interaction was shown, intention-to-treat analysis was also carried out; the participants who received the intervention but did not claim Long-Term Care Insurance for three consecutive months were included in the intention-to-treat analysis. A significant difference was set as $P < 0.05$.

Results

Demographic data of the participants are shown in Table 1. Analysis of 158 participants in the intervention group and 54 in the control group was carried out (Fig. 1). The number of participants who took donepezil during the intervention/observation period was two in both groups ($P = 0.269$, χ^2-test).

Cognitive tests

Participants in the intervention group showed significant improvement in HDS-R score compared with those in the control group (interaction F[1, 196] = 5.190, $P = 0.024$; post-hoc intra-subject analysis: intervention group, $P = 0.001$, control group $P = 0.480$). There were no significant differences observed in MMSE (Table 2).

Questionnaire

The intervention group showed significant improvement compared with the control group in DBD[13] (F[1,197] = 4.506, $P = 0.035$; post-hoc intra-subject analysis: intervention group, $P = 0.004$, control group $P = 0.413$) and NM Scale (F[1,198] = 9.550, $P = 0.002$; post-hoc intra-subject analysis: intervention group, $P < 0.001$, control group $P = 0.380$). Regarding the sub-items of the NM Scale, significant differences in interaction were observed for social interaction (F[1,198] = 15.736, $P < 0.001$), memory (F[1,198] = 7.635, $P = 0.006$) and orientation (F[1,198] = 4.220, $P = 0.041$).

Although the interaction was not significant, comparison between pre- and post-intervention showed significant improvement in ADL (Barthel Index), Social Activity Scale, motivation (Vitality Index) and mood (GDS) only in the intervention group after multiple correction (Table 2).

Intention-to-treat analysis

Significant differences remained in the intention-to-treat analysis in the HDS-R and NM Scale; HDS-R, interaction (F[1, 230] = 4.466, $P = 0.036$), post-hoc analysis within subjects: intervention group $P < 0.001$, control group $P = 0.585$; NM Scale, interaction (F[1, 236) = 8.113, $P = 0.005$), post-hoc analysis: intervention

Table 2 Outcome of intensive cognitive rehabilitation

	Intervention group			Control group			Interaction		Intra-subject†	
	Pre	Post	*n*	Pre	Post	*n*	F (DF)	*P*	Intervention	Control
	mean ± SD	mean ± SD		mean ± SD	mean ± SD					
Cognitive test										
MMSE	19.1 ± 4.5	19.4 ± 5.5	100	19.5 ± 4.9	18.2 ± 7.4	13	1.780 (1,110)	0.185	0.542	0.234
HDS-R	16.9 ± 5.7	17.9 ± 6.5	149	17.0 ± 5.9	16.7 ± 6.3	50	5.190 (1,196)	0.024*	0.001**	0.480
Questionnaire										
NM	30.4 ± 9.1	32.1 ± 9.5	149	31.4 ± 9.8	30.7 ± 10.9	52	9.550 (1,198)	0.002**	$P < 0.001$***	0.380
ADL	16.4 ± 7.1	17.3 ± 7.1	152	15.7 ± 7.0	15.9 ± 6.9	53	1.448 (1,202)	0.230	0.001**	0.621
Activity	8.6 ± 3.3	8.8 ± 3.4	150	8.5 ± 3.1	8.6 ± 3.2	53	1.169 (1,200)	0.281	0.038*	0.972
Vitality	8.0 ± 1.7	8.2 ± 1.6	149	8.1 ± 1.8	8.2 ± 1.8	53	1.792 (1,199)	0.182	0.004**	0.864
DBD	4.5 ± 5.1	4.0 ± 4.1	150	4.5 ± 4.2	4.8 ± 4.7	50	4.506 (1,197)	0.035*	0.004**	0.413
GDS	2.5 ± 1.8	2.4 ± 1.9	148	2.3 ± 1.5	2.4 ± 1.5	51	2.048 (1,196)	0.154	0.042*	0.634

†Intra-subject: post-hoc analysis of intra-subject (comparison between pre- and post-intervention analysis). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Activity, Original Activity Scale; ADL, Activities of daily living; DBD, Dementia Behavior Disturbance Scale; DF, degree of freedom; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale revised; MMSE, Mini-Mental State Examination; NM, N-Memory Scale; Post, post-intervention assessment; Pre, pre-intervention assessment; Vitality, Vitality Index.

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group $P < 0.001$, control group $P = 0.410$. The interaction of DBD was marginal; interaction ($F[1, 232] = 3.717$, $P = 0.055$), post-hoc analysis: intervention group $P = 0.007$, control group $P = 0.439$.

Discussion

Significant improvement by the intervention was shown in multiple domains; therefore, the intensive rehabilitation for dementia was beneficial for the individuals with dementia and also their caregivers. Pharmacological effects were thought to be negligible, as just two participants in both groups took donepezil during the intervention/observation period.

Regarding cognitive function, the effects of intensive rehabilitation for dementia were shown in both a cognitive test and observational evaluation of memory and orientation measured by NM Scale. In the symptomatic treatment of dementia, amelioration in daily living rather than in neuropsychological factors should be the therapeutic objectives, and thus the emphasis would be laid on improving performance in everyday life rather than on scores of cognitive tests.[16] Besides, it is often pointed out that scores of cognitive tests cannot always be generalized to daily living, although cognitive tests are moderately predictive of functional status in everyday life.[17] Therefore, mere enhancement of cognitive test scores is not sufficient, and beneficial changes in daily living are required. In the present study, cognitive improvement was shown in observational evaluation, in addition to a cognitive test. Cognitive enhancement is also beneficial for caregivers, because the severity of cognitive impairment could be a predictor of burden, in addition to BPSD.[18,19] The effects of non-pharmacological approaches on cognitive function have not yet been established,[16,19] and the present study could provide additional evidence for their benefit.

Amelioration of BPSD was also attained in the present study. Care for demented individuals requires allocation of longer times than for care of the elderly suffering from physical diseases. In particular, the presence of BPSD might induce more stress than do medical problems,[4,20–23] and could result in depression or strain in caregivers.[24] Consequently, caregivers' burden is associated with an increased risk of institutionalization.[25] However, institutionalization could not solve caregivers' distress; a year after institutionalization, distress still persisted in caregivers.[26] In contrast, treatment of BPSD could help diminish caregiver burden.[27] Thus, it is beneficial both for individuals with dementia and their caregivers to reduce BPSD by rehabilitation in intermediate facilities between hospital and home.

