approximately 30–35% (Petracca et al., 1996, 2001), and the remission rate in our study is much higher than that expected using placebo. In addition, in Cases 1, 2, and 3, previous antidepressant therapy was ineffective, and after milnacipran treatment their depression improved. Case 10 aggravated her depression by discontinuation of milnacipran and recovered by its resumption. These clinical observations argue against the concern regarding placebo effects, although a further double-blind study is needed.

In our study, no serious adverse reactions were observed, although adverse reactions were noted in three patients, who recovered quickly after discontinuation or a decreased dose. The average MMSE scores of the 11 patients did not change significantly with the treatment of milnacipran, although some variations in the alteration patterns of MMSE scores were observed in each patient. It has been reported that depressive AD patients taking TCAs such as imipramine and clomipramine demonstrate decreased MMSE scores compared with depressive AD patients taking a placebo (Teri et al., 1991; Petracca et al., 1996). Milnacipran has a lack of anti-cholinergic and sedative effects (Moret et al., 1985), and it is reported to be free from disruptive effects on cognitive function in elderly healthy volunteers (Hindmarch et al., 2000) as well as elderly depressive patients (Tignol et al., 1988). Our study suggests that milnacipran is also a safe medicine for the cognitive function of AD patients. However, it has been reported that dysuria is observed significantly more frequently with milnacipran than with TCAs and SSRIs (Puech et al., 1997; Tignol et al., 1988). Thus, it is important to watch for the development of dysuria during the treatment, especially in the case of elderly male patients.

Nowadays, SSRIs are recommended as a first-line medicine for depression in AD because of their efficacy and safety (Taragano et al., 1997; Lyketsos et al., 2003), although some studies have failed to show their efficacy (Petracca et al., 2001; Magai et al., 2000). It has been documented that in those aged 50 years or older, milnacipran has a tendency to be more effective than SSRIs such as fluvoxamine and paroxetine (Morishita and Arita, 2004). Furthermore, milnacipran has metabolic advantages over SSRIs, since the latter are metabolized via and inhibit cytochrome P450 isoenzymes and therefore have an important interactive potential, while milnacipran has no inhibition on any cytochrome P450 isoenzymes (Puozzo and Leonard, 1996), thus reducing the risk of adverse effects due to drug interactions. In addition, postmortem studies have shown that depression in AD has been associated with a selective loss of noradrenergic cells in the locus ceruleus (Zubenko et al., 1990). Taking these findings together, milnacipran is expected to be better than SSRIs with regard to efficacy and safety in treating depression in AD patients.

There were some limitations in this study. First, it was an open-label study and not a double-blind study with a placebo. Second, the number of patients was small. To confirm the efficacy of milnacipran in treating depression in AD patients, these limitations must be addressed in future studies.

In conclusion, our preliminary study suggests that milnacipran is a promising medicine for depression with Alzheimer's disease due to its efficacy and safety, although further studies, including a double-blind placebo control study, are needed.

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Efficacy of perospirone in the management of aggressive behavior associated with dementia

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Abstract

We assessed the efficacy of the serotonin dopamine antagonist, perospirone (PER) on aggressive and agitated behavior in demented patients. Eighteen outpatients with dementia diagnosed according to the DSM-IV were enrolled in this study, and their behavioral symptoms and cognitive impairments were assessed with the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) and Mini-Mental State Examination (MMSE) instruments for a period of 6 weeks. The maximum benefit of PER was achieved at a mean dose of 7.4 mg/day. Post-hoc analysis showed significant improvement in verbal outbursts after 4 weeks and in agitation scores after 4 and 6 weeks. Only 2 patients dropped out of the study, because of adverse effects, and no serious adverse effect was observed. The data suggest that PER is effective in improving aggressive and agitated behavioral symptoms in demented patients and that it is safe to use in elderly patients.

Keywords: Aggressive behavior; Behavioral and psychological symptoms of dementia; Dementia; Perospirone

1. Introduction

The behavioral and psychological symptoms of dementia (BPSD), which include aggression, agitation, screaming, wandering, hallucination, and delusion, have a negative impact on patients' activities of daily living and on caregivers' quality of life. Among the BPSD, aggression and agitation are especially serious and problematic symptoms for family caregivers, and these symptoms are often the primary cause of hospital admission or institutional care (American Psychiatric Association, 1997; Schneider et al., 1996). In addition, it is reported that aggression and agitation occur in about 20–80% of patients with Alzheimer's disease (AD) (Burns et al., 1990; Cooper et al., 1990; Lyketsos et al., 2000; Mega et al., 1996), and that patients with vascular dementia (VD) also often exhibit aggression and agitation (Cohen et al., 1993).

Although non-pharmacological interventions, such as the verbal environmental intervention, should be first-line for milder BPSD (American Psychiatric Association, 1997; Asada et al., 2000), many psychotropic agents (e.g. conventional antipsychotics, benzodiazepines, antidepressants, anticonvulsants, and beta-blockers) have been used to manage aggressive behavior. However, their efficacy is insufficient (Cohen et al., 1993; Schneider et al., 1996) and their use has been limited because of adverse effects such as orthostatic hypotension, arrhythmia, extrapyramidal symptoms (EPS), urinary retention, constipation, sedation, and delirium (Brodaty et al., 2003; De Deyn et al., 1999; Katz et al., 1990; Schneider et al., 1996). Recently, newer atypical antipsychotics, characterized by the serotonin (5-HT2) and dopamine (D2) antagonists, have been used for the treatment of aggression in demented patients. Double-blind, placebo-controlled trials have demonstrated that

Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease; BPSD, behavioral and psychological symptoms of dementia; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EPS, extrapyramidal symptoms; MMSE, Mini-Mental State Examination; VD, vascular dementia.

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some atypical neuroleptics, such as risperidone and olanzapine, have beneficial effects and are well tolerated (American Psychiatric Association, 1997; Brodaty et al., 2003; De Deyn et al., 1999; Schneider et al., 1996; Street et al., 2000) in the treatment of aggression and agitation in demented patients.

Perospirone(*cis*-*N*-[4-[4-(1,2-benzisothiazole-3-yl)-1-piperazinyl]butyl]cyclohexane-1,2-dicarboximide monohydrochloride) (PER) is a novel antipsychotic agent available in Japan for the treatment of schizophrenia. PER has a unique pharmacologic profile and acts as a serotonin-dopamine antagonist (Ourust and McClellan, 2001) as well as a partial serotonin (5-HT1A) agonist (de Paulis, 2002). Buspirone, which exhibits 5-HT1A agonist effects, has been reported to be effective in the treatment of aggressive and agitated behaviors associated with dementia (Cantillon et al., 1996; Hermann and Eryavec, 1993; Sakauye et al., 1993). Previous studies demonstrating buspirone efficacy led us to hypothesize that PER would be effective and safe in the treatment of aggressive and agitated behaviors in patients with dementia. We previously reported six patients with dementia, in whom PER reduced aggression (Sato et al., 2006). This article further presents the effects of PER on aggressive and agitated behaviors associated with dementia.

2. Methods

2.1. Patient population

A consecutive series of 18 patients were enrolled in this study. All patients were referred to the outpatient clinic of Ishizaki Hospital between April 2003 and March 2004. Eligibility criteria for the present study were: meeting the diagnosis of dementia of the Alzheimer's type (AD) or vascular type (VD) according to DSM-IV (American Psychiatric Association, 1994); and exhibiting moderate to severe agitation or aggressive behavior requiring pharmacotherapy for at least 1 month. This study protocol was approved by the Internal Review Board of Ishizaki Hospital. Patients and their caregivers provided written informed consent for study participation. However, if the patient was lack of ability to give it, we obtained it from only their caregivers. The patients underwent physical, neurologic, and laboratory examinations as well as brain magnetic resonance imaging. If they had a serious physical illness or a past history of mental disorders, they were excluded from the study.

2.2. Drug administration

Initially, the administration of PER started at 8 mg/day divided into morning and evening doses. If efficacy was deemed insufficient, the dose was increased weekly by 4 mg/day. However, if the initial dosage of PER was associated with any adverse effects, the dose was decreased weekly by 2 or 4 mg/day. The maximum effective dose was determined based on clinical judgment and the BEHAVE-AD scores.

Basically, the patients treated with PER monotherapy during the study period. However, 9 cases had previously received other medications (sodium valproate 6 cases, tiapride 4 cases, donepezil 3 cases, risperidone 1 case, olanzapine 1 case). In these cases, risperidone and olanzapine were discontinued, while the other previous medications were continued, and their dosage was unchanged during the study.

2.3. Study design and assessment instruments

The patients were assessed four times, at baseline and at 2, 4 and 6 weeks after the start of PER administration. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Clinical Dementia Rating (CDR) (Hughes et al., 1982) were used to assess the severity of cognitive deficits. Psychiatric and behavioral symptoms were evaluated with the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) instrument (Reisberg et al., 1987). The BEHAVE-AD scale measures behavioral disturbances in the seven major categories of "paranoid and delusional ideation," "hallucination," "activity disturbances," "aggressiveness," "diurnal rhythm disturbances," "affective disturbances," and "anxieties and phobias." In this study, the change in the total score and aggressiveness score including "verbal outbursts," "physical threats and violence," and "agitation" subscales of the BEHAVE-AD were evaluated.

