0203	0.107
	ParaHippocampal R	-0.0257	0.000025		0.0303	0.079
	Amygdala L					
	Amygdala R	-0.0112				
	ACC pre L	-0.032	0.000031		0.031	0.055
	ACC pre R	-0.0408	0.000035		0.0374	
	ACC sub L					0.067
	ACC sub R					0.06
	ACC sup L		0.000057	-0.0422		0.052
	ACC sup R		0.000039	-0.0409		
	OFCant L					
	OFCant R					
	OFClat L					
	OFClat R				-0.0496	
	OFCmed L					
	OFCmed R		0.000036			
	OFCpost L		0.000055			
	OFCpost R		0.00011			0.089
	Temporal Pole Mid L					0.099
	Temporal Pole Mid R	-0.0096	0.000019			0.098
	Temporal Pole Sup L	-0.0185	0.000063			0.0115
	Temporal Pole Sup R	-0.0155	0.000057			0.123

Figure 3

Heat map of differences in fractional anisotropy (FA), mean diffusivity (MD), neurite density index (NDI), orientation dispersion index (ODI), and isotropic volume fraction (FISO) values in memory-related regions with healthy controls. Red and blue indicate statistically significant increases and decreases, respectively, in patients compared with healthy controls. Numbers in the boxes indicate the between-group differences in mean diffusion tensor imaging and neurite orientation dispersion and density imaging metric values. ACC pre, anterior cingulate cortex, pregenual; ACC sub, anterior cingulate cortex, subgenual; ACC sup, anterior cingulate cortex, supracallosal; Cingulate Ant, anterior cingulate and paracingulate gyri; Cingulate Mid, middle cingulate and paracingulate gyri; Cingulate Post, posterior cingulate gyrus; OFCant, anterior orbital gyrus; OFClat, lateral orbital gyrus; OFCmed, medial orbital gyrus; OFCpost, posterior orbital gyrus; Temporal Pole Mid, temporal pole: middle temporal gyrus; Temporal Pole Sup, temporal pole: superior temporal gyrus; Thal AV, thalamus, anteroventral nucleus; Thal MDm, thalamus, mediodorsal medial magnocellular;

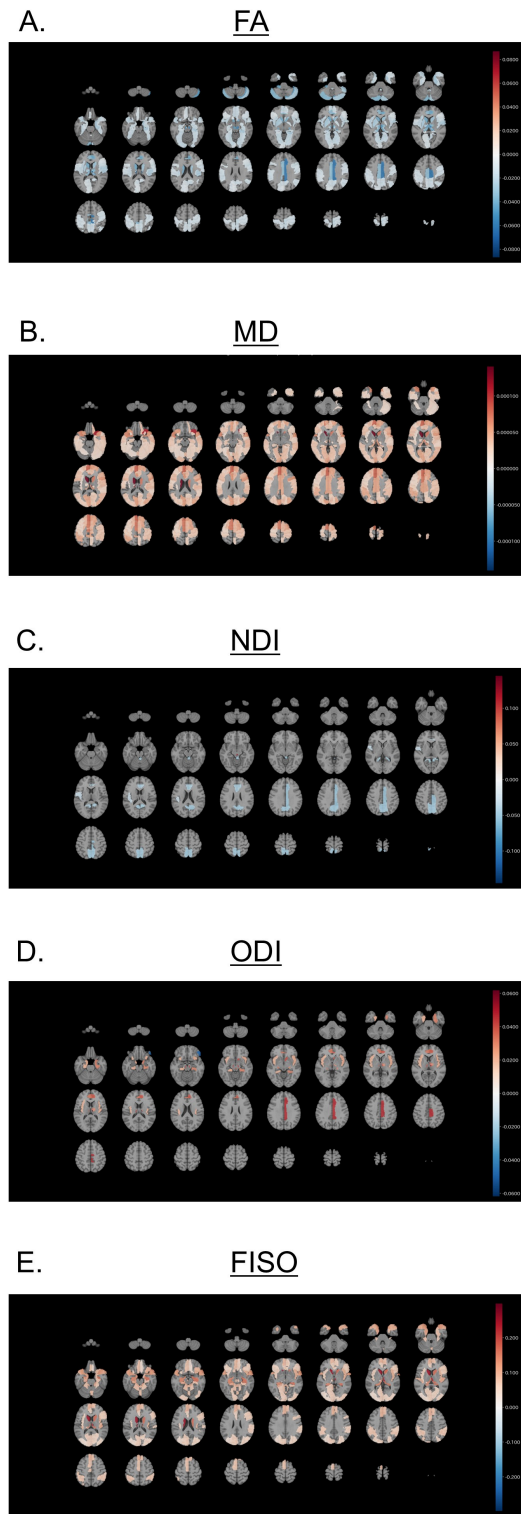


Figure 4

Heat map of differences in fractional anisotropy (FA) (A), mean diffusivity (MD) (B), neurite density index (NDI) (C), orientation dispersion index (ODI) (D), and isotropic volume fraction (FISO) (E) values between patients and healthy controls in gray matter regions with significant differences evaluated using the Benjamini and Hochberg method with a false discovery rate of 0.1. Red and blue indicate increased and decreased values in patients, respectively.

Supplementary Files

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