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ORIGINAL PAPER

Longitudinal changes of fractional anisotropy in Alzheimer's disease patients treated with galantamine: a 12-month randomized, placebo-controlled, double-blinded study

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Abstract Diffusion tensor imaging (DTI) demonstrates decline of fractional anisotropy (FA) as a marker of fiber tract integrity in Alzheimer's disease (AD). We aimed to assess the longitudinal course of white matter microstructural changes in AD and healthy elderly control (HC) subjects and to evaluate the effects of treatment with the cholinesterase inhibitor galantamine on white matter microstructure in AD patients. We enrolled 28 AD patients and 11 healthy elderly control subjects (HC). AD patients were randomly assigned to 6-month double-blind galantamine treatment or placebo, with a 6-month open-label extension phase. DTI was performed at baseline, as well as at 6 and 12-month follow-up in AD patients. The HC subjects underwent DTI at baseline and 12-month follow-up without treatment. We measured FA in regions of interest covering the posterior cingulate and corpus callosum. At 6-month follow-up, the AD group showed significant FA decline in the left posterior cingulate. FA decline was significantly preserved in the posterior body of the corpus callosum in AD group with treatment compared to placebo. At 12-month follow-up, the AD patients showed no differences in FA decline between initial treatment and placebo groups after the 6-month open-label extension phase. A significant FA decline occurred in the left posterior cingulate across the AD and HC groups without between-group differences. DTI demonstrated FA decline in intracortically projecting fiber tracts in aging and AD over 1 year. Galantamine had limited impact on regional FA decline, which was not preserved after additional 6-month open-label treatment.

Keywords Diffusion tensor imaging · Longitudinal changes · Posterior cingulate · Corpus callosum · Alzheimer's disease · Galantamine

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Introduction

Neuropathological studies in Alzheimer's disease (AD) demonstrate progressively reduced synaptic density, cortical cell loss, deposition of amyloid plaques, and neurofibrillary tangles in brain gray matter [7, 9]. In addition, white matter changes occur that have been associated with

both neuronal degeneration and vascular pathology [14, 51]. Cortical neuronal loss and degeneration of neuronal fiber tracts contribute to the cortical disconnection underlying the dementia syndrome of AD [8, 33]. Diffusion tensor imaging (DTI) has been increasingly used to identify subtle white matter abnormalities in brain diseases [28]. Various studies on neurodegenerative diseases demonstrated the value of DTI in the detection of microstructural alterations of the brain white matter [50]. Thus, DTI may be useful to identify microstructural changes in AD. Consistently, several cross-sectional DTI studies revealed white matter integrity changes in AD patients compared to healthy elderly controls in different areas of the brain, including cingulate gyrus, corpus callosum, parahippocampal gyrus as well as frontal, temporal, parietal, and occipital white matter [5, 6, 10, 23, 31, 34, 43, 44, 56, 57]. These findings largely correspond to findings from histopathological and structural MRI studies in AD [41, 49]. In addition, previous longitudinal MRI studies revealed progression of corpus callosum and white matter atrophy in AD in addition to cortical gray matter loss [29, 47]. Longitudinal data on white matter changes based on DTI are still rare. Longitudinal DTI studies were performed in traumatic brain injury [42], Huntington's disease [55], and healthy elderly subjects [1]. The results suggest that longitudinal fractional anisotropy (FA) changes may serve as a biomarker of dynamic changes in fiber tract integrity. To the best of our knowledge, there is only one report of a 3-month longitudinal DTI study in AD, which revealed no change in FA values in the investigated groups over this short time period [32].

Cholinesterase inhibitors (ChEIs) are the approved drugs of choice in mild to moderate AD. ChEIs showed benefits on cognitive functions and delaying the course of AD in mild and moderate stages [3]. Imaging studies provided evidence for significantly lower hippocampal atrophy rates [20] in AD patients who received ChEIs compared to placebo. ChEIs also showed treatment effects on brain function in AD patients including decrease in compensatory cortical activation in the dorsal visual pathway during object recognition demonstrated by functional MRI (fMRI) [4], increased regional blood flow demonstrated by single-photon emission computed tomography (SPECT) [53], and preserved or slightly increased glucose metabolism in cortical areas demonstrated by positron emission tomography (PET) [48, 52]. A retrospective cohort study did not reveal effects of treatment with ChEIs on cerebral white matter changes associated with cerebrovascular disease in patients with AD [13]; however, the effects of ChEIs treatment on cerebral white matter microstructure related to neurodegeneration in the absence of significant vascular pathology have not yet been investigated in AD.

In this study, we explored the effects of 6-month treatment with ChEI galantamine on white matter integrity in AD patients. For comparison, we assessed longitudinal changes of FA over 12-month follow-up in a healthy elderly control group.