2.4. Data analysis

Initial and end-point MMSE scores were compared using the Wilcoxon signed-rank test. Changes in the total BEHAVE-AD scores and each subscale of BEHAVE-AD at each time point were analyzed by means of repeated-measures analysis of variance (ANOVA). Dunnett test was used for Post-hoc analysis of ANOVA comparing baseline and 2, 4 and 6 weeks after scores. The significant level was set at $p<0.05$.

3. Results

The 6-week course of treatment was completed by 16 patients (88.9%); and 2 patients discontinued PER due to adverse effects. Table 1 shows the background characteristics of

Table 1
Demographic characteristics of 18 patients

	Variable
Age (years, mean ± SD) (range)	78.1 ± 6.6 (65–89)
Sex	
Male	7
Female	11
Diagnosis	
AD	15
VD	3
MMSE (mean ± SD)*	
Baseline	12.3 ± 6.3
End-point ($n=16$)	15.6 ± 8.9
CDR (mean ± SD)	2.2 ± 0.4
Perospirone dose (mg/day, mean ± SD) (range) ($n=16$)	7.4 ± 3.5 (2–12)

AD: Alzheimer's disease.
VD: vascular dementia.
MMSE: Mini-Mental State Examination.
CDR: Clinical Dementia Rating.
* Not significant, Wilcoxon signed-rank test.

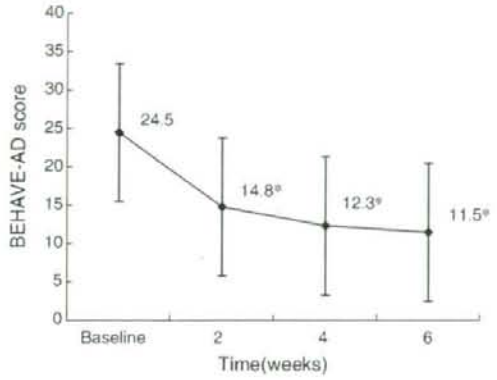

Fig. 1. Changes in total BEHAVE-AD score in patients with dementia during PER treatment. Post-hoc analysis showed significant total score reductions after 2, 4 and 6 weeks (*$p<0.05$).

the 18 patients analyzed. Their mean age was 78.1±6.6 (range 65–89) years. Of the original 18 patients, 11 (61.1%) were women. Among the patients analyzed, 15 (83.3%) had AD, while 3 (16.7%) had VD.

The patients' mean±SD baseline MMSE score was 12.3 ±6.3 (range 0–22) and the severity of dementia (on the CDR) was moderate (mean±SD 2.2±0.4, range 2–3). There were no significant differences in MMSE score between baseline and end-point. The maximum benefit of PER was seen in the dose range of 2–12 mg/day (mean dosage±SD 7.4±3.5 mg/day).

Two patients dropped out of this study because of adverse effects. One was an 82-year-old man diagnosed with AD. After receiving PER 8 mg/day for 2 weeks, he began to show an unsteady gait and tendency to stumble. The other patient was a 76-year-old man with AD. After 3-week administration of PER 12 mg/day, he had muscle weakness and fell repeatedly. Both patients quickly recovered from these adverse symptoms after the discontinuation of PER. In addition, although slight sedation (2 patients) and slight muscle weakness (5 patients) were observed during improvement of aggressive behavior, these adverse effects were quickly resolved after modification of dosage. No serious adverse effect was observed in this study.

Analysis of variables in the total BEHAVE-AD score showed a significant improvement with PER treatment ($F=6.03$, $p=0.007$). Post-hoc analysis revealed that there were significant score reductions at 2, 4 and 6 weeks after the initiation of PER administration (Fig. 1). The analysis also showed a significant improvement in the subscale scores for verbal outbursts after 6 weeks and for agitation after 4 and 6 weeks (Fig. 2). Physical threat and/or violence scores did not change significantly.

4. Case report

A 74-year-old woman with AD was referred to our outpatient unit for psychiatric evaluation. She had a 13-year history of gradually progressive cognitive impairment. She did not have any history of marked physical or psychiatric problems. At the age of 72 years, she easily became angry and excited by inconsequential matters and exhibited aggressive and violent behavior against her family. On her first visit, her total BEHAVE-AD and MMSE scores were 21 and 18, respectively. She was administered PER 8 mg/day. One week later, her agitation, excitement, and violent speech had markedly decreased. Her aggressive behavior disappeared in 4 weeks and she became better able to perform housekeeping tasks than previously.

5. Discussion

In the present study, PER at low doses (mean dose 7.4 mg/day) significantly improved aggression and agitation in demented patients. No serious adverse effects were observed in this study. Only 2 of 18 patients dropped out of the study because of adverse effects such as muscle weakness and unsteady gait, which were not serious and resolved quickly after the discontinuation of PER. In addition, anticholinergic effects, EPS, or decline in cognitive function as measured using the MMSE were not observed. PER displays the characteristics of

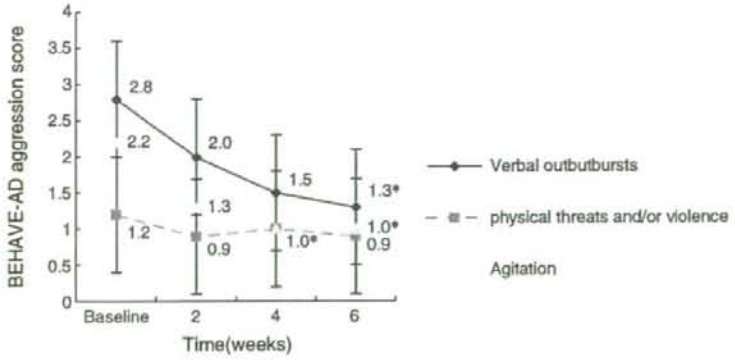

Fig. 2. Changes in BEHAVE-AD aggression scores in patients with dementia during PER treatment. Post-hoc analysis showed significant reductions after 6 weeks (*$p<0.05$) in verbal outburst and, after 4 and 6 weeks (*$p<0.05$) in agitation scores.

an atypical antipsychotic agent, and is better tolerated than haloperidol (Onrust and McClellan, 2001; de Paulis, 2002). In particular, EPS tended to occur less often and were generally milder with PER than with haloperidol (Murasaki et al., 1997) or mosapramine (Kudo et al., 1997). Ichikawa et al. (2001) pointed out that 5-HT1A agonists reduce neuroleptic adverse effects such as EPS. Moreover, some studies reported that PER therapy improved psychotic symptoms with few side effects (Kudo et al., 1997; Murasaki et al., 1997; Masui et al., 2003) in elderly (more than 60 years of age) patients with schizophrenia. The results of this study suggest that PER is well tolerated also in elderly demented patients.

It is noteworthy that low-dose PER exerted its effects immediately, as shown by the reduction in the BEHAVE-AD aggression score. The scores for verbal outbursts and agitation were reduced within 4 or 6 weeks after the initiation of treatment.

De Deyn et al. (1999) pointed out that risperidone may have a direct effect on aggression in treating dementia-related behavioral problems. They explained that the antipsychotic effects of risperidone caused by serotonin-dopamine blockade improved behavioral disturbances in demented patients. Furthermore, PER is not only a serotonin-dopamine antagonist but also a serotonin 5-HT1A partial agonist. A growing body of evidence suggests that there is a correlation between decreased cerebrospinal fluid serotonin levels and aggressive behavior (Lai et al., 2002; Linnoila et al., 1983; Mintzer, 2001; Stanislav et al., 1994). Lai et al. (2002) reported that 5-HT1A receptor density in the brains of Alzheimer's disease patients correlated negatively with the maladaptive behavior of aggression. There are numerous reports that buspirone, a serotonin 5-HT1A partial agonist, inhibits aggression and agitation in demented patients (Cantillon et al., 1996; Hermann and Eryavec, 1993; Sakauye et al., 1993). Cantillon et al. (1996) conducted a double-blind trial of buspirone (15 mg/day) and haloperidol (1.5 mg/day). They reported that the tension subscale scores of the Brief Psychiatric Rating Scale in patients receiving buspirone were more significantly reduced than those in patients receiving haloperidol. They concluded that some behavioral symptoms, especially agitation, observed in demented patients may be linked to a serotonergic system and be well managed with the 5HT-1A partial agonist buspirone. However, randomized placebo-controlled trials are required to determine the efficacy of buspirone on agitation and aggressive behavour in demented patients.

Taking the cumulative results together, it can be assumed that PER, acting as a serotonin-dopamine antagonist as well as serotonin 5-HT1A partial agonist, is effective and safe in the management of aggression and agitation in demented patients due to its unique pharmacologic properties.

In April 2005, The Food and Drug Administration (2005) issued a warning that the use of atypical antipsychotic medications in elderly patients with dementia may be associated with an increased mortality, while Liperoti et al. (2005) suggested that there was no increased risk for arrhythmias or cardiac arrest with the use of atypical antipsychotics in a case-control study. Therefore, before the start of pharmacotherapy with atypical antipsychotics for elderly patients with dementia, it is inevitable to carefully judge the necessity of the pharamacotherapy in consideration of the balance between benefits and risks associated with the therapy, and to carefully monitor the occurrence of adverse effects during the therapy.

There were some limitations in this study. First, it was an open-label study and not a double-blind study with a placebo. Thus, our findings cannot be generalized to all demented patients with agitation and aggressive behavior. Second, the number of patients was small and included those with both AD and VD. However, De Deyn et al. (1999) reported that there were no differences among diagnostic groups in the results of risperidone treatment for aggressive behavior. When we divided our patients into the AD and VD groups and analyzed each subgroup, the results demonstrated that aggression and agitation were significantly reduced only in AD patients, while VD patients failed to show a significant difference in those scores. This result may be attributable to the small number of patients. To confirm the efficacy of PER in treating aggression and agitation in demented patients, these limitations must be addressed in future studies.