In addition to enhancement of cognitive function and reduction of BPSD, improvement of social functioning and quality of life (QOL) should be the main outcomes of rehabilitation for dementia.[16]

Social isolation is associated with increased risk of mental decline,[28] whereas a rich social network and interaction might protect against mental decline.[29,30] In demented individuals, symptoms of depression were a consistent predictor of QOL.[31] In the present study, the intervention group showed improvement of social functioning measured by the Social Activity Scale, and amelioration of depressive mood measured by GDS.

Regarding the intervention, individualized tailor-made therapies were carried out, because the aim of the present study was to enhance each participant's ability to meet their individual needs, and not to show the efficacy of any specific method. Personally-relevant goals were identified, and the therapist worked with the individuals with dementia to devise strategies to cope with difficulties in their everyday lives by building on the person's strengths and developing ways of compensating for impairment.[15] Personal selection was considered an essential therapeutic element to enhance the motivation and optimize the emotional impact of the training. Changing and combining methods were allowed during the intervention period.

The present study showed that intensive rehabilitation should be beneficial for both individuals with dementia and caregivers. To promote community-based care and dehospitalization, continuity of rehabilitation is desirable to maintain function after returning home; another mission of Roken is to offer community-based rehabilitation and various care services to support home-based care.

As a limitation, the participants were not randomized. By data cleaning, data including missing values were excluded so that the numbers of valid data were different among assessments. Finally, for evaluation of the effects on dehospitalization, a longitudinal follow-up study is required.

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Cerebrospinal fluid levels of phosphorylated tau and Aβ1-38/Aβ1-40/Aβ1-42 in Alzheimer's disease with PS1 mutations

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Abstract

We studied seven cases of Alzheimer's disease (AD). Six of the patients had presenilin 1 (PS1) mutations (PS1AD). Three novel PS1 mutations (T99A, H131R and L219R) and three other missense mutations (M233L, H163R and V272A) were found in the PS1AD group. We measured the levels of phosphorylated tau (ptau-181, ptau-199) and Aβ (Aβ1-42, Aβ1-40 and Aβ1-38) in the cerebrospinal fluid (CSF) of PS1AD patients, early-onset sporadic AD (EOSAD), late-onset sporadic AD (LOSAD) and non-demented subjects (ND). The CSF levels of Aβ1-42 in the three AD groups were significantly lower than those of the ND group ($p < 0.0001$). CSF levels of Aβ1-42 in the PS1AD group were significantly lower than those in the two sporadic AD groups. The Aβ1-40 and Aβ1-38 levels in the CSF of the PS1AD group were significantly lower than those of the three other groups ($p < 0.0001$, respectively). The levels of Aβ1-40, Aβ1-38 and Aβ1-42 in the CSF of the PS1AD group remained lower than those of the ND group for 4 years. Not only CSF Aβ1-42, but also Aβ1-40 and Aβ1-38 decreased in the advanced stages of PS1AD.

Keywords

Alzheimer's disease, amyloid β protein, cerebrospinal fluid, phosphorylated tau, presenilin 1

History

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Abbreviations: Aβ, amyloid β protein; AD, Alzheimer's disease; ADL, activities of daily living; ApoE, apolipoprotein E; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; EOSAD, early-onset sporadic AD; LOSAD, late-onset sporadic AD; MCI, mild cognitive impairment; ND, non-demented subject; PIB-PET, Pittsburgh compound B-positron emission tomography; PS1, presenilin 1; ptau, phosphorylated tau; PS1AD, Alzheimer's disease patient with presenilin 1 mutation; S.D., standard deviation; ^{99m}Tc-ECD SPECT, ^{99m}Tc-ethyl cysteinate dimer single photon emission computerized tomography

Introduction

The extracellular deposition of amyloid-β (Aβ) peptides (preferentially Aβ42) into neuritic plaques and the formation of neurofibrillary tangles consisting of phosphorylated tau (ptau) are hallmarks of Alzheimer's disease (AD) [1,2]. In cases of AD with autosomal dominant inheritance, presenilin 1 (PS1) is the most prevalent causative gene for early-onset familial AD [3–6]. The major component of neurofibrillary tangles is tau, a microtubule-associated protein that undergoes excessive phosphorylation at multiple sites (e.g. ptau-199, ptau-181 and ptau-231) and aggregates into paired helical filaments in the brains of AD patients [7,8]. In the cerebrospinal fluid (CSF) of AD patients, the levels of Aβ1-42 are selectively reduced [9,10] and the CSF levels of total-tau and ptau were reported to be elevated [11–13]. Carboxy-terminal truncated Aβ peptides other than Aβ1-40/42, Aβ1-37/38/39 have been identified physiologically in CSF [14]. Aβ1-42, Aβ1-40 and Aβ1-38 have been reported in the CSF in AD, dementia with Lewy bodies (DLB) and progressive aphasia (PA) [15–17]. In the present study, we found that the CSF levels of Aβ1-40 and Aβ1-38 in AD patients with PS1 mutations were significantly decreased compared to those of early- or late-onset sporadic AD patients and subjects without

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AD. We also obtained longitudinal data showing the low levels of Aβ1-40 and Aβ1-38 in the CSF of the four PS1AD patients with a long-term duration of illness.

Materials and methods

Subjects

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Boards (IRB) of Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital, and Maebashi Red Cross Hospital. The spouse or family members of each AD patient provided written informed consent for the patient to participate in the study. One hundred and twenty-seven subjects (40 early-onset sporadic AD (EOSAD) patients, 40 late-onset sporadic AD (LOSAD) patients, 40 subjects without dementia and seven PS1AD patients), who underwent lumbar punctures, were recruited at Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital (Maebashi, Gunma, Japan), and Maebashi Red Cross Hospital (Maebashi, Gunma, Japan). Upon entering the study, subjects underwent a standardized clinical assessment, including medical history, physical and neurological examinations, Mini-Mental State Examination (MMSE) [18], brain MRI and/or CT scan. AD was diagnosed for patients scoring 23 points or less on the MMSE [19], combined with caregivers' information of patients' daily activities. Diagnostic criteria of the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) were used for AD [20]. Subjects were classified as non-demented (ND) if they scored more than 24 points on MMSE, and if, based upon information on activities of daily living (ADL) provided by the family, they were considered to have a normal daily life not requiring any intellectual assistance. The ND group comprised patients suffering from tension headache (14 cases), polyneuropathy (eight cases), epilepsy (seven cases), spinal canal stenosis (five cases), myasthenia gravis (three cases) and migraine (three cases). Lumbar puncture and follow-up assessments were performed once a year for 4 years after obtaining informed consent annually.