Methods and materials

We examined 28 subjects with AD and 11 healthy elderly control (HC) subjects. Patients with AD fulfilled the NINCDS-ADRDA criteria for clinically probable AD [30]. Neuropsychological assessment included the "Mini-Mental State Examination" (MMSE) [17], Clinical Dementia Rating scale (CDR) [16], and CERAD cognitive battery [2]. All control subjects scored 0 in the CDR [16]. The clinical assessment additionally included complete medical history and clinical, psychiatric, and neurological examinations. Blood tests consisted of complete blood count, electrolytes, glucose, blood urea nitrogen, creatinine, liver-associated enzymes, cholesterol, HDL, triglycerides, serum B12, folate, thyroid function tests, coagulation, and serum iron. Selection of subjects included a semiquantitative rating of T2-weighted MRI scans [40]. Only those subjects were included who had no subcortical white matter hyperintensity exceeding 10 mm in diameter or 3 in number. All patients and control subjects were only examined if they had given their written informed consent. The study was approved by the institutional review board of the Medical Faculty of the University of Munich. The treatment trial was registered at Clinicaltrials.gov (Identifier: NCT00523666).

Magnetic resonance imaging

Magnetic resonance imaging was performed using a clinically approved high-field 3.0 Tesla scanner (Magnetom TRIO, Siemens, Erlangen, Germany) with maximum gradient strength, 45 mT/m, maximum slew rate, 200 T/m/s, 12-element head coil. Subjects were scanned in a single session without changing their position in the scanner. For anatomical reference, a sagittal high-resolution three-dimensional gradient-echo sequence was performed (magnetization prepared rapid gradient echo MPRAGE, field-of-view 250 mm, spatial resolution $0.8 \times 0.8 \times 0.8$ mm^3, repetition time 14 ms, echo time 7.61 ms, flip angle 20°, and number of slices 160). Diffusion-weighted imaging was performed using an echo-planar-imaging sequence (field-of-view 256 mm, repetition time 9,300 ms, echo time 102 ms, voxel size $2.0 \times 2.0 \times 2.0$ mm^3, four-repeated acquisitions, *b*-value 1 = 0, *b*-value 2 = 1,000, 12 directions, noise level 10, slice thickness 2.0 mm, 64 slices, and no gap). Parallel

imaging was performed using a generalized auto-calibrating partially parallel acquisition (GRAPPA, [19]) reconstruction algorithm and an acceleration factor of 2.

Study design

The study was a 6-month, double-blinded, randomized placebo-controlled trial with additional 6-month open-label period. Sample size was calculated for a presumed effect of 25% difference for the mean value and standard deviations for FA measurements in AD patients from previous studies at power 0.8 [15, 43]. Galantamine treatment and placebo were randomized in blocks of 4 with 2 galantamine and 2 placebo. Computer randomization was used before the start of the study with randomization code generated by Janssen-CILAG (Neuss, Germany). Participants and investigators were blinded to the randomization. The participants were enrolled by the Department of Psychiatry, University of Munich. All eligible AD patients were double blindly assigned to either galantamine treatment or placebo (Fig. 1). The treatments with galantamine and placebo were continued for 6 months. Afterward, all AD patients were treated open-label with galantamine for additional 6 months. Galantamine/placebo administration was started at a daily single dose of 8 mg for 4 weeks then increased to 16 mg daily for 4 week and continued with 24 mg through the study. For AD patients MRI, DTI, and neuropsychological tests were performed at baseline, 6- and 12-month follow-up. HC subjects were assigned to MRI and DTI examinations as well as neuropsychological tests at baseline and 12-month follow-up. The imaging study in the HC group was only performed at baseline and after 12 months, because we did not expect significant changes of FA over a relatively short time interval of 6 months in HC subjects. HC subjects were followed up without treatment. The HC group served as a reference group to determine the level of change of FA over time that has to be expected by aging alone. The main outcome, however, was the comparison between the verum and placebo-treated AD groups.