6. Conclusion

Although this was a preliminary, open study, it appears that the serotonin-dopamine antagonist PER may be effective in controlling the aggressive and agitated behavior associated with dementia and be well tolerated. More patients must be analyzed in a randomized, placebo-controlled trial of the efficacy of PER for the treatment of aggression and behavioral disturbances associated with dementias.

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Relationship between antisocial behavior and regional cerebral blood flow in frontotemporal dementia

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Objective: **To examine the relationship between antisocial behaviors and reduction of regional cerebral blood flow (rCBF) in patients with frontotemporal dementia (FTD).**

Methods: **Brain perfusion single photon emission computed tomography (SPECT) was performed in 22 patients with FTD and 76 age-matched healthy volunteers. The statistical analysis was conducted using the SPM99 software. The antisocial behavioral symptoms were assessed independently by three geriatric psychiatrists, who had not been given the information of the SPECT images.**

Results: **Compared with normal controls, FTD patients showed significant reduction of rCBF in the widespread frontal cortical areas. The correlation analysis showed that antisocial behavioral symptoms are associated with reduction of rCBF in the orbitofrontal cortex.**

Conclusion: **The functional decline of orbitofrontal cortex is related to antisocial behavioral symptoms in patients with FTD.**

Keywords: Frontotempotal dementia; Antisocial behaviors; SPECT; Regional cerebral blood flow

Introduction

Frontotemporal lobar degeneration (FTLD) is composed of a spectrum of dementing disorders with degeneration of the frontal lobes, the anterior temporal lobes, or the both (Neary et al., 1998). Frontotemporal dementia (FTD) is the main FTLD syndrome and manifests as prominent personality and behavioral disturbances. Behavioral symptoms such as antisocial behaviors are observed in patients with FTD, and presence of them often makes it difficult to care for such patients. Moreover, such symptoms will prompt their institutionalization. Development of appropriate management methods for the behavioral symptoms may lessen the care-giving burden and lead to postponement of institutionalization. Evaluation of antisocial behavioral symptoms in FTD patients must be the basis for such development.

Systematic functional neuroimaging studies using single photon emission computed tomography (SPECT) or positron computed tomography (PET) have demonstrated that patients with FTD show hypoperfusion of anterior cerebral cortex with relative sparing of posterior cortex (Ishii et al., 1998; Miller and Gearhart, 1999; Charpentier et al., 2000; Hodges, 2001; Lojkowska et al., 2002). These evidences have become useful to make clinical diagnosis of FTD. However, systemic studies examining the association between antisocial behavior and regional cerebral blood flow (rCBF) in patients with FTD are few and mostly based on visual inspection (Mychack et al., 2001) using the region of interest (ROI) method. Although this approach has been popular, accuracy depends on the observer's experience and working-hypothesis, thus such evaluation is apt to lack morphological accuracy of brain regions and leaves large areas of the brain unexplored. An alternative method is voxel-by-voxel analysis of stereotactic space, which adopts the principle of data-driven analysis and can avoid subjectivity. Such an approach is well established in the field of functional neuroimaging analysis; a software package known as statistical parametric mapping (SPM), that not only spatially normalizes PET or SPECT images to a standardized stereotactic space but also statistically analyzes group of images, has been

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developed (Frackowiack et al., 1997). The objective of this study is to evaluate the relationship between antisocial behavior and rCBF abnormalities in FTD patients by application of SPM to brain perfusion SPECT images.

Materials and methods

Subjects

Twenty-two consecutive patients (14 men, 8 women; age range, 58–74 years; mean age, 62.9 years) newly referred to the memory disorder clinic of the National Center Hospital for Mental, Nervous, and Muscular Disorders, National Center of Neurology and Psychiatry, Tokyo, Japan, between 1994 and 2003, were enrolled. The mean age at onset was 57.5 years (range, 47–68 years). The clinical diagnosis of FTD was based on the Lund and Manchester criteria and the more recent consensus criteria (Neary et al., 1998) after detailed examination, including magnetic resonance imaging (MRI), SPECT, and neuropsychological examination. The clinical criteria of FTD are reported to have high diagnostic specificities (Rosen et al., 2002). The neuropsychological battery consisted of tests that have been shown to be useful in the differential diagnosis of FTD and other dementia. The following tests were employed: Mini Mental State Examination (MMSE) (Folstein et al., 1975), Revised Version of Hasegawa's Dementia Scale (HDS-R) (Imai and Hasegawa, 1999), Raven's Colored Progressive Matrices (RCPM) (Hodges, 1993), Digit Span Task, learning of a list of 10 words and Story Recall (Hodges, 1993), Ray-Osterrieth Complex Figure Test (Hodges, 1993), Stroop Test, and Trail Making Test (Anne and Stephan, 1969). All tests were performed and scored according to the standard protocols. The demographic characteristics of the patients including age, sex, MMSE, and HDS-R at the time of the first evaluation are listed in Table 1.

Seventy-six normal healthy volunteers (37 men, 39 women; age range, 67–87 years; mean age ± SD, 71.0 ± 7.1 years) were also studied. They had no neurologic or psychiatric disorders, including alcoholism, substance abuse, atypical headache, head trauma with loss of consciousness, and asymptomatic cerebral infarction detected by T2-weighted MRI. They did not significantly differ in age, sex, or education from the FTD patients.

SPECT image data of the normal healthy volunteers in the present study have previously been reported (Imabayashi et al., 2004).

Written informed consent was obtained from all the participants or their family according to the Declaration of Helsinki. The study was approved by the Ethical Committee of the National Center of Neurology and Psychiatry.

Assessment of antisocial behaviors

Semi-structured interviews with the family members were conducted to obtain information regarding the behaviors of interest. For the interview, we used the modified version of Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). By applying the method of NPI, which assesses the Behavioral and Psychological Symptoms of Dementia (BPSD) in patients basically with Alzheimer's disease, the antisocial behaviors were evaluated as follows. The frequency and severity were respectively graded for the 5 behavioral symptoms based on the study by Miller et al. (1997): (1) stealing, (2) traffic accident (e.g. hit and run), (3) physical assault, (4) sexual comments/advances, and (5) public urination. The frequency was assessed on the basis of the observation during the previous 2 months (1 = once in 2 months, 2 = once per month, 3 = 2 or 3 times per month, 4 = once or more every week). The severity was assessed according to the degree of patient's awareness of his or her own antisocial behaviors (0 = full awareness, 1 = moderate awareness, 2 = mild awareness, 3 = no awareness). The NPI assesses BPSD on the basis of both frequency and severity; BPSD scores are obtained by multiplying the severity and the frequency scores. Therefore, the frequency and the severity scores were multiplied for each behavior, respectively, and then summed (maximum score = 60) to be used as covariate factor for SPM analysis in this study.

Table 1
Demographic variables of FTD patients

n	22	
Age (year)	62.9 (5.9)	Range: 52–74
Sex (M/F)	14/8	
Duration of illness (years)	4.1 (1.8)	Range: 2–9
Mini mental state examination (MMSE)	14.8 (7.7)	Range: 0–26
Hasegawa's dementia scale revised (HDS-R)	13.8 (7.1)	Range: 0–24
Raven's colored progressive matrices (RCPM)	22 (8.7)	Range: 5–33
Digit span		
Forward	4.6 (1.0)	Range: 3–7
Backward	2.3 (1.5)	Range: 0–4
Word learning (10 words)		
Immediate recall	1.6 (1.6)	Range: 0–4
Delayed recall (30 min)	1.1 (1.7)	Range: 0–4
Story recall (15 elements)		
Immediate recall	2.3 (2.4)	Range: 0–7.5
Delayed recall (30 min)	0.2 (0.6)	Range: 0–2
Ray-Osterrieth complex figure test		
Copy	27.5 (11.0)	Range: 5.5–36
Immediate recall	4.9 (6.9)	Range: 0–23
Delayed recall (30 min)	3.6 (7.1)	Range: 0–24
Stroop test		
Dot	58 (sec) (44.5)	Range: 19–132 (sec)
Word	120.7 (sec) (82.2)	Range: 27–165 (sec)
Word-dot	63.1 (sec) (47.4)	Range: 38–134 (sec)
Trail making		
Set A	335.6 (sec) (130.2)	Range: 255–621 (sec)

Note. Values are expressed as mean and (standard deviation). M = male, F = female, *n* = size, sec = second.

These antisocial behaviors were assessed independently by three geriatric psychiatrists (TA, SH, NK), who had not been given the information of the SPECT images. Whenever the scores were different among the psychiatrists, the mean score of the three psychiatrists was employed.

Brain SPECT procedure

Each subjects received an intravenous injection of 600 MBq of ^{99m}Tc-ECD while lying supine with eyes closed in a dimly lit, quiet

Table 2
Scores of antisocial behavior

Behavior	Scores of antisocial behavior	n
	Mean (SD; range)	
Stealing	6.38 (3.42; 0–12)	8/22
Traffic accident	3.46 (3.46; 0–12)	4/22
Physical assault	4.50 (4.34; 0–12)	8/22
Sexual comments/advances	7.67 (2.31; 0–9)	3/22
Public urination	3.67 (1.86; 0–6)	6/22
Total	9.67 (6.82; 0–25)	18/22

n = number of subjects who showed the behavior. n for total means of subjects who showed at least one of the behavior.

room. Ten minutes after injection, brain SPECT was performed using a triple-headed gamma camera (MULTISPECT 3; Siemens, Hoffman Estates, IL) equipped with high-resolution fanbeam collimators. For each scan, projection data were obtained in 128 × 128 matrix, and camera was rotated through 120° with 24 steps of 50 s per step. SPECT images were reconstructed using a Shepp and Logan Hanning filter at 0.7 cycles per centimeter. Attenuation correction was performed using Chang's method.