The AD patient group comprised patients with PS1AD (seven AD patients in six AD families, referred to as GFAD1-6), EOSAD (younger than 64 years at onset) and LOSAD (65-years-old and older at onset). Genetic analyses revealed the following PS1 mutations in the seven patients with familial AD (Table 1): GFAD1-1 (M233L), GFAD1-2 (M233L), GFAD2 (H163R), GFAD3 (L219R), GFAD4 (H131R), GFAD5 (V272A) and GFAD6 (T99A). L219R, H131R and T99A in the PS1 gene are novel mutations, and the clinical information for these three AD patients is described in the supplementary data. Mutations of M233L, H163R and V272A in the PS1 gene were already reported elsewhere [6]. In the seven cases of PS1AD, the mean age of onset was 44.43 ± 5.74 years; the mean age of first CSF examination of PS1AD was 51.43 ± 4.35 years; the mean MMSE score at first CSF examination of PS1AD was 6.86 ± 4.34; and the mean duration between onset and the first CSF examination was 7.43 ± 2.44 years. In the 40 cases of EOSAD, the mean age of onset was 57.4 ± 5.13 years; the mean age of CSF examination was 62.73 ± 5.54 years; the mean MMSE score at the CSF examination was 16.67 ± 2.35; and the mean duration between onset and CSF examination was 5.33 ± 2.35 years. In the 40 cases of LOSAD, the mean age of onset was 72.07 ± 3.94 years; the mean age of CSF examination was 75.9 ± 4.01 years; the mean MMSE score at the CSF examination was 16.27 ± 2.55; and the mean duration between onset and CSF examination was 3.80 ± 1.81 years. In the ND group, the 40 subjects had a mean age of onset as 65.77 ± 9.02 years; MMSE score at the CSF examination was 29.90 ± 0.38.

Genetic analysis of PS1 and apolipoprotein E

After obtaining informed consent for genetic testing, we purified genomic DNA from lymphocytes in the peripheral blood of affected subjects. For the analysis of apolipoprotein E, purified genomic DNA was examined as previously described [21]. DNA fragments containing Exon 3-13 of PS1 were amplified by PCR using primers [3–5].

Measurement of CSF Aβ1-42, Aβ1-40 and Aβ1-38

CSF was obtained by a lumbar puncture in the L3/L4 or L4/L5 intervertebral space. CSF samples were centrifuged for 10 min at 1800*g* at 4 °C within 3 h of collection. Samples were divided into aliquots of 0.5 mL in polypropylene tubes and stored at −80 °C until analysis with an ELISA kit for human CSF Aβ1-40 (Wako Pure Chemical Industries, Tokyo, Japan), human CSF Aβ1-42 (Wako Pure Chemical Industries) and human CSF Aβ1-38 (IBL, Gunma, Japan) [22–24].

Measurement of CSF phosphorylated tau 199 and 181

Quantitative measurement of CSF levels of tau protein phosphorylated at serine 199 (CSF ptau-199) by a sandwich ELISA is an excellent biomarker for distinguishing AD patients from non-AD patients [11]. Measurement of ptau-181 in CSF was also performed by the sandwich ELISA (Innogenetics, Ghent, Belgium) as described elsewhere [25].

Table 1. Clinical features of seven PS1AD cases.

Patient	#1	#2	#3	#4	#5	#6	#7	
PS1 mutation	M233L	M233L	H163R	L2I9R	H13IR	V272A	T99A	
Gender	Female	Female	Male	Female	Female	Female	Male	Mean ± S.D.
Age of Onset	41	37	41	51	45	53	43	44.43 ± 5.74
MMSE*	8	3	6	16	5	4	6	6.86 ± 4.34
Age*	48	47	49	57	55	56	48	51.43 ± 4.35
Duration (years)	7	10	8	6	10	3	8	7.43 ± 2.44

This table shows PS1 mutations, gender, age of onset, MMSE, age at CSF first lumbar puncture (*) and duration (years) in seven PS1AD cases.

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Statistical analysis

Differences between AD groups (PS1AD, EOSAD, LOSAD) and subjects without dementia (ND group) were compared using a two-way ANOVA with the Bonferroni correction for multiple comparisons. The level of significance was set at $p<0.05$. All analyses were performed with the GraphPad Prism Software (GraphPad Prism Version 5.0, GraphPad software, San Diego, CA).

Results

Apolipoprotein E genotypes

The apolipoprotein E genotypes of PS1AD patients were M233L-1 (ε3/ε4), M233L-2 (ε3/ε4), H163R (ε3/ε4), L219R (ε3/ε4), H131R (ε3/ε3), V272A (ε3/ε4) and T99A (ε3/ε4).

Comparative analysis of CSF data from ND, PS1AD, EOSAD and LOSAD groups

The CSF levels of ptau-199 were significantly higher in the AD groups (PS1AD (M233L-1, M233L-2, H163R, L219R), 6.66 ± 3.12 pg/ml; EOSAD, 9.89 ± 4.69 pg/ml; LOSAD, 9.39 ± 4.15 pg/ml) than in the ND group (2.64 ± 0.44 pg/ml) (Figure 1(A), $p<0.01$, $p<0.0001$, $p<0.0001$, respectively). The CSF levels of ptau-181 in the AD groups (PS1AD, 50.31 ± 19.03 pg/ml; EOSAD, 72.01 ± 36.30 pg/ml; LOSAD, 67.19 ± 33.93 pg/ml) were significantly higher than in the ND group (32.27 ± 12.56 pg/ml) (Figure 1(B), $p<0.01$, $p<0.0001$, $p<0.0001$).

The CSF levels of Aβ1-42 in the AD groups (PS1AD, 68.10 ± 22.59 pg/ml; EOSAD, 117.52 ± 64.32 pg/ml; LOSAD, 144.57 ± 70.03 pg/ml) were significantly lower than in the ND group (309.05 ± 105.02 pg/ml) (Figure 1(C), $p<0.0001$, respectively). The CSF level of Aβ1-42 in the PS1AD group was significantly lower than the levels in the EOSAD and LOSAD groups ($p<0.01$, $p<0.01$, respectively).