Image data processing

We created FA maps and color-coded tensor orientation maps using DTIstudio, Version 2.4.01 [24]. Before evaluation, all images were manually realigned using rigid body rotation. First, images were aligned along the interhemispheric plane. To place regions of interest (ROI) on posterior cingulate white matter, images were rotated parallel to the line connecting the anterior and posterior commissure (AD-PC line). For selecting corpus callosum regions, images were rotated according to the most anterior edge and the most posterior edge of the mid-sagittal corpus callosum cross-section. We defined a total of eight ROIs including two regions on posterior cingulate (right and left), 4 subregions of the corpus callosum (genu, anterior body, posterior body, and splenium), cerebellar vermis, and lateral ventricle. Right and left posterior cingulate ROIs were placed on the axial view of the color map images. Placing of ROI was based on the mid-part of the superior-inferior portion or the posterior cingulate in the sagittal view (represented as blue fiber bundle in the color maps). Each posterior cingulate ROI consisted of a circle with a diameter of 4 mm^2. Four ROIs of corpus callosum were defined on the mid-sagittal slice, where the length of corpus callosum from the most anterior to the most posterior edge was divided into four equal distances separating the corpus callosum into the following parts: genu, anterior part of the body, posterior part of the body, and splenium. Image orientation and ROI placing are illustrated in Fig. 2. Additionally, we placed a circular ROI with a diameter of 10 mm^2 in the lateral ventricle in the axial view at the level of the first full view of the lateral ventricle and in the cerebellar vermis on the mid-sagittal view in order to control the stability of FA values over time. We expected no significant changes of FA in ventricle and cerebellum during the follow-up period. All ROIs that had been defined on the color maps were overlaid on the corresponding FA maps of each subject to obtain the FA values in each region. We also measured the corpus callosum area from the selected corpus callosum ROI in order to determine structural changes during the follow-up period. The numbers of pixels within the corpus callosum ROIs were multiplied by pixel size in order to obtain the absolute value in square millimeters. To determine the reliability of ROI measurement, scans from 10 subjects were randomly measured by two independent researchers (Y. L. and Stefanie Kranz).

Statistical analysis

At baseline, the mean FA in each ROI between AD and controls was compared using analysis of covariance (ANCOVA). For the AD group, an additional ANCOVA was used to test for differences between galantamin treatment and placebo groups. In all ANCOVAs, age was included as a covariate. At the 6-month follow-up study of the AD group, the interaction between time and treatment groups for FA change in each ROI was assessed by repeated measures analysis of variance with treatment group as between-subjects factor. For the 12-month follow-up study, diagnosis was used as the between-subjects factor to assess the interaction of time and diagnostic groups on FA change in each ROI. In addition, at the 12-month follow-up, FA changes in the AD group were assessed for interaction between treatment and time. Statistical tests for the corpus callosum areas were performed in the same way as for the

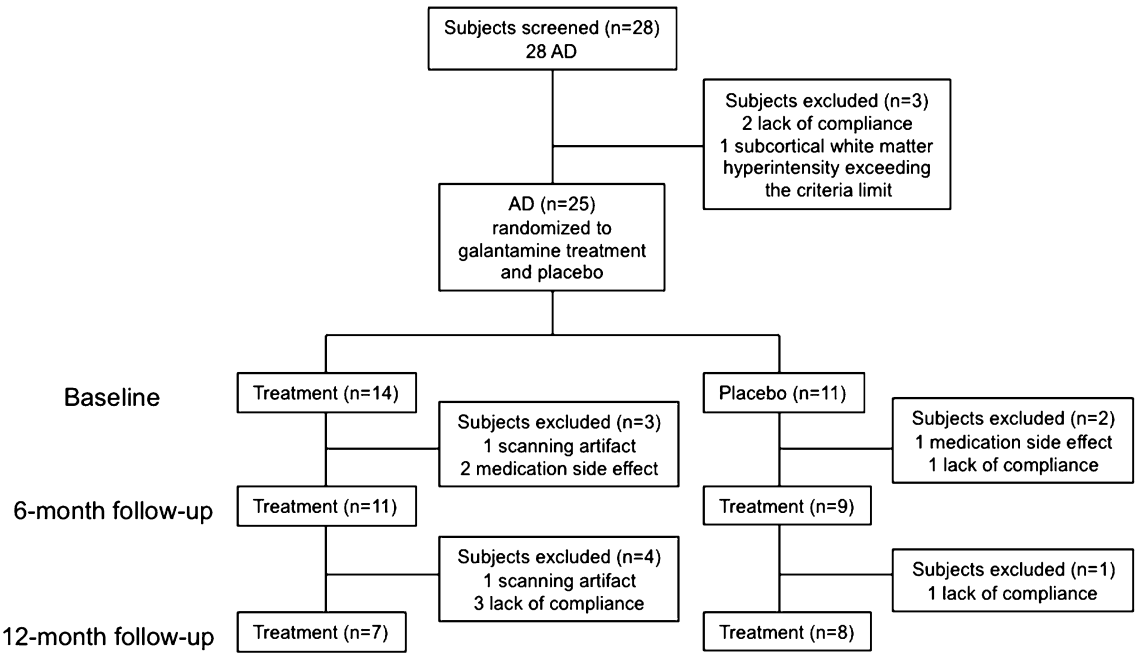

Fig. 1 Flow chart of the intervention study in the AD group. Numbers of subjects screened and randomized to the study, dropouts and completers. The study was a randomized controlled trial for 6 months with a 6-month open-label extension phase