Image analysis

Voxel-based analysis of SPECT data was performed using Statistical Parametric Mapping 99 (SPM99) (Wellcome Department of Cognitive Neurology, London, U.K.) run on MATLAB (The MathWorks, Inc., Sherborn, MA). The images were spatially normalized to an original template for ^{99m}Tc-ECD using SPM99 (Ohnishi et al., 2000). Images were then smoothed with a gaussian kernel of 12 mm in full width half maximum (FWHM). The washout correction for ^{99m}Tc-ECD was not applied, because brain SPECT was started at 10 min after injection.

Statistical analysis of SPECT data

The processed images were analyzed using SPM99 as described by Ohnishi et al. (2000). The effect of global differences in CBF among scans was removed by proportional scaling with the gray matter threshold at 0.5. The subject and the covariate effects were estimated with a general linear model at each voxel. To test hypotheses about regional population effects, the estimates were compared using linear compounds or contrasts. The resulting sets of t values constituted statistical parametric maps (SPM$\{t\}$). The SPM$\{t\}$ were transformed to unit normal distribution (SPM$\{Z\}$) and thresholded at $P < 0.005$. To correct for the multiple non-independent comparisons that were inherent in this analysis, the resulting foci were characterized for their spatial extent. This characterization, regarding probability, is to assess whether the region of the observed number of voxels could have occurred by chance over the entire volume analyzed.

Correlation analysis was performed to study the relationship between rCBF changes and antisocial behavioral profiles. The correlations between the scores of antisocial behaviors and CBF, MMSE scores and CBF, and the duration of illness and CBF were respectively computed on a pixel-by-pixel basis by covariance analysis. Gender and age were treated as nuisance variables.

Statistical analysis of antisocial behavioral symptoms

Statistical data analysis of antisocial behavioral symptoms in FTD patients was performed using the R software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Antisocial behavioral symptoms in FTD patients

Eighteen of the 22 FTD patients had a history of antisocial behavior. The mean score of the antisocial behavior was 9.67 ± 6.82 (range, 0–25). The mean value of Cohen's κ coefficient of all the items for inter-rater was 0.82 (range, 0.67–0.91), which appears to be satisfactory. Table 2 shows the subscale score of the 5 antisocial behaviors of the patients.

Changes in rCBF in FTD patients

Decreases of rCBF in the FTD patients compared with the normal healthy volunteers were identified in the superior, the middle, and the inferior frontal gyrus. In addition, there were reductions of rCBF in the subcortical structures, particularly the caudate nuclei and the thalami (Fig. 1).

As a result of the correlation analysis, a positive correlation was observed between the scores of antisocial behavioral symptoms

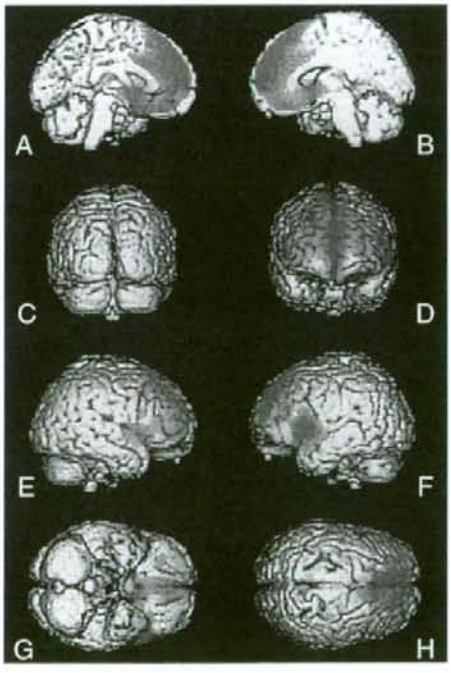

Fig. 1. Result of SPM analysis (normal healthy volunteers vs. FTD patients). The colored areas show the regions with lower perfusion in the FTD patients compared with the normal healthy volunteers ($P < 0.005$, uncorrected for multiple comparisons). View from medial right (A), medial left (B), posterior (C), anterior (D), right lateral (E), left lateral (F), inferior (G), and superior (H). Rt = right, Lt = left.

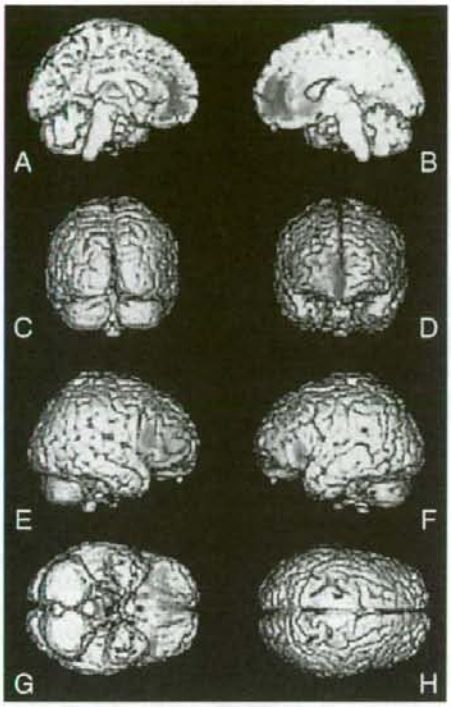

Fig. 2. Result of SPM analysis: the areas of regional cerebral blood flow that correlated with the score of antisocial behaviors in patients with FTD. Representation in stereotaxic space of cerebral regions that correlated positively with the score of antisocial behaviors ($P < 0.005$, uncorrected for multiple comparisons), displayed on 3D-surface anatomical template. View from medial right (A), medial left (B), posterior (C), anterior (D), right lateral (E), left lateral (F), inferior (G), and superior (H). Rt = right, Lt = left.

and the rCBF in partial areas of the orbitofrontal cortex (Fig. 2): the bilateral inferior frontal gyri (Broadmann area, BA 47), the left anterior cingulated gyrus (BA 32), the right caudate nucleus, and the left insula (BA 13). The results were similar even when the scores were independently analyzed for the severity scores and the frequency scores. We searched for a negative correlation between rCBF and the scores of antisocial behavioral symptoms, but no significant finding was found in any of the regions.

On the other hand, the MMSE scores positively correlated with rCBF in the bilateral posterior cingulate gyri (BA 31), the right parahippocampal gyrus (BA 30), and the right insula (BA 13) (Fig. 3). Furthermore, a correlation between the duration of illness and rCBF was observed in the right middle frontal gyrus (BA 47) and the bilateral inferior frontal gyri (BA 46, 47), as well as the left superior temporal gyrus (BA 22), the middle temporal gyrus (BA 21), and the parahippocampal gyrus (BA 27) (Fig. 4). The two analyses have resulted to have BA 47, which constitutes the orbitofrontal cortex, in common.

Discussion

FTD is the third most common neurodegenerative dementia syndrome after Alzheimer's disease and dementia with Lewy bodies. Although criteria for clinical diagnosis of FTD, such as the Lund and Manchester criteria and the more recent consensus criteria (Neary et al., 1998), have high sensitivities and specificities for diagnosing FTD (Lopez et al., 1999), clinicians frequently fail to recognize FTD or misdiagnose it as Alzheimer's disease, manic-depressive illness, schizophrenia, depression, hypochondriasis, obsessive–compulsive disorder, or sociopathy (Litvan et al., 1997; McKhann et al., 2001). The core diagnostic features of FTD are early loss of personal and social awareness, early loss of insight, early decline in social interpersonal conduct, impaired regulation of personal conduct, and emotional blunting. Thus, the most common and early symptom of FTD can be summarized as a decline in social interpersonal conduct (Neary et al., 1998).

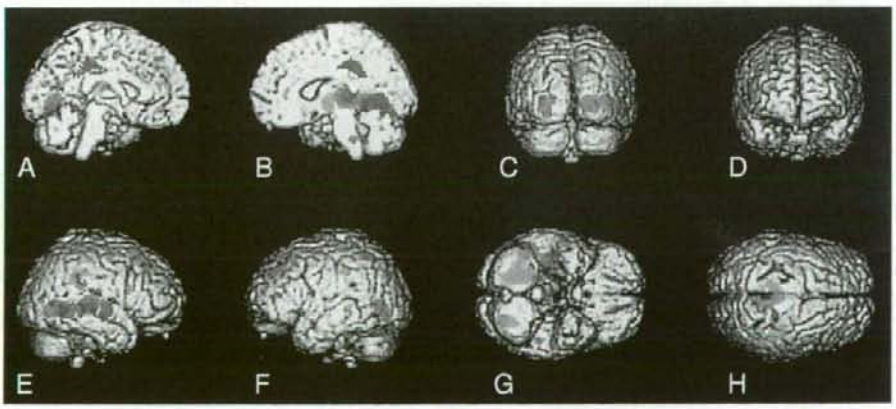

Fig. 3. Result of SPM analysis: the areas of regional cerebral blood flow that correlated with the score of MMSE in patients with FTD. Representation in stereotaxic space of cerebral regions that correlated positively with the score of MMSE ($P < 0.005$, uncorrected for multiple comparisons), displayed on 3D-surface anatomical template. View from medial right (A), medial left (B), posterior (C), anterior (D), right lateral (E), left lateral (F), inferior (G), and superior (H). Rt = right, Lt = left.