In terms of the CSF levels of Aβ1-40, there were no significant differences amongst the EOSAD groups (3163.27 ± 1442.55 pg/ml), the LOSAD group (3072.37 ± 1674.86 pg/ml) and the ND group (2995.52 ± 1227.93 pg/ml) (Figure 1D). The CSF level of Aβ1-40 in the PS1AD group (1011.06 ± 392.61 pg/ml) was significantly lower than that in the ND group ($p<0.0001$), the EOSAD group ($p<0.0001$) and the LOSAD group ($p<0.0001$) (Figure 1D). The CSF level of Aβ1-38 in the PS1AD group (655.17 ± 253.62 pg/ml) was significantly lower than the levels in the EOSAD group (2337.27 ± 1048.33 pg/ml), the LOSAD group (2511.47 ± 1221.74 pg/ml) and the ND group (2113.35 ± 1028.57 pg/ml) (Figure 1(E), $p<0.0001$, $p<0.0001$, $p<0.0001$, respectively).

Combined ratios of Aβ molecules and ptau-181

The ratios of CSF Aβ1-42/Aβ1-40 in the CSF of the EOSAD, LOSAD and PS1AD were significantly lower than that of the ND group (Figure 2(A), $p<0.0001$, $p<0.0001$, $p<0.001$, respectively). The ratios of Aβ1-42/Aβ1-38 in the CSF of the EOSAD and LOSAD groups were significantly lower than that of the ND group (Figure 2(B), $p<0.0001$, $p<0.0001$). There was no significant difference in the Aβ1-38/Aβ1-40

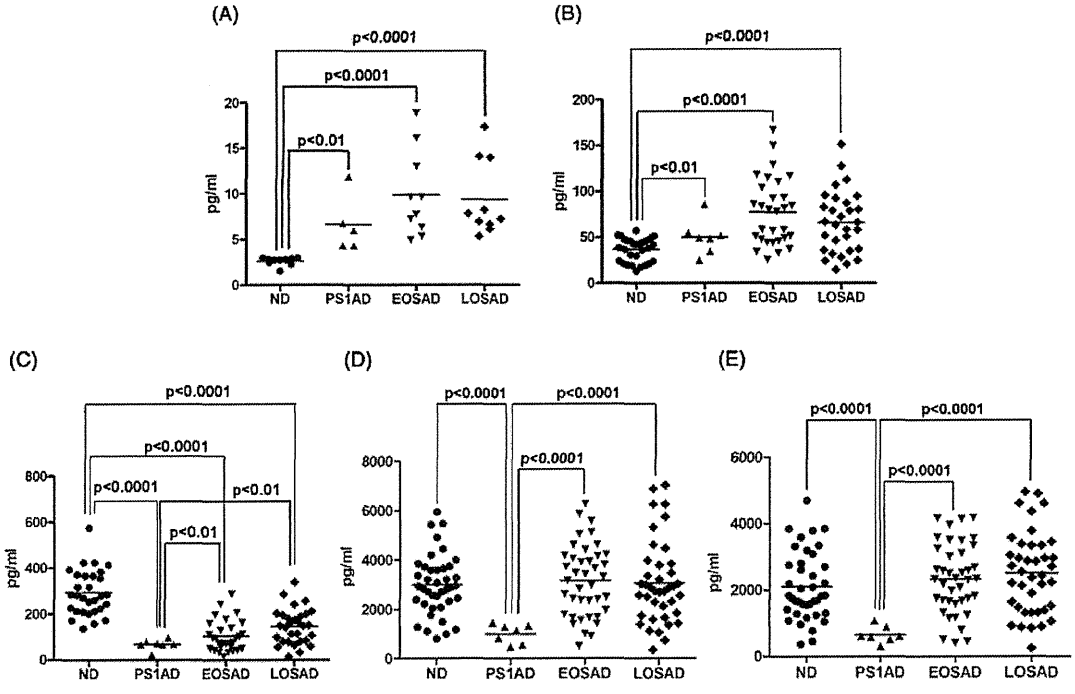

Figure 1. Measurement of CSF Aβ molecules and phosphorylated tau (PS1AD, EOSAD, LOSAD and ND). (A) CSF levels of ptau-199 and (B) ptau-181 showed significant increases in the AD groups (PS1AD, EOSAD, LOSAD) compared to the ND group ($p<0.01$, $p<0.0001$, $p<0.0001$). (C) CSF level of Aβ1-42 in the AD groups (PS1AD, EOSAD, LOSAD) showed a significant decrease compared to the ND group ($p<0.0001$, $p<0.0001$, $p<0.0001$). The CSF level of Aβ1-42 in the PS1AD group was significantly decreased as compared to the EOSAD, LOSAD groups (shown in bold lines, $p<0.01$, $p<0.01$, respectively). (D) The CSF level of Aβ1-40 in the PS1AD group was significantly decreased as compared to the sporadic AD groups (EOSAD, LOSAD) ($p<0.0001$, $p<0.0001$) and the ND group ($p<0.0001$). (E) The CSF level of Aβ1-38 in the PS1AD group was significantly decreased compared to the sporadic AD groups (EOSAD, LOSAD) ($p<0.001$, $p<0.0001$) and the ND group ($p<0.0001$).