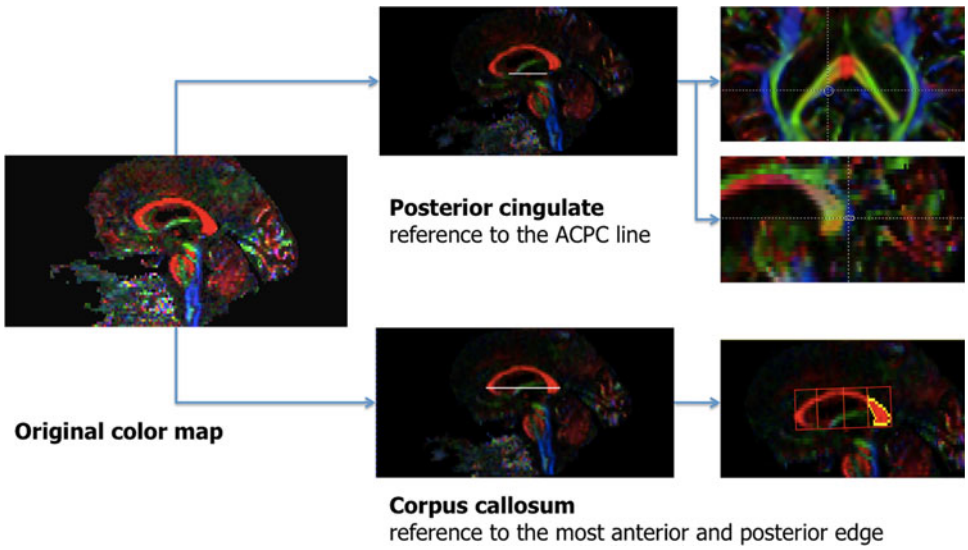

Fig. 2 Image realignment and ROI definition. ROI on posterior cingulate: images were rotated parallel to the AD-PC line. ROI on corpus callosum: images were rotated according to the most anterior edge and the most posterior edge of the mid-sagittal corpus callosum cross-section. For details refer to method description in the text

FA measurements. The level of significance was set at $P < 0.05$. The analyses were performed using the statistical package for the social sciences (SPSS) release 11.5

Results

Participants were recruited between September 2006 and September 2008. A total of 39 subjects including 28 AD subjects and 11 HC subjects were enrolled. After screening, 3 patients with AD were excluded. Fig. 1 shows the flowchart of AD patient randomization and excluded subjects through the study. All HC subjects continued through the 12-month follow-up. Baseline demographics, MMSE and CERAD subtests scores at baseline are demonstrated in Table 1. There were significant differences in age, years of education, MMSE, and all CERAD subtests scores between the two groups, whereas gender was not significantly different. Independent t-test analysis showed that the AD group was significantly older and had significantly less years of education compared to controls. As expected, the MMSE and CERAD subtests scores were significantly lower in the AD patients than in the controls. Within the AD group, there were no significant differences

Table 1 Demographic and neuropsychological characteristics at baseline

	AD	HC	$t(34)$	P value
Gender (M/F)[$]	10/15	7/4	–	–
Age (year)[#]	74.9 ± 7.6	67.4 ± 7.7	−2.74	0.010
Years of education[#]	9.8 ± 1.7	12.6 ± 3.6	3.24	0.003
MMSE[#]	22.5 ± 2.7	29.3 ± 0.7	7.43	<0.001
Verbal fluency[#]	12.7 ± 4.4	25.9 ± 6.4	7.20	< 0.001
Boston naming test[#]	12.0 ± 2.4	14.5 ± 0.6	3.10	0.004
Word list learning[#]	11.3 ± 5.6	22.7 ± 3.3	6.30	<0.001
Constructional praxis[#]	8.2 ± 2.1	10.9 ± 0.3	4.30	<0.001
Word list recall[#]	1.6 ± 1.8	8.0 ± 1.8	9.53	<0.001
Word list recognition[#]	6.2 ± 2.2	9.6 ± 0.7	4.90	<0.001
Recall of constructional praxis[#]	3.0 ± 3.0	10.5 ± 1.0	7.92	<0.001

[$] No difference between groups $X^2 = 1.71$ with 1 df, $P = 0.19$

[#] Significant difference between groups

Table 2 Demographic and neuropsychological characteristics at baseline and follow-up in AD patients