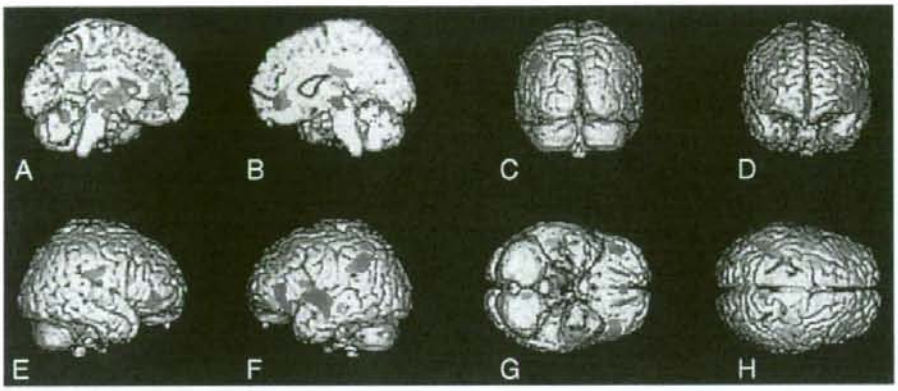

Fig. 4. Result of SPM analysis: the areas of regional cerebral blood flow that correlated with the duration of illness in patients with FTD. Representation in stereotaxic space of cerebral regions that correlated positively with the score of the duration of illness ($P < 0.005$, uncorrected for multiple comparisons), displayed on 3D-surface anatomical template. View from medial right (A), medial left (B), posterior (C), anterior (D), right lateral (E), left lateral (F), inferior (G), and superior (H). Rt = right, Lt = left.

Antisocial behavior, from Pick's case report (Pick, 1892), has been reported in association with FTD for decades (Gustafson, 1987; Lindau et al., 2000; Hokoishi et al., 2001; Hodges, 2001). They include stealing, traffic accident, physical assault, sexual comments/advances, public urination, and so on. In fact, 18 of 22 (82%) FTD patients of the present study showed such behaviors. This figure is similar with the results reported in the previous studies (Miller et al., 1997).

Although a variety of scales to rate the Behavioral and Psychological Symptoms of Dementia (BPSD) observed in patients with AD is reported, to our knowledge, no scale is available for the assessment of BPSD observed in FTD patients. Thus, we employed the assessment method of the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) for AD patients. The NPI assesses BPSD on the basis of both frequency and severity. The focused symptoms are derived from the report by Miller et al. on BPSD of FTD patients.

In the comparison between the FTD patients and the normal healthy volunteers, a significant reduction of rCBF in the widespread frontal lobes was observed in the former. No other region with significantly decreased rCBF was found. The results seem to be compatible with the neuropathological and functional changes of the disease and are consistent with the findings of previous FDG-PET studies (Ishii et al., 1998; Salmon et al., 2003; Grimmer et al., 2004). Although the diagnosis of the present study was not confirmed by postmortem examination, the result appears to support the validity of our diagnosis of FTD, the frontal variants of FTLD.

Regarding the frontal lobe function, it is well known that prefrontal cortex dysfunction is linked to social misconduct (Harlow, 1868; Eslinger, 1999; Bassarath, 2001; Brower and Price, 2001). Stuss and Benson (1986) have noted that orbitofrontal pathology would most frequently be associated with disinhibition, facetiousness, sexual and personal hedonism, and lack of concern for others. Moreover, a recent PET study evaluating patients with various frontal lobe pathologies (including FTD) (Sarazin et al., 1998) with ROI approach has revealed that the behavioral abnormalities are associated with metabolic decline of orbitofrontal cortex. Also, it is now well known that prefrontal cortex plays a major role in executive function and working memory (Lezak, 1983). Anterior cingulate gyrus and cortex are associated with sustained attention (Posner and Petersen, 1990). Although dysfunction of the orbitofrontal cortex plays a major role, failure of these cognitive functions may be functionally involved together and contribute to the development of the antisocial behaviors.

The highlight of our voxel-by-voxel SPECT study using the SPM technique is the finding that the decrement of orbitofrontal rCBF is associated with antisocial behaviors as well as the duration of illness in the patients with FTD. MMSE score, on the contrary, did not correlate with rCBF of the orbitofrontal cortex. A recent longitudinal study in FTD has shown that the metabolic activity in the orbitofrontal cortex decreases as the disease progresses (Grimmer et al., 2004). In this multicenter study, the conjunction analysis using SPM has demonstrated that the metabolic impairment of orbitofrontal cortex is affected in every FTD patients (Grimmer et al., 2004). Although this study did not examine the association between metabolic impairment of orbitofrontal cortex and antisocial behaviors, it may support the results of the present study to some extent. Taking these findings together, the association between antisocial behaviors and rCBF of orbitofrontal cortex in FTD may appear to be robust.

We must refer to several limitations of the present study. As described above, we did not pathologically confirm the clinical diagnosis. However, clinical criteria of FTD are reported to have high specificities (Rosen et al., 2002). SPM analysis for SPECT study also has limitations; it can be affected by partial volume effect (PVE). Matsuda et al. (2002) have established a PVE correction method for SPECT study and reported its utility. In this study, however, we did not correct the PVE. In future study, correlation analysis between antisocial behavior and rCBF using PVE correction is necessary. We also attempted to clarify the relationship between the duration of illness and rCBF, but since the onset of FTD is insidious and its progression is gradual, the duration of illness remained uncertain (Neary et al., 1998). Moreover, the number of the subjects was relatively small. Future studies should overcome these limitations.

In summary, the orbitofrontal dysfunction appears to play a major role in the emergence of antisocial behaviors in FTD patients.

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Age-related degeneration of corpus callosum measured with diffusion tensor imaging

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The corpus callosum is the major commissure connecting the cerebral hemispheres, and there is evidence of its change with aging. The sub-regions of the corpus callosum (genu, rostral body, anterior midbody, posterior midbody, isthmus, splenium) respectively comprise fibers connecting heteromodal- and unimodal-associated cortical regions, and it is known that abnormalities of the corpus callosum are correlated with abnormalities in cognition and behavior. Yet, little is known about changes in the tissue characteristics of its sub-regions. We assessed age-related changes in fractional anisotropy and mean diffusivity in the sub-regions of the corpus callosum using diffusion tensor imaging. We studied 42 healthy right-handed individuals aged 21 – 73 years. There were no significant interactions of sex × region. Age has significant negative correlation with fractional anisotropy in the genu ($P < 0.001$), rostral body ($P < 0.001$), and isthmus ($P = 0.005$). Fractional anisotropy of the anterior midbody was correlated negatively with age at a trend level ($P = 0.022$). Age was significantly positively correlated with mean diffusivity in the genu ($P = 0.001$), rostral body ($P = 0.002$), anterior midbody ($P = 0.001$), and isthmus ($P = 0.001$). Age-related changes were detected in the sub-regions where their projection areas are thought to be vulnerable to normal aging. This suggested that fractional anisotropy and mean diffusivity values of the corpus callosum sub-regions could serve as markers of disturbance across the respective projection areas.

Keywords: Corpus callosum sub-region; Diffusion tensor imaging; Fiber tract; Projection area

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Introduction

The corpus callosum is the major white matter tract that crosses the interhemispheric fissure in the human brain. It consists of approximately 200 million interhemispheric fibers, most of which connect homologous regions of the cerebral cortex (Biegon et al., 1994). The corpus callosum plays an integral role in relaying sensory, motor, and cognitive information between homologous regions in the two cerebral hemispheres (Mazziotta et al., 2001). The corpus callosum is heterogeneous in its microstructural composition (Aboitiz et al., 1992), heterotopic in its anteroposterior cortical connectivity (de Lacoste et al., 1985; Seltzer and Pandya, 1986; Schwartz and Goldman-Rakic, 1991), and differentially susceptible to aging (Aboitiz et al., 1996). Furthermore, specific regions of the corpus callosum (i.e., genu, rostral body, anterior midbody, posterior midbody, isthmus, splenium) are respectively comprised of fibers connecting heteromodally and unimodally associated cortical regions (Huang et al., 2005; Witelson, 1989), and the corpus callosum sub-regions are assumed to have individually different roles of cognition (Baird et al., 2005; Colvin et al., 2005; Madden et al., 2004) that were revealed by the use of diffusion tensor imaging (DTI). Since the corpus callosum sub-regions have their respective original characteristics, the age-related changes they undergo are of particular interest.