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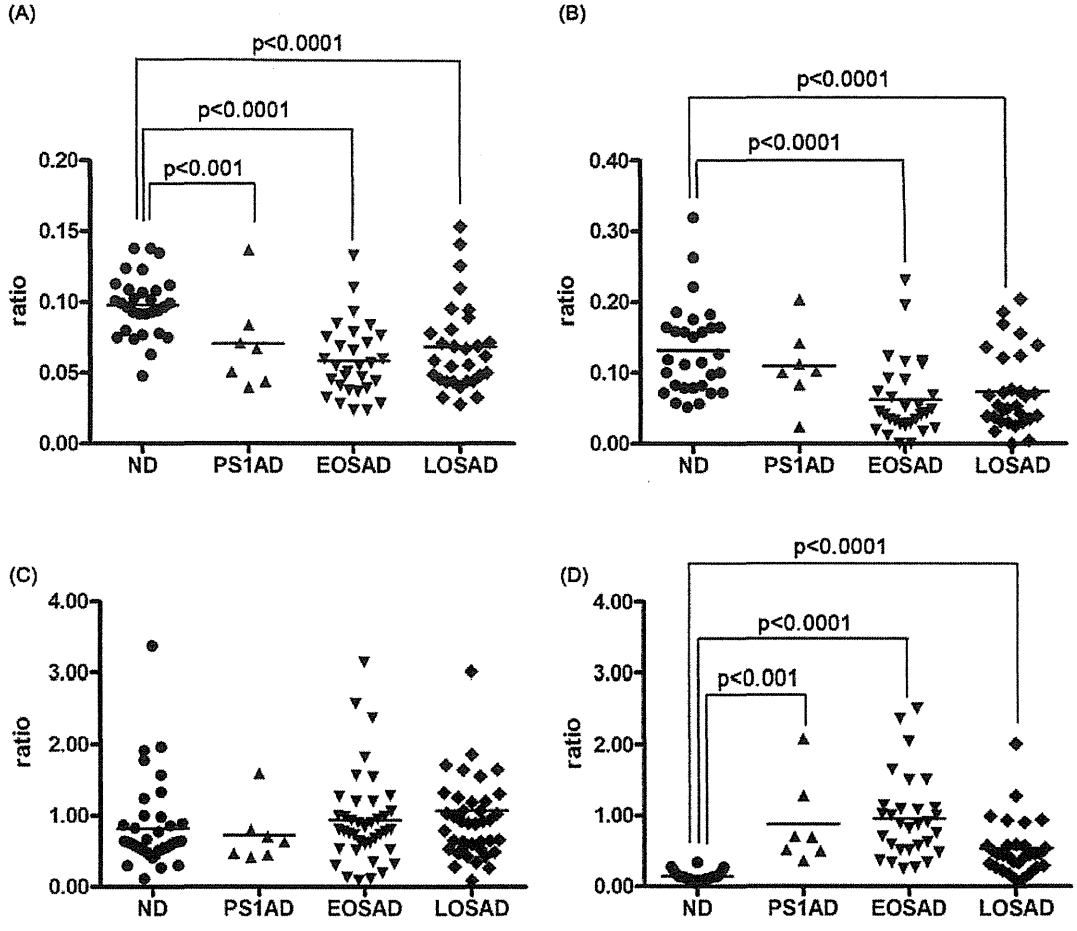

Figure 2. Ratios of CSF Aβ molecules and phosphorylated tau (ptau-181). (A) The ratio of Aβ1-42/Aβ1-40 significantly decreased between the PS1AD and the ND ($p<0.001$) groups and between the sporadic AD (EOSAD and LOSAD) and the ND group ($p<0.0001$, $p<0.0001$, respectively). (B) The ratio of Aβ1-42/Aβ1-38 of the sporadic AD groups (EOSAD and LOSAD) significantly decreased compared to those of the ND group ($p<0.0001$, $p<0.0001$, respectively). (C) No significant difference in the ratio of Aβ1-38/Aβ1-40 in CSF was observed amongst EOSAD, LOSAD and PS1AD. (D) The ratio of ptau-181/Aβ1-38 significantly increased between the three AD groups (PS1AD, EOSAD, LOSAD) compared to the ND group ($p<0.001$, $p<0.0001$, $p<0.0001$).

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ratios in the CSF of the four groups (Figure 2C). The ptau-181/Aβ1-42 ratios in CSF of the EOSAD, LOSAD and PS1AD were significantly higher than that of the ND group (Figure 2(D), $p<0.001$, $p<0.0001$, $p<0.0001$, respectively).

Temporal profiles of MMSE scores and CSF levels of Aβ molecules and ptau-181 in the PS1AD group

MMSE scores of four PS1AD patients (M233L-1, M233L-2, H163R, L219R) who underwent CSF analysis every year, decreased over the 4-year study period (Figure 3A). The CSF levels of ptau-181 in four PS1AD patients were significantly higher than those of ND subjects (Figure 3(B), $p<0.01$), while the CSF levels of Aβ1-42, Aβ1-40 and Aβ1-38 of four PS1AD patients were lower than those of ND subjects (Figure 3(C), (D), (E), $p<0.0001$, respectively).

Discussion

The most reliable AD biomarkers are CSF Aβ1-42 and PIB-PET of imaging studies, followed by CSF ptau-181 and the total tau included in the new AD criteria [26,27]. In our study, the CSF level Aβ1-42 in the three AD groups was significantly lower than that of the ND group, with the PS1AD group having a lower level than the two sporadic AD groups. The CSF levels of Aβ1-42, Aβ1-40 and Aβ1-38 in the PS1AD group were significantly lower than those of the other three groups (ND, EOSAD and LOSAD). The ratios of Aβ1-42/Aβ1-40 in the three AD groups were lower than that in the ND group. The ratios of CSF Aβ1-42/Aβ1-38 in the CSF of the EOSAD and LOSAD groups were significantly lower than that of the ND group. This suggests that the CSF level of Aβ1-38 increased in the sporadic AD groups as compared to the ND group, although the increase was not statistically significant. In contrast to these results, the CSF ratio of Aβ1-38/Aβ1-40 did not show a significant difference amongst the four groups (ND, PS1AD, EOSAD and LOSAD). In the PS1AD patients, the level of Aβ1-38 was lower than that in other sporadic AD groups; therefore, the ratio of Aβ1-42/Aβ1-38 in PS1AD did not differ from ND, while it did differ between ND and the other AD groups.

We analyzed the temporal profiles of CSF (ptau-181, Aβ1-42, Aβ1-40, Aβ1-38) in four PS1AD patients for 4 years. The CSF levels of Aβ1-42, Aβ1-40 and Aβ1-38 were lower in