	Baseline		6-month		12-month	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
N (men/women)	14 (6/8)	11 (4/7)	11 (5/6)	9 (4/5)	7 (3/4)	8 (3/5)
Age (years)	73.5 ± 7.2	76.4 ± 7.9	73.1 ± 7.4	73.8 ± 7.3	71.1 ± 8.5	74.3 ± 7.7
Years of education	10.1 ± 1.8	9.6 ± 1.5	9.7 ± 1.7	9.4 ± 1.4	9.00 ± 1.0	9.63 ± 1.4
MMSE	22.1 ± 2.4	23.0 ± 3.5	21.6 ± 2.4	22.3 ± 3.4	20.4 ± 1.9	22.0 ± 3.5
Verbal fluency	12.5 ± 4.9	13.0 ± 3.8	14.8 ± 6.6	10.89 ± 3.95	12.4 ± 4.9	9.1 ± 2.2
Boston naming test	12.1 ± 2.69	11.8 ± 2.1	12.6 ± 2.5	10.8 ± 3.0	12.4 ± 3.2	11.5 ± 1.9
Word list learning	11.3 ± 4.0	11.4 ± 7.3	10.3 ± 4.2	11.7 ± 3.4	9.1 ± 2.9	9.5 ± 2.1
Constructional praxis	8.7 ± 1.6	7.5 ± 2.5	10.2 ± 1.1	8.0 ± 3.1	9.1 ± 1.6	7.4 ± 2.4
Word list recall	1.4 ± 1.6	2.0 ± 2.1	0.7 ± 1.0	1.0 ± 2.3	0.1 ± 0.4	0.9 ± 1.1
Word list recognition	6.5 ± 2.4	5.9 ± 2.1	5.4 ± 3.2	5.9 ± 3.0	3.8 ± 3.1	3.1 ± 1.7
Recall of constructional praxis	2.6 ± 2.4	3.5 ± 3.8	2.2 ± 2.7	1.7 ± 2.4	0.9 ± 1.2	0.3 ± 0.7

There was no significant difference in these variables between galantamine treatment and placebo group at baseline as well as 6- and 12-month follow-up ($P > 0.05$)

of age, gender, years of education, MMSE, and CERAD subtests between galantamine treatment and placebo groups at any time point (Table 2).

Inter-rater reliability of ROI measurements

The relative error between two independent researchers on right and left posterior cingulate was 4.0 and 3.8%, respectively, and relative error for genu, anterior body, posterior body, and splenium of the corpus callosum measurements was 3.2, 2.5, 5.0, and 2.2%, respectively. The intraclass correlation coefficients for inter-rater reliability were 0.89 and 0.90 for right and left posterior cingulate, respectively. For corpus callosum, intraclass correlation coefficients were 0.71, 0.94, 0.86, and 0.84 for genu, anterior body, posterior body, and splenium, respectively.

Baseline analyses

The findings on baseline FA are illustrated in Fig. 3. Significant differences between AD and HC group were observed in corpus callosum subregions including genu ($F(1, 33) = 4.97$; $P = 0.033$) and splenium ($F(1, 33) = 13.219$; $P = 0.001$). Within the AD group, FA was not significantly different between the galantamine treated and placebo group in any measured area ($P > 0.05$). There was no significant difference of corpus callosum area between the AD and HC group in any subregion with the effects in

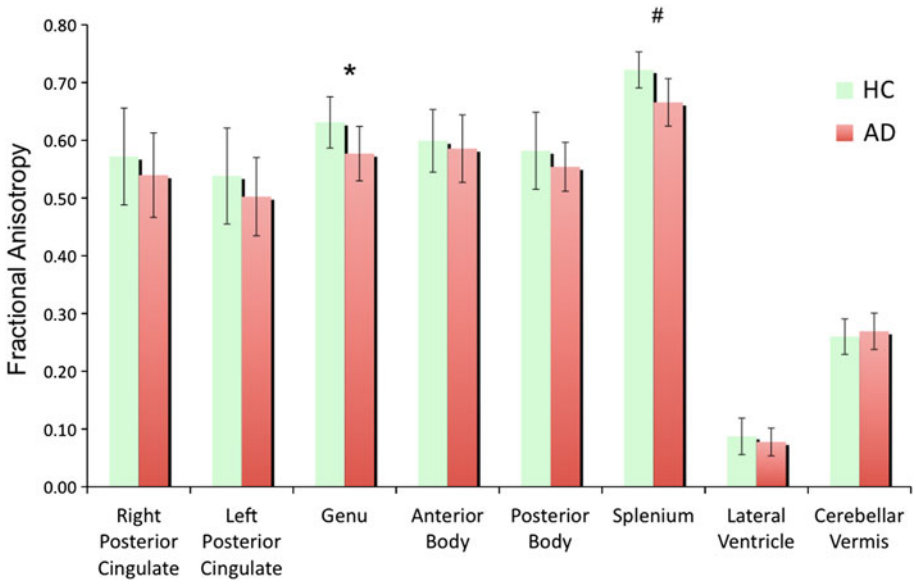

Fig. 3 Fractional anisotropy at baseline in AD and controls. Significant difference between groups $^{*}P = 0.034$, $^{\#}P = 0.001$