Using magnetic resonance imaging (MRI), the morphology of the corpus callosum has been extensively studied. Such studies have shown that abnormalities of the corpus callosum are correlated with abnormalities in cognition (Duara et al., 1991) and behavior (Yazgan and Kinsbourne, 2003) and that callosal features becoming modified during aging indicates modest thinning of its cross-sectional area, measured on midsagittal sections, through young to middle adulthood (Pfefferbaum et al., 1996) with accelerated thinning in older age (Driesen and Raz, 1995; Salat et al., 1997). The gross morphology of the corpus callosum revealed on

conventional MRI, however, does not necessarily reflect the underlying quality of tissue in its microstructure, which is measurable with DTI (Le Bihan, 1995, 2003). DTI allows white matter tracts to be imaged in vivo (Basser and Pierpaoli, 1996) and provides measures of both diffusivity (a measure of mean diffusivity (MD), averaged in all spatial directions) and fractional anisotropy (FA), a measure of the directionality of diffusion (Pierpaoli and Basser, 1996). Degeneration of white matter tracts would be expected to result in a reduction in FA, owing to a loss of directionality of diffusion as a result of the loss of myelin and axonal membranes and possibly due to Wallerian degeneration (Kantarci et al., 2001). With the use of fiber orientation information, one can identify various axonal tracts within the homogeneous-looking white matter. White matter fibers in the brain are essential for linking functional regions. This capability of DTI may be useful for studying the effects of development, aging, and diseases on specific white matter tracts of interest.

There have been several reports on the topic of DTI and aging, and some studies have examined the change of FA in the corpus callosum (Abe et al., 2000; Pfefferbaum et al., 2000; Salat et al., 2005; Sullivan et al., 2001; Hasan et al., 2004; Bhagat and Beaulieu, 2004; Nusbaum et al., 2001; Chepuri et al., 2002). Yet, little is known about changes in the tissue characteristics of the corpus callosum sub-regions. In this study, we investigated the age-related changes of FA and MD in the corpus callosum sub-regions. A full characterization of the patterns of the corpus callosum sub-region microstructure deterioration occurring in normal aging would lead to an understanding of the pathophysiology of normal cognitive decline and would provide a proper background for interpreting the observed changes in neurodegenerative diseases of the aged beyond those of normal aging.

Methods and materials

Subjects

Forty-two healthy individuals (32 men, 10 women; mean age: men 47.3 ± 19.5 years, 21 to 72 years; women 43.0 ± 18.1 years, 24 to 73 years, see Table 1) participated in this study. All individuals were right-handed according to the Edinburgh inventory (Oldfield, 1971). Conventional MR images of all subjects were acquired to exclude brain morphometric abnormalities. Subjects with neurological illness, head trauma, loss of consciousness, or psychiatric disorder were also excluded. This study was approved by the Ethics and Radiation Safety Committees of the National Institute of Radiological Sciences, Chiba, Japan. All participants gave written informed consent.

DTI data acquisition and processing

Images were acquired by Philips Intera, 1.5 T (Philips Medical Systems, Best, The Netherlands). Diffusion-weighted images were acquired by single-shot echo-planar imaging with sensitivity-encoding (SENSE), parallel-imaging scheme (reduction factor = 2.0, TR = 8645 ms, TE = 96 ms). The imaging matrix was 96 × 96, with a field of view of 240 × 240 mm^2 (nominal resolution, 2.5 mm) zero-filled to 256 × 256 pixels, 60 continuous transverse slices, slice thickness 2.5 mm, b value 0 s/mm^2 (1 measurement) and 700 s/mm^2. Diffusion was measured along six non-collinear directions: $(x, y, z) = [(1, 0, 0), (0, 1, 0), (0, 0, 1), (-1/\sqrt{2}, 1/\sqrt{2}, 0), (1/\sqrt{2}, 0, -1\sqrt{2}), (0, 1/\sqrt{2}, -1/\sqrt{2})]$. The diffusion gradient pulse duration and separation were δ = 24 ms and Δ = 24 ms, respectively. Acquisition time per data set was approximately 80 s, and total scan time was 40 min. To enhance the signal-to-noise ratio, acquisition was repeated 30 times. We evaluated signal-to-noise ratio in subjects under 30 years of age (n = 13) (see Statistical analysis). The averaged images obtained with a b value of 0 s/mm^2 were used for signal-to-noise determination (Hunsche et al., 2001). Signal-to-noise ratio was defined as the quotient of the mean signal intensity in image of b value of 0 s/mm^2 and the standard deviation (SD) within centrum semiovale (Ogura et al., 2003). We did not use SD in the background noise because parallel imaging methods such as SENSE reduce the background noise level. Average signal-to-noise ratio was 22.0. This is large enough to accurately estimate parameters derived from diffusion tensor imaging, eigenvalues, and anisotropy in particular (Hunsche et al., 2001).

The DTI data sets were transferred to a workstation, and DTI quantification was preceded by eddy current correction. Each directional volume from the diffusion data set was resampled to the b = 0 image to correct for remaining eddy current distortion (Kim et al., 2002) as well as to correct for participant motion. These data realignments were performed with the use of software written in IDL Version 5.5 Win32 (×86) (Research Systems Inc., 2001). After these processes, we analyzed these data sets by using DtiStudio (H. Jiang, S. Mori; Johns Hopkins University) after all diffusion-weighted images were visually inspected for apparent artifacts due to subject motion and instrument malfunction. From b = 0 and six diffusion-weighted images, six maps of the apparent diffusion coefficient (ADC) were calculated. Solving six simultaneous equations with respect to ADC_{xx}, ADC_{xy}, etc. yielded the elements of the diffusion tensor. The diffusion tensor was then diagonalized, yielding eigenvalues $\lambda_1, \lambda_2, \lambda_3$, as well as eigenvectors that define the predominant diffusion orientation. Based on the eigenvalues, FA and MD were calculated on a voxel × voxel basis (Pierpaoli and Basser, 1996; Basser and Pierpaoli, 1998; Basser and Jones, 2002).

FA was used for the anisotropy map. The eigenvector associated with the largest eigenvalue was used as an indicator of fiber orientation. For 3D tract reconstruction, fiber assignment by means of continuous tracking, called the FACT method (Mori et al., 1999), was used. Fiber tractography was obtained with the threshold value of fiber tracking termination as FA = 0.2 and trajectory angle = 50° (Huang et al., 2005). To reconstruct tracts of interest, we used a multiple region-of-interest (ROI) approach (Mori et al., 2002). Firstly, tracking was performed from all pixels inside the brain, and results that penetrated the manually defined ROIs were assigned to the specific tracts associated with the ROIs (Wakana et al., 2004). When multiple ROIs were used for selecting tracts in the corpus callosum sub-regions, we used the CUT operation (Fig. 1) with the DtiStudio (Huang et al., 2004). ROIs for measurement of the corpus callosum sub-regions were placed using landmarks adopted previously (Witelson, 1989). The rostrum was

Table 1
Age–gender distribution of each age group

Age group	Male	Female
21–38 years	15	4
39–56 years	9	3
57–73 years	8	3

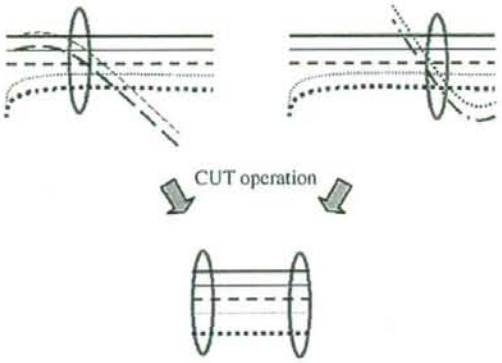

Fig. 1. CUT operation for fractional anisotropy and mean diffusivity. Diagram shows the CUT operation in this study. Two ROIs (circles) were placed on the anatomic landmarks of Fig. 2. When the CUT operation is used, tracts that run through the ROIs are selected.

treated as an extension of the genu as Witelson had pointed out in his article. In summary, six callosal subdivisions were defined as follows. The maximal length of the corpus callosum was taken as the line joining the most anterior and posterior points of the callosum. Perpendiculars to this axis were drawn at specific arithmetic divisions, resulting in six callosal segments (see Fig. 2). The ROIs of each region were plotted on the two parallel parasagittal planes located 2.8–8.4 mm (3–9 planes) on either side of the midsagittal corpus callosum. The ROIs were drawn directly onto the FA maps (Sullivan et al., 2005). The size of the fibers depended on the configuration of each region, with the fibers

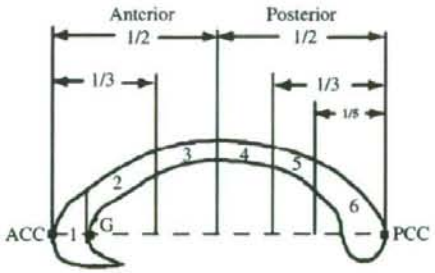

Fig. 2. Corpus callosum sub-regions. Diagram of the midsagittal view of the corpus callosum of the human adult shows the six regional subdivisions numbered 1–6. ACC and PCC indicate the anteriormost and posteriormost points of the callosum, with ACC–PCC defined as the length of the callosum. G indicates the anteriormost point on the inner convexity of the anterior callosum. ACC–PCC was used as the linear axis to subdivide the callosum into anterior and posterior halves; anterior, middle, and posterior thirds, and the posterior one-fifth region (region 6) that is roughly congruent with the splenium. The line perpendicular to the axis at point G was used to define the anteriormost division of the callosum, roughly congruent with the genu (region 1). The rostral body (region 2) was defined as the anterior one-third minus region 1. The anterior midbody (region 3) was defined as the anterior one-half minus the anterior one-third. The posterior midbody (region 4) was defined as the posterior one-half minus the posterior one-third. The isthmus (region 5) was defined as the posterior one-third minus the posterior one-fifth.

to be plotted being visually confirmed between the bilateral lateral ventricles in the $b = 0$ image. Mean FA, MD, and eigenvalues of each voxel comprising each set of fibers were measured. The object was to obtain solely white matter areas, and for the purpose of excluding visibly apparent areas of white matter hyperintensity, some fibers located on the area of white matter hyperintensity were manually excluded by NOT operation (Wakana et al., 2004). A fiber tracking example showing the parcellation of the corpus callosum of a young woman is shown in Fig. 3. Two trained operators placed the ROIs, and the reproducibilities of FA and MD values were evaluated. The coefficients of variation for these measurements were as follows: MD, 4.5%; FA, 4.7%. These were in the same range as previously reported (O'Sullivan et al., 2004).