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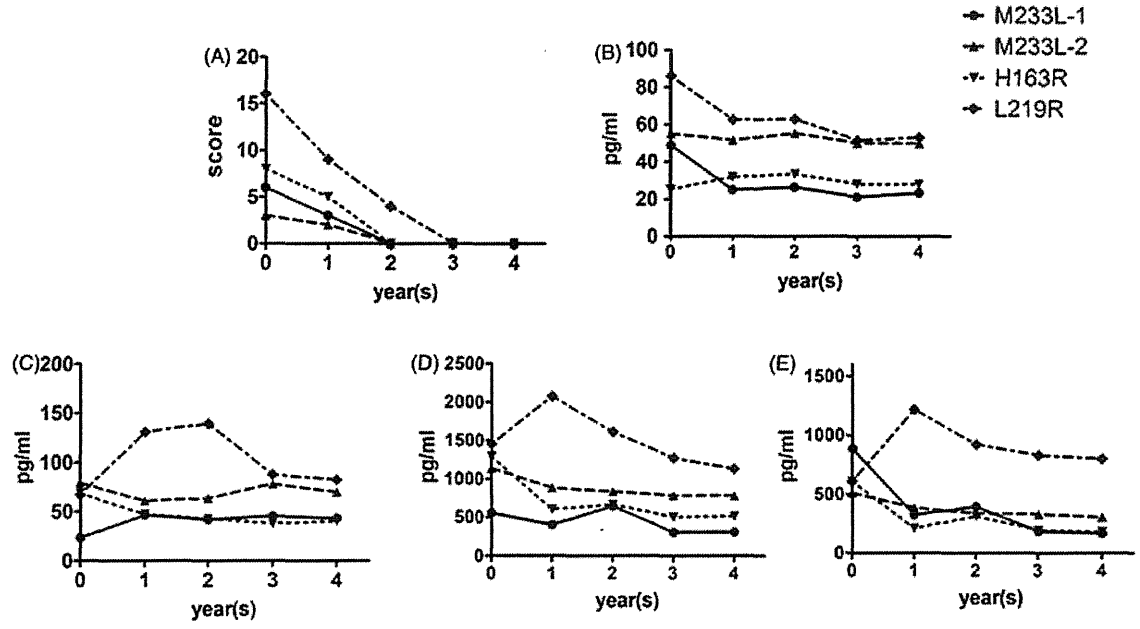

Figure 3. Temporal change of MMSE scores and CSF levels (ptau-181, Aβ1-38, Aβ1-40, Aβ1-42) in PS1AD. (A) Four PS1AD patients (M233L-1, M233L-2, H163R, L219R) who underwent CSF analysis, have shown a decrease in MMSE scores over the 4-year period. (B) First CSF levels of ptau-181 of these four PS1AD patients were significantly higher than those of ND subjects as shown in Figure 1(B) ($p<0.01$). (C) The CSF level of Aβ1-42 was stable in M233L-1, M233L-2 and H163R, while in L219R, it increased and then decreased to levels lower than those in ND subjects. First CSF levels of Aβ1-42 of these four PS1AD patients were significantly lower than those of ND groups as shown in Figure 1(C) ($p<0.0001$). (D) The CSF level of Aβ1-40 of PS1AD patients was less than 2500 pg/ml, which was lower than that in the ND group. First CSF levels of Aβ1-40 of these four PS1AD patients were significantly lower than those of ND groups as shown in Figure 1(D) ($p<0.0001$). (E) The CSF levels of Aβ1-38 of PS1AD patients were less than 1500 pg/ml, which was lower than those of the ND group. First CSF levels of Aβ1-38 of these four PS1AD patients were significantly lower than those of ND groups as shown in Figure 1(E) ($p<0.0001$).

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these patients as compared to the ND group during the 4-year period (Figure 3C, D, E). Unlike our results, it was reported that CSF Aβ1-42 in patients with AD, mild cognitive impairment (MCI) and subjective complaints (SC) increased during 1–3.5 years [28]. The reasons for the differences from our results of PS1AD might be associated with the long duration of the illness and severe aggregative AD biochemical change, likely due to PS1 mutations. Age differences amongst the three AD groups (EOSAD, LOSAD and PS1AD), age of onset and duration of the illness might contribute to differences in the levels of CSF markers, with or without genetic background (PS1 mutation in this study).

In a recent article, the ratio of Aβ1-42/Aβ1-38 was largely proportional to that of Aβ1-40/Aβ1-43, and the two cleavage processes are tightly coupled. Therefore, both the CSF Aβ1-40 and Aβ1-38 were generally higher in MCI/AD patients compared with control subjects, the CSF Aβ1-43 and Aβ1-42 decreased in MCI/AD patients [24].

In our study, PS1AD patients with long-term severe dementia presented and remained characterized by lower CSF Aβ1-42, Aβ1-40 and Aβ1-38 in the examined period, as compared to sporadic AD and subjects without dementia. Unlike Kakuda's article [24], our results of PS1AD presumably reflect more severe pathological processes during the long-term duration of the illness.

To date, only A431E mutation of PS1AD showed a decrease of CSF Aβ1-38 and Aβ1-42 [29]. Pathologically, PS1AD brains frequently showed aggravating Lewy bodies [30,31]. Some relationship between α-synuclein and Aβ1-38 might be of pathological relevance for Aβ aggregation [32]. They may generate a nucleation center for subsequent Aβ amyloidogenesis and the formation of Lewy bodies. In long-term PS1AD, various molecular relationships amongst Aβ1-38/40/42 molecules with aberrant accumulation of α-synuclein and tau still require further elucidation.

Conclusion

In PS1AD patients with severe dementia and advanced stage disease, CSF levels of Aβ1-42, Aβ1-40 and Aβ1-38 were significantly lower than those of ND subjects, in which CSF levels of Aβ1-40 and Aβ1-38 were significantly lower than sporadic AD (EOSAD and LOSAD). We showed that CSF levels of ptau-181 in PS1AD patients were significantly higher than the ND subjects, but were not as high as in patients with sporadic AD (EOSAD and LOSAD). These findings were observed in known mutations (M233L, H163R and V272A) as well as novel mutations (T99A, H131R and L219R).

Declaration of interest

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Communicative Competence in Alzheimer's Disease: Metaphor and Sarcasm Comprehension

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Abstract

The purpose of this study was to evaluate the deficits of metaphor and sarcasm comprehension in Alzheimer's disease (AD), as pragmatic interpretation such as metaphor and sarcasm comprehension is required in social communication. A total of 31 young normal controls, 104 aged normal controls (ANC), 42 patients with amnesic mild cognitive impairment (aMCI), and 30 patients with mild AD were evaluated by Metaphoric and Sarcastic Scenario Test, which consists of 5 metaphoric and 5 sarcastic questions with 5 answer choices. Scores were analyzed using the repeated measures analysis of variance (metaphor/sarcasm vs 4 participant groups). Sarcasm comprehension, which requires second-order Theory of Mind (ToM), started to deteriorate in ANC, and metaphor comprehension, which requires first-order ToM, started to deteriorate in aMCI, and both deteriorated as disease progressed. Literal interpretation of pragmatic language is characteristic in patients with mild AD. Such misinterpretation would result in social miscommunication, even if they still retained semantic-lexical competence.