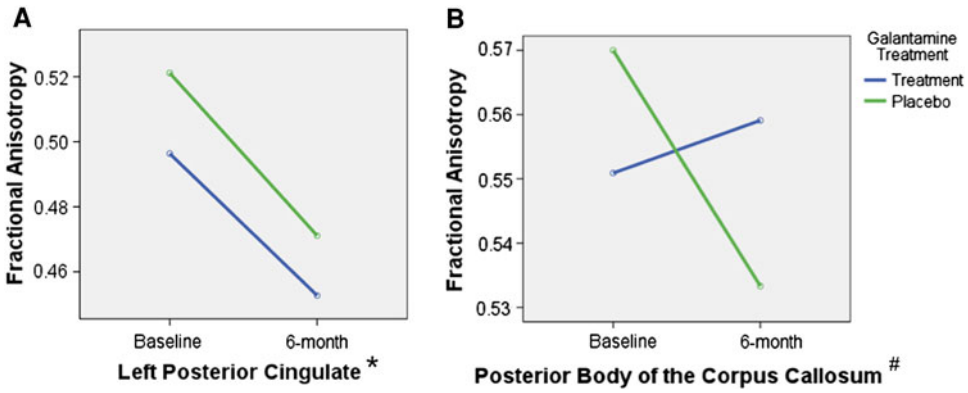

Fig. 4 Time and treatment effects on fractional anisotropy at 6-month follow-up in the AD patients. *Significant FA decline at $P = 0.012$, $^{\#}$FA decline in placebo more than treatment group at $F(1, 18) = 5.90$, $P = 0.026$

the posterior body showing a trend toward significant reduction in AD ($F(1, 33) = 4.018$; $P = 0.053$).

Six-month follow-up

In the AD patients, there was no significant change in MMSE scores observed during the 6-month follow-up irrespective of treatment. The performance in the subtests of the CERAD battery showed significant increase in constructional praxis ($F(1, 18) = 8.57$; $P = 0.009$) across the treatment and placebo groups, but no change in any other subtest. There was no time by treatment effects on MMSE and CERAD subtests including constructional praxis. Combining the two groups, there was significant FA decline over time in the left posterior cingulate (Fig. 4), but no effect in right posterior cingulate and any corpus callosum subregions ($P > 0.10$). A significant interaction between time and treatment on FA change was detected in the posterior body of the corpus callosum. The treatment group showed an increase in FA, while the placebo group showed a decrease in FA (Fig. 4). The other regions showed no significant differences in FA changes between treatment and placebo groups ($P > 0.30$). Across the two treatment groups, a significant increase in FA at 6-month follow-up was observed in the cerebellar vermis ($F(1, 18) = 5.50$; $P = 0.031$), but there was no difference between groups ($P = 0.81$). The FA in the lateral ventricle revealed no significant change ($P = 0.77$). None of the corpus callosum subregions revealed significant area changes at 6-month follow-up ($P > 0.60$).

Twelve-month follow-up

There were no significant changes in MMSE scores and the performance in the subtests of the CERAD during the 12-month follow-up in the AD and HC groups. Time effects on FA over the 12-month period are illustrated in Fig. 5. Significant FA decline over time across the two diagnostic groups (AD and HC) was observed in the left posterior cingulate ($F(1, 24) = 6.93$; $P = 0.015$). The