Statistical analysis

Statistical analyses were performed with SPSS for Windows 11.0.1. j (SPSS Inc, 1989–2001). At first, sex differences for FA and MD values of the corpus callosum sub-regions were tested with analysis of variance (ANOVA) with repeated measures. Then, the relationships of the FA and MD values of the corpus callosum sub-regions with age were evaluated by Pearson's correlation method. A P value less than 0.008 (0.05/6) was considered significant to avoid type 1 errors in the multiplicity of statistical analysis. For further understanding of the environmental alterations in the aging process of the corpus callosum, the eigenvalues of the diffusion tensor were also evaluated by Pearson's correlation method (Suzuki et al., 2003; Bhagat and Beaulieu, 2004). A P value less than 0.003 (0.05/18) was considered significant.

For evaluation of the differences among the 6 divided regions of the corpus callosum, regional differences for FA values were tested with ANOVA in subjects under 30 years of age ($n = 13$) to avoid the aging effect of FA. Dunnett T3 correction was used. A P value less than 0.05 was interpreted as being statistically significant.

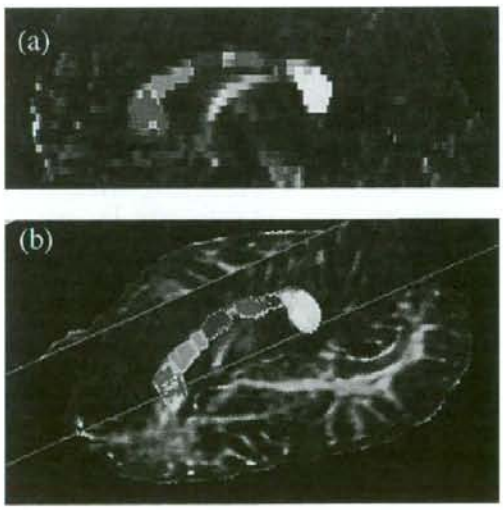

Fig. 3. Six fiber bundles projected in the corpus callosum sub-regions in midsagittal (a) and oblique from right anterior angles (b). Red, green, blue, pink, forest green, and white fibers run through the genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium, respectively.

Results

When FA in men vs. women was compared by ANOVA with repeated measures across the 6 regions, there were no significant interactions of sex × region ($F_{5200} = 1.768$; $P = 0.12$). This result corresponds well with a previous study (Hasan et al., 2005) and with the findings of a postmortem study (Aboitiz et al., 1992). MD was also compared by ANOVA with repeated measures, and there were no significant interactions of sex × region ($F_{5200} = 0.827$; $P = 0.53$). Thus, the male and female data were pooled to reduce redundant comparisons and the possible loss of statistical power due to the small populations.

The decline of FA showed a significant negative correlation with age in the genu, rostral body, and isthmus. The results are summarized in Table 2 and Fig. 4. FA of the anterior midbody correlated negatively with age at a trend level ($P = 0.025$, $r = -0.35$). The increase of MD showed a significant positive correlation with age in the genu, rostral body, anterior midbody, and isthmus. The results are summarized in Table 2 and Fig. 5. The changes of eigenvalues are summarized in Table 3 and Fig. 6. The increase of λ_2, λ_3, the perpendicular diffusivities, showed significant positive correlation with age in the genu, rostral body, anterior midbody, and isthmus (only λ_2 of the anterior midbody was correlated at a trend level ($P = 0.005$)). All λ_1, the parallel diffusivities, showed no correlation with age.

To assess the differences in the division of the corpus callosum into 6 regions, 13 young volunteers out of the 42 volunteers, age under 30 years (23.7 ± 1.5, mean ± SD), were evaluated for regional differences using ANOVA. ANOVA revealed that the FA values of the genu and splenium were statistically larger than those of the rostral body, anterior midbody, posterior midbody, and isthmus ($P < 0.001$, corrected). There were no differences between the genu and splenium nor between the rostral body, anterior midbody, posterior midbody and isthmus (Fig. 7).

Discussion

Previous study showed the FA values of 7 segments of the corpus callosum and the age-related change of FA in the genu and splenium (Hasan et al., 2004, 2005). In the present study, we showed the age dependence of FA, MD, and eigenvalues of the corpus callosum sub-regions with a larger number of subjects ($n = 42$). Our results showed that age is significantly correlated with FA and MD in the genu, rostral body, anterior midbody, and isthmus. FA in the genu showed a steeper decline with age than that in the splenium, a finding consistent with postmortem results (Aboitiz et al., 1996). Previous studies showed that FA declines in the genu with advancing age (Abe et al., 2000; Pfefferbaum et al., 2000; Salat et al., 2005; Sullivan et al., 2001; Hasan et al., 2004), relative anisotropy declines in the genu and splenium (Nusbaum et al., 2001), and FA declines in the genu and splenium by using fluid-attenuated inversion recovery-prepared diffusion imaging sequences (Bhagat and Beaulieu, 2004), whereas one study failed to detect age-related declines in anisotropy in the corpus callosum (Chepuri et al., 2002). However, no study had investigated the age-related decline in FA in the corpus callosum sub-regions. Using postmortem material, volume loss in the splenium with advanced age was indicated (Clarke et al., 1989), although there was no significant correlation of FA or MD with age in our study. Clarke et al. and Nusbaum et al. studied subjects more than 80 years old, while those of our study were somewhat younger. It is suggested that the splenium has subtle but increasing sensitivity to aging. Bhagat and Beaulieu showed a slight decrease in FA of the splenium compared to the genu as the FA value of older subjects (61–74 years) in the genu had reduced by 13% compared to young subjects (21–25 years) but that in the splenium decreased by only 3%. They used fluid-attenuated inversion recovery prepared diffusion imaging sequences, which allowed precise quantification of the FA values. In addition, our study showed that the observed decrease in anisotropy was due to a lack of change in λ_1 and an increase in λ_2, λ_3. It is consistent with a previous study (Bhagat and Beaulieu, 2004) and a basic pathology study that indicated a decrease in the number of myelinated nerve fibers with aging (Meier-Ruge et al., 1992).

We also showed that the mean FA values of 13 subjects in the genu and splenium were statistically larger than those in the rostral body, anterior midbody, posterior midbody, and isthmus. This result corresponds well with previous studies (Hasan et al., 2004, 2005). The trend of FA (splenium) > FA (genu) has been shown in some studies (Hasan et al., 2004, 2005; Chepuri et al., 2002; Sullivan et al., 2001). On the other hand, some studies regard FA values in the splenium and in the genu of younger subjects as almost equal (Bhagat and Beaulieu, 2004; Abe et al., 2000; Salat et al., 2005; Foong et al., 2000). Only Hasan et al. had divided the corpus callosum using landmarks adopted previously (Witelson, 1989) and showed that the FA was lower in the genu than in the splenium, but they compared FA values of subjects from 20 to 60 years old. The decrease of FA in the genu according to aging may affect the results. Some studies used a method in which the corpus callosum was subdivided into 3 regions: genu, body and splenium (Chepuri et al., 2002; Westerhausen et al., 2004). Our results showed that the FA value of the anterior one-third differs from that of the genu or rostral body. The posterior one-third also differed from the isthmus or splenium. This highlights the availability of landmarks as used in the present study for the corpus callosum subdivision (Witelson, 1989).

The sub-regions of the corpus callosum correspond to each of the specific projection areas. In this study, we found the aging

Table 2
Associations of age and FA and MD analyzed by Pearson's correlation coefficient

		Genu	RB	AMB	PMB	Isthmus	Splenium
FA	Correlation Coefficient	−0.66	−0.53	−0.35	−0.29	−0.42	−0.17
	P value	<0.001[a]	<0.001[a]	0.025[b]	0.066	0.005[a]	0.294
MD	Correlation Coefficient	0.51	0.46	0.49	0.25	0.51	0.28
	P value	0.001[a]	0.002[a]	0.001[a]	0.115	0.001[a]	0.074

RB, rostral body; AMB, anterior midbody; PMB, posterior midbody. $n = 42$.

[a] A P value less than 0.008 (0.05/6) was considered significant.

[b] Fractional anisotropy correlated negatively with age at a trend level.