Keywords

Alzheimer's disease, theory of mind, empathy, communication difficulties, pragmatic competence

Introduction

Communicative competence occupies a central place in participation in social activities and it can be impaired in patients with Alzheimer's disease (AD). In AD, lexical-semantic competence is deteriorated as a result of cognitive decline.[1] However, patients could also have communicative difficulties even from the stage where lexical-semantic competence is still preserved. In social communication, literal lexical-semantic comprehension is not sufficient.[2] Comprehension of nonliteral implication is often required to infer a speaker's intended meaning (Theory of Mind [ToM]),[3] which is not always expressed explicitly.

Theory of Mind is considered to consist of 2 stages, first-order ToM is the ability to grasp the intentions of the speaker and second-order ToM is the ability to infer the speakers' evaluation for an attributed thought.[4-7] Metaphor and sarcasm comprehension are considered to be appropriate materials of ToM.[8] First-order ToM is sufficient for metaphor comprehension.[9] Metaphor suggests meanings through mental linkage and comparison of similarities between different expressions normally not related to each other.[10,11] Second-order ToM is required for sarcasm comprehension.[5] Sarcasm expresses something other than explicitly stated and especially the opposite of the literal meaning of the utterance.[12] Thus comprehension of sarcasm requires the ability to reflect on the speakers' evaluation about the attributed thought, adding to utterance intention.[4]

Metaphoric and sarcastic competence has been mainly studied to evaluate the social communicative competence in the phases of development and its disorders,[13] as interaction with other people is critical for normal neurocognitive development.[14] In the phase of aging and degeneration, it is also meaningful to evaluate the decline of social communicative competence. However, a recent review on nonliteral language in AD noted a severe lack of evidence.[15] Furthermore, previous reports on metaphor and sarcasm comprehension are inconsistent; for example, deficits in metaphor comprehension were reported from early stages of AD,[16-18] whereas concerning irony and sarcasm, previous studies did not find a significant impairment relative to an aged control group,[19,20] which is surprising because irony involves more cognitive processes than metaphor.[21]

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The controversy could be partly due to the material in the test; it is a prerequisite that difficulty level of lexical-semantic aspects is even among sentences used in the tests. Thus, we conducted the present study to evaluate the deficits of metaphor and sarcasm in AD using a questionnaire that consists of the same type of sentences with similar difficulty levels and whose efficacy was validated for differential diagnosis of developmental disorders in children.[22] For a better understanding of characteristics of AD, error patterns were analyzed. We hypothesized that comprehension might be deteriorated at the early stages of disease and sarcasm comprehension might be deteriorated earlier than metaphor comprehension.

Methods

Participant

The participants were 31 young normal controls (YNC), 104 aged normal controls (ANC), 42 patients with amnesic mild cognitive impairment (aMCI), and 30 patients with mild AD in Clinical Dementia Rating scale (CDR) 1. The YNC were university students and ANC were recruited from community dwellers, who underwent clinical interviews by a clinician who specialized in evaluation of dementia. Patients were recruited from the outpatient clinics. The exclusion criteria were psychiatric diseases and delirium. Verbal incomprehension was also an exclusion criterion. The participants were required to read out the questions and those who lacked fluency were excluded. Concerning language ability, the participants received the Mini-Mental State Examination (MMSE) and were confirmed to have the capacity to name simple objects, repeat phrases, follow written commands, and write a sentence with a noun and a verb. The participants were diagnosed based on the criteria for AD by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association[23] and on the criteria for aMCI by the report of the International Working Group on Mild Cognitive Impairment.[24] Patients with aMCI were limited to those free from objective symptoms of other types of dementia such as dementia with Lewy bodies or frontotemporal dementia. The Ethics Board of the Gunma University School of Health Sciences approved all procedures (No. 21-26), and written informed consent was obtained from all the participants.

Task

Metaphor and sarcasm comprehension was evaluated by the Metaphoric and Sarcastic Scenario Test (MSST), which was developed for discrimination of high functioning pervasive developmental disorders from attention deficit/hyperactivity disorders in young children.[22] This test consists of 5 metaphoric and 5 sarcastic sentences; metaphoric sentences are odd numbered and sarcastic sentences even. The words and sentences in MSST were selected from standard textbooks of Japanese language (Mitsumura Press) for 1st, 2nd, and 3rd grades in elementary school. Therefore, the lexical-semantic components were not above the levels for those who completed 6 years of elementary school education. The test employed a multiple-choice style, that is, 1 choice was correct and 4 were incorrect. The wrong choices included a literal interpretation, an answer associated with part of the sentence, misunderstanding of the sentence, and not knowing. The number of correct answers represented the metaphor score and sarcasm score, respectively. Each pattern of incorrect answers was totaled. Cognitive performance was assessed using MMSE.

Analysis

Group comparison of scores and the 4 error scores were conducted using the repeated measures analysis of variance (metaphor/sarcasm vs 4 participant groups).

Among aged groups, we conducted the repeated measures analysis of covariance (metaphor/sarcasm vs 3 participant groups) with covariates of age, sex, education, and MMSE scores. A post hoc test was conducted with multiple comparisons with Bonferroni correction. All analyses were conducted using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, New York). Significance was set as $P < .05$.

Results

Demographic scores are shown in Table 1. The results of the MSST are shown in Table 2 and Figure 1. The main effect indicated that sarcasm was more difficult to comprehend than metaphor ($F_{1,203} = 54.634$, $P < .001$), and interaction with participant groups was also significant ($F_{3,203} = 3.354$, $P = .020$). According to within-subject post hoc analysis, no significant difference was observed between metaphor and sarcasm scores in YNC ($P = .442$), whereas in ANC, aMCI, and mild AD, scores of sarcasm was significantly lower than that of metaphor ($P < .001$ in all the groups). According to between-subject post hoc analysis, metaphor scores were not different between YNC and ANC, whereas metaphor scores were significantly better in ANC than in aMCI ($P = .011$) and in aMCI than mild AD ($P < .001$). Sarcasm scores were significantly better in YNC than in ANC ($P = .040$), in ANC than in aMCI ($P = .005$), and in aMCI than in mild AD ($P = .002$).