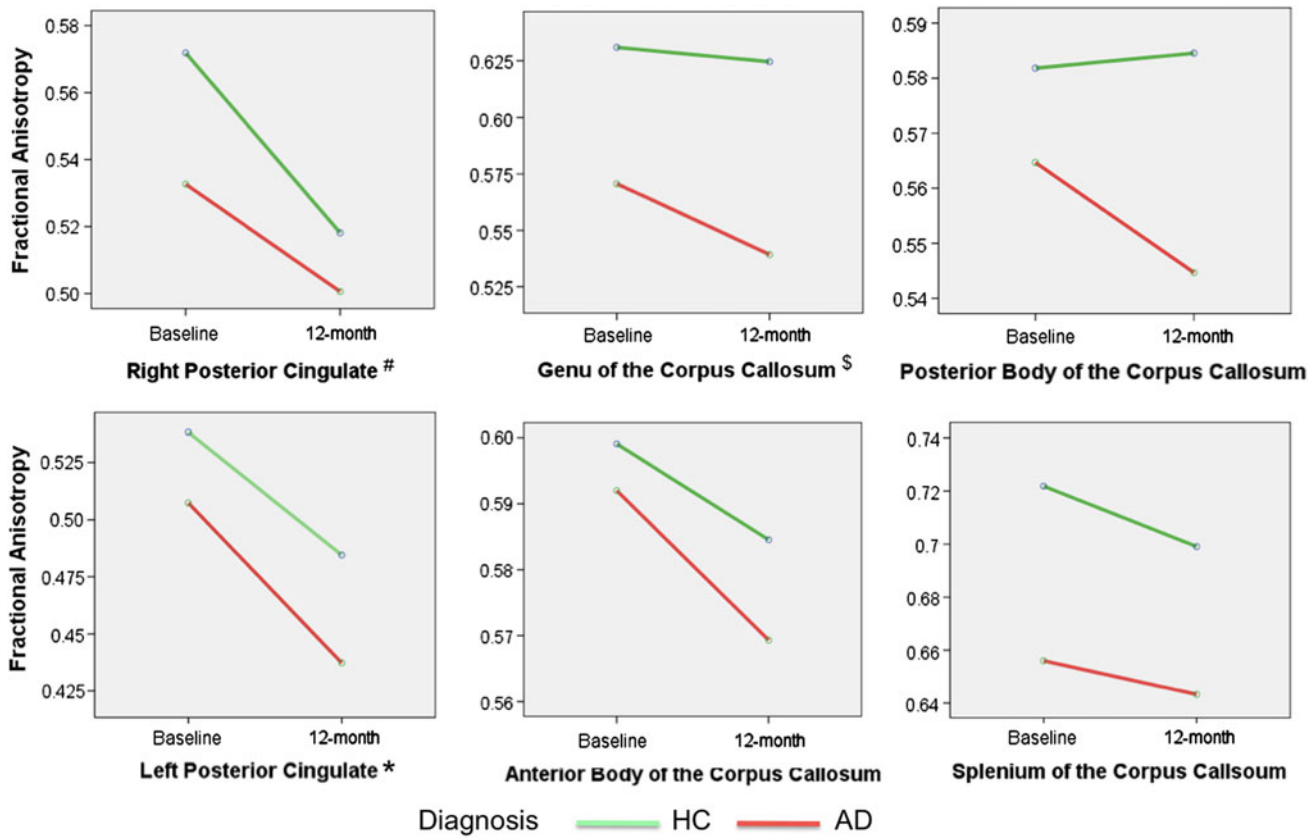

Fig. 5 Time effect on fractional anisotropy at 12-month follow-up in AD, and controls. *Significant FA decline across the 2 groups at $P = 0.015$, #approached significant FA decline across the 2 groups $P = 0.059$, $approached significant FA decline across the 2 groups $P = 0.061$

right posterior cingulate ($F(1, 24) = 3.93$; $P = 0.059$) and the genu of the corpus callosum ($F(1, 24) = 3.85$; $P = 0.061$) showed a trend toward significant decline. In the cerebellar vermis, increase in FA approached significance ($F(1, 24) = 3.90$; $P = 0.060$). FA values in the lateral ventricle remained unchanged across both groups at the 12-month follow-up ($P = 0.41$). Corpus callosum area showed no significant change over time across the two groups ($P > 0.08$). Within the AD group, there was no significant interaction between time and treatment on FA values in any region or corpus callosum areas ($P > 0.30$). FA values did not change at 12-month follow-up in cerebellar vermis ($P = 0.94$) and lateral ventricle ($P = 0.59$).

Discussion

In this study, we investigated the effect of 6-month treatment with galantamine and a potentially preserved effect of galantamine treatment after a 6-month open-label extension phase on fiber tract integrity in AD patients. For comparison, we determined longitudinal FA changes in a group of HC subjects over 12 months. We had selected regions of interest in brain areas previously shown to be affected in cross-sectional DTI studies of AD patients, such as posterior cingulate and corpus callosum [5, 21, 38, 45, 56]. In order to minimize variability of FA value measurements, all images were realigned into the same anatomical orientation; this was done using rigid body rotation in order to avoid any effect on fiber tract orientations. This approach yielded high inter-rater reliability of the measurements.

Our cross-sectional findings at baseline on FA reductions in genu and splenium of the corpus callosum in the AD patients compared to the controls are consistent with previous cross-sectional studies [21, 34, 37, 56, 57]. We did not observe significant differences of FA values in posterior cingulate between the two groups, in contrast to some, but not all cross-sectional studies [15, 37, 57]. Corpus callosum area was not significantly reduced in the AD patients compared to controls, possibly related to a smaller sample size than in previous studies on cross-sectional areas [22, 26, 36, 46, 54].