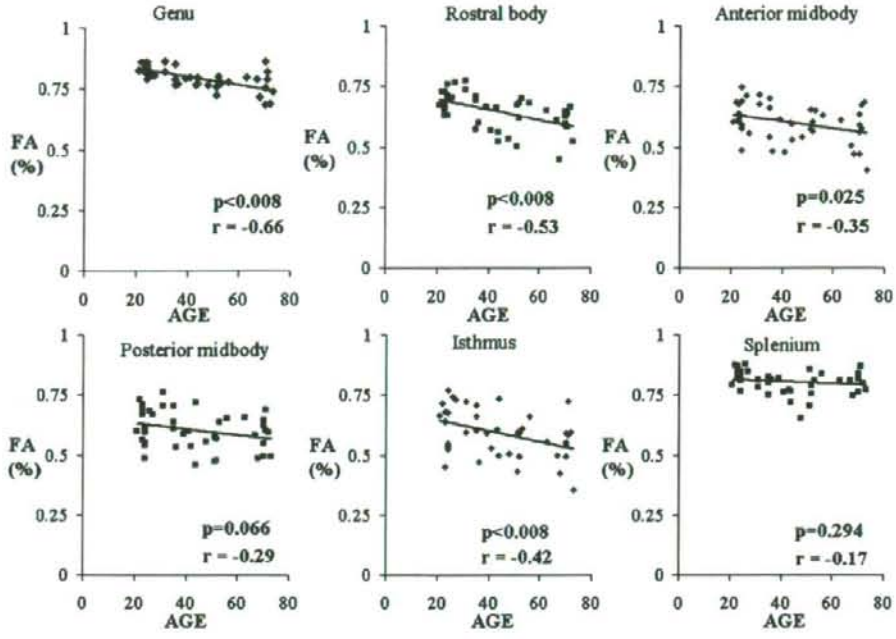

Fig. 4. FA values plotted against age. The decline of FA showed a significant negative correlation with age in the genu, rostral body, and isthmus. A P value less than 0.008 (0.05/6) was considered significant.

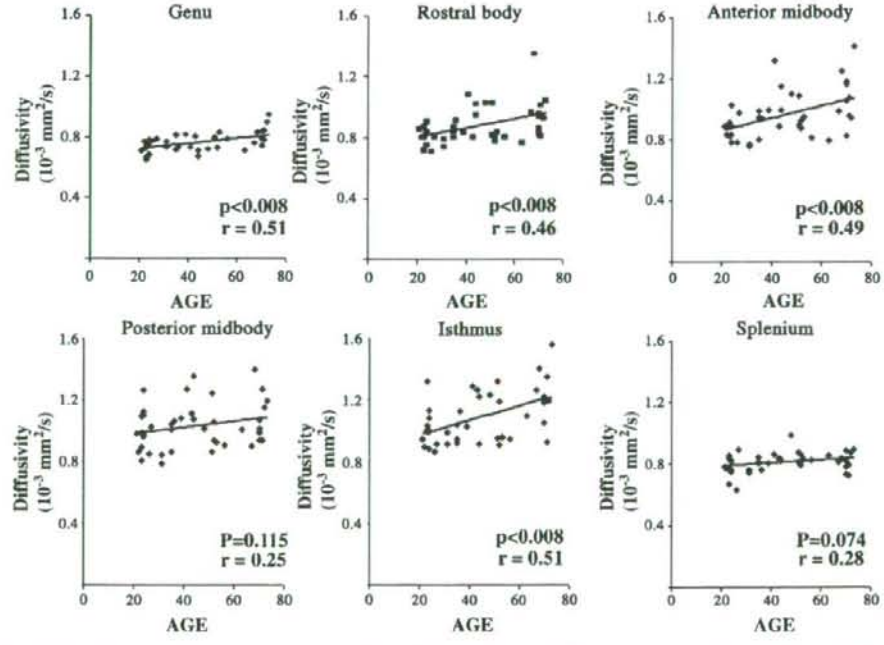

Fig. 5. MD values plotted against age. The increase of MD showed a significant positive correlation with age in the genu, rostral body, anterior midbody, and isthmus. A P value less than 0.008 (0.05/6) was considered significant.

Table 3
Associations of age and eigenvalues analyzed by Pearson's correlation coefficient

		Genu	RB	AMB	PMB	Isthmus	Splenium
λ_1	Correlation Coefficient	−0.14	0.15	0.35	0.13	0.38	0.63
	P value	0.378	0.355	0.021	0.429	0.013	0.692
λ_2	Correlation Coefficient	0.64	0.45	0.43	0.23	0.51	0.18
	P value	<0.001[a]	0.003[a]	0.005[b]	0.137	0.001[a]	0.248
λ_3	Correlation Coefficient	0.75	0.53	0.49	0.29	0.49	0.15
	P value	<0.001[a]	<0.001[a]	0.001[a]	0.068	0.001[a]	0.346

RB, rostral body; AMB, anterior midbody; PMB, posterior midbody. $n = 42$.
[a] A P value less than 0.003 (0.05/18) was considered significant.
[b] Eigenvalue correlated positively with age at a trend level.

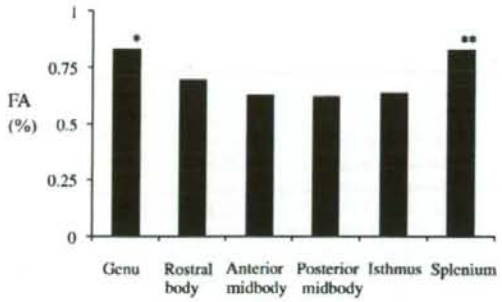

Fig. 7. Mean FA values of 13 subjects in 6 corpus callosum sub-regions. Regional differences for FA values were tested with analysis of variance (ANOVA). A P value less than 0.05 (corrected) was interpreted as being statistically significant. FA value of genu (*) was statistically larger than those of rostral body, anterior midbody, posterior midbody, and isthmus ($P < 0.001$, corrected). FA value of splenium (**) was statistically larger than those of rostral body, anterior midbody, posterior midbody, and isthmus ($P < 0.001$, corrected). There were no differences between genu and splenium nor between rostral body, anterior midbody, posterior midbody, and isthmus.

effect on FA in the genu, rostral body, and isthmus, which correspond to the frontal and parietal regions (Huang et al., 2005; Witelson, 1989) where age-related gray matter volume loss and decline in FA are observed (Good et al., 2001; Resnick et al., 2003; Sullivan et al., 2001). Relation of the corpus callosum sub-regions with disease, cognition, and development has recently been reported. The directionality of diffusion in an Alzheimer's disease group was significantly decreased in the splenium and caudal portion of the body of the corpus callosum compared with age-matched normal volunteers (Rose et al., 2000). Fibers from the splenium and caudal portion of the corpus callosum body originate from temporoparietal regions that are characteristically affected in Alzheimer's disease (Brun and Englund, 1986). In periventricular white matter injury patients with motor deficit, reduced FA was found in the body region of the corpus callosum, corresponding to the motor cortices (Thomas et al., 2005). A relation was reported between splenium FA and visual target detection task (Madden et al., 2004). Some MRI and DTI studies suggested that information on normal maturational processes from within each of the corpus callosum sub-regions could serve as markers of the developmental process across cortical regions (Innocenti, 1994; Keshavan et al., 2002; Snook et al., 2005). From these results, we suppose that fewer cortical neurons could be associated with fewer callosal fibers and that changes in FA or MD in the corpus callosum sub-

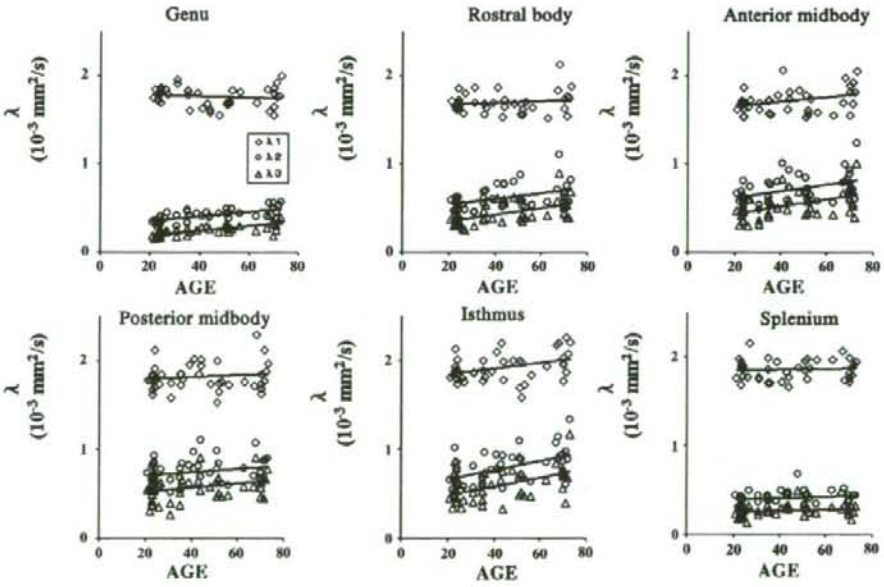

Fig. 6. Eigenvalues plotted against age. The increase of λ_2, λ_3 showed a significant positive correlation with age in the genu, rostral body, anterior midbody, and isthmus (λ_2 of the anterior midbody was at the trend level). A P value less than 0.003 (0.05/18) was considered significant.

regions may imply the degeneration of the respective projection areas. In this study, we did not detect any significant change of MD or FA in the posterior midbody or splenium nor did we find significant change of FA in the anterior midbody. These results may reflect the slight sensibility to aging of the thalamus, occipital, and temporal lobe structure (Resnick et al., 2003; Salat et al., 2005). These projection areas may obscure the aging effect on FA and MD in these sub-regions.

There is limitation to this study. In this study, the sample size of female was small. However, it has often been reported that there was no significant difference in MD or FA between males and females (Hasan et al., 2005). The smaller number of females would not be expected to make a difference. Further work with larger study populations using the same method will be necessary to confirm our results.

Correct evaluation of FA and MD in subcortical regions requires high signal-to-noise ratio, spatial resolution, and well-experienced neuroradiologists. The results of this study suggest that simple evaluation of projection areas using FA or MD in the corpus callosum sub-regions may aid in the comprehension of neurological disorders that disrupt the corresponding cortical neurons or axons.

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