At 6-month follow-up, significant decline of FA was observed in the left posterior cingulate in the AD group across both treatment conditions. The posterior cingulate is closely connected to the hippocampus, an early predilection area of AD pathology. This effect corresponds to asymmetrical hippocampal atrophy which was found in a

longitudinal study on hippocampus atrophy [18]. Consistent with the reported hippocampus atrophy in previous studies, the decline of posterior cingulate FA suggests degeneration of fiber tracts maintaining structural connectivity between hippocampus and posterior cingulate. Compared to placebo, galantamine treatment was associated with preserved FA at 6-month follow-up in the posterior body of the corpus callosum. A 3-month follow-up study using fMRI reported significant treatment effects of galantamine on visual processing in AD [4]. In combination, these findings may relate to a functional effect of galantamine on the posterior association cortex that sends interhemispheric connections through the posterior corpus callosum [12]. These findings, however, require further replication in an independent sample. At 12-month follow-up, we did not find significant treatment effects of galantamine suggesting that the difference in treatment effects on FA decline after the first 6-month treatment period was not preserved in the 6-months open-label extension phase where all patients received galantamine.

At 12-months follow-up, FA decline was observed in left posterior cingulate across the AD and control groups without a significant effect of diagnosis. The FA decrease in this area may explain the cross-sectional finding of age-associated regional anisotropy decline in elderly subjects [27, 35]. We expected to find greater degree of FA decline over time in AD compared to controls. However, higher variation of longitudinal FA values in the AD patients compared to controls may have masked between-group differences of FA. FA values in the AD patients at 12-month follow-up had higher coefficients of variation (CV) in all areas compared to baseline (CV of the AD group at baseline: 0.06–0.14; 12-month follow-up: 0.09–0.27) compared to the HC groups (CV of HC group at baseline: 0.04–0.15, 12-month follow-up: 0.05–0.17). These variation differences may be related to the heterogeneity in the clinical course of AD [11], but also to the limited compliance of AD patients with the MRI and DTI examinations. The decline of FA in healthy elderly subjects agrees with the findings in a study of elderly subjects which demonstrated widespread decline of FA across different fiber tracts over a 2-year period [1], supporting the validity of the longitudinal FA changes in our study. We found no significant reduction at 12-month follow-up in corpus callosum areas. This may be due to the shorter follow-up period than the previous longitudinal study on corpus callosum area [47].

Unexpectedly, we observed a trend toward a significant FA increase in the vermis of the cerebellum across the AD and control groups, which was also found in the AD group at 6-month follow-up. However, an increase in FA in the cerebellar vermis was also observed in Huntington's disease subjects in a longitudinal diffusion tensor imaging study [55]. The actual cause of this FA increase over time is uncertain. The finding may either represent fluctuations of scanner parameters between the two time points or true neurobiological effects. If this increase would only reflect changes in scanner parameters, it would suggest a tendency for an increase in FA values over time in all regions, which were studied. This would indicate that the effects of FA reduction were underestimated across the AD and control groups. However, the stability of values in the ventricular control region and the increase at both time points at 6 and 12-month follow-up suggested that this effect was not mainly related to scanner parameter changes. Fiber tracts are nonuniformly distributed within the cerebellar vermis due to a large number of crossing fibers [39]. The observed increase in the FA may therefore reflect the net effect from the loss of crossing fiber tracts with age and neurodegeneration [25].

Our study was limited to detect a short-term effect of Galantamine on fiber tract integrity over 6 months as main outcome. In addition, we assessed potentially preserved effects after a 6-month open-label extension phase. Future studies are needed to determine potentially long-term effects of treatment with Galantamine. Another limitation was the high number of dropouts in the AD group. Part of these dropouts was due to insufficient scan quality resulting from movement artifacts. This suggests that DTI acquisitions demand a high compliance of the patients that may be limiting for examinations in more advanced stages of the disease. One could speculate that the effect of treatment may have masked some differences in FA decline between the AD patients and the HC subjects after 12 months. However, due to the lack of longitudinal FA data on 12-month untreated AD subjects, we presently can not answer this question.

In summary, Galantamine treatment slowed the decline of FA in the posterior body of the corpus callosum over a 6-month period compared to placebo, but this effect was not preserved after a 6-month open-label treatment of all AD patients. In addition, we found significant decline of FA in the left posterior cingulate over 12 months both in healthy aging and in AD. FA changes over time seemed to be more sensitive than structural changes in the corpus callosum to detect effects of aging and neurodegeneration. Future studies with more subjects and longer follow-up duration are needed to establish the precise pattern of changes in fiber tract integrity in cognitively healthy aging and AD-related neurodegeneration.

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Conflict of interest None.

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