Concerning the error patterns, group differences were observed only in literal interpretation and there were no group differences in the other 3 error patterns (an answer associated with a part of the sentence, misunderstanding of the sentence, and not knowing; Table 3, Figure 2). The main effect was significant ($F_{1,203} = 34.283$, $P < .001$) and interaction was also significant ($F_{3,203} = 6.887$, $P < .001$). According to the between-subject post hoc analysis, frequency of the errors of literal interpretation of metaphor and sarcasm comprehension were not different between YNC and ANC ($P = 1.000$ in both), and ANC and aMCI ($P = .115$, $P = .349$, respectively), whereas a significant difference was observed between aMCI and mild AD ($P < .001$ in both). According to within-subject post hoc analysis, the errors of literal interpretation were more in sarcasm than in metaphor in aMCI ($P = .038$) and in mild AD ($P < .001$), whereas there was no significant difference in YNC ($P = .187$) and in ANC ($P = .072$).

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Table 1. Demographic Data.[a]

	n	Age Mean ± SD	Gender Male, Female	Education Mean ± SD	MMSE Mean ± SD
YNC	31	19.3 ± 1.4	M10, F21	13.3 ± 0.6	
ANC	104	72.1 ± 4.2	M25, F79	12.0 ± 2.3	28.4 ± 1.4
aMCI	42	74.0 ± 5.4	M18, F24	11.1 ± 3.0	25.8 ± 1.7
AD	30	78.0 ± 7.2	M6, F24	9.3 ± 2.3	21.4 ±4.0

Abbreviations: YNC, young normal controls; ANC, aged normal controls; aMCI, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1; MMSE, Mini-Mental State Examination; SD, standard deviation.

[a] The rate of gender difference was not different among the groups ($P = .088$, chi-squared statistic). Concerning age, there was no difference between ANC and aMCI, but patients with mild AD were significantly older than ANC and aMCI ($P < .001$, $P = .004$, respectively). Concerning years of education, there was not difference between ANC and aMCI, but patients with mild AD received significantly shorter education than the patients with ANC and aMCI did ($P < .001$, $P = .006$, respectively). Scores of MMSE was significantly different among groups ($P < .001$, among all the groups).

Table 2. Correct Answers.

	Metaphor Mean ± SD	Metaphor P Value[a]	Sarcasm Mean ± SD	Sarcasm P Value[a]	P Value[b]
YNC	5.0 ± 0.2		4.8 ± 0.4		.442
YNC vs ANC		1.000		.040*	
ANC	4.8 ± 0.7		4.1 ± 1.2		<.001**
ANC vs aMCI		.011*		.005*	
aMCI	4.3 ± 1.2		3.4 ± 1.3		<.001**
aMCI vs AD		<.001**		.002*	
AD	3.3 ± 1.2		2.3 ± 1.6		<.001**

Abbreviations: YNC, young normal controls; ANC, aged normal controls; aMCI, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1; SD, standard deviation.

[a] The difference among groups analyzed by between-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

[b] The difference between metaphor and sarcasm analyzed by within-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

* $P < .05$.

** $P < .001$.

There was weak correlation between MMSE scores and metaphor ($r = .362$ $P < .001$) and sarcasm scores ($r = .337$, $P < .001$).

The difference among the aged groups of ANC, aMCI, and mild AD remained by the repeated measures analysis of covariance with covariates of age, sex, education, and MMSE scores. According to within-subject post hoc analysis, in ANC, aMCI, and mild AD, scores of sarcasm was significantly lower than that of metaphor ($P < .001$, $P < .001$, $P = .004$, respectively). According to between-subject post hoc analysis, metaphor scores were significantly better in ANC than in aMCI ($P = .040$) and in aMCI than mild AD ($P = .002$). Sarcasm comprehension was significantly better in ANC than in aMCI ($P = .021$) and in aMCI than in mild AD ($P = .023$).

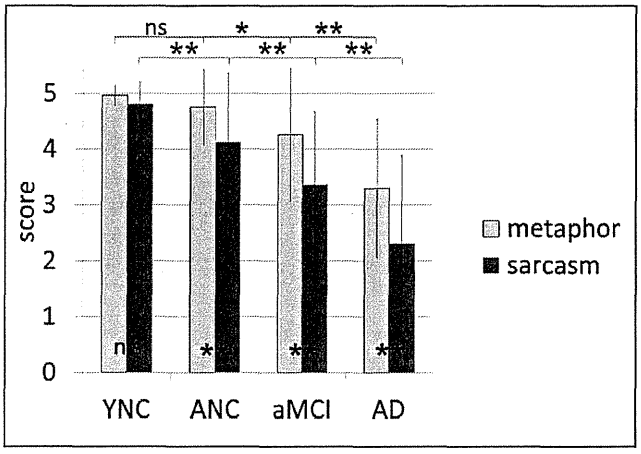

Figure 1. Scores of correct answers. Sarcasm scores were significantly lower in ANC than YNC, whereas metaphor scores were not different between the 2 groups. Metaphor scores were deteriorated from MCI. Post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups) was conducted; * in upper row indicates statistical significance of between subject analysis of metaphor, * in middle row indicates that of sarcasm, and * in the bottom row indicates statistical significance calculated by intrasubject analysis. *$P < .05$, $P < .001$. YNC indicates young normal controls; ANC, aged normal controls; aMCI, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1.

Table 3. Errors of Literal Answers.

	Metaphor Mean ± SD	Metaphor P Value[a]	Sarcasm Mean ± SD	Sarcasm P Value[a]	P Value[b]
YNC	0.00 ± 0.00		0.19 ± 0.40		.187
YNC vs ANC		1.000		1.000	
ANC	0.05 ± 0.21		0.19 ± 0.44		.072
ANC vs aMCI		.115		.349	
aMCI	0.21 ± 0.47		0.48 ± 0.77		.038*
aMCI vs AD		<.001**		<.001**	
AD	0.87 ± 0.82		1.77 ± 1.72		<.001**

Abbreviations: YNC, young normal controls; ANC, aged normal controls; aMCI, amnestic mild cognitive impairment; AD, patients with mild Alzheimer's disease in clinical dementia rating 1; SD, standard deviation.

[a] The difference among groups analyzed by between-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

[b] The difference between metaphor and sarcasm analyzed by within-subject post hoc analysis of 2 × 4 analysis of variance (metaphor and sarcasm; 4 groups).

* $P < .05$.

** $P < .001$.

Discussion

Scores for both metaphor and sarcasm were not significantly different from each other in YNC, which confirmed that the difficulty level of metaphor and sarcasm comprehension tested by MSST was not different, at least among young participants.

The result suggested that deterioration of sarcasm comprehension was an age-related change. Sarcasm scores were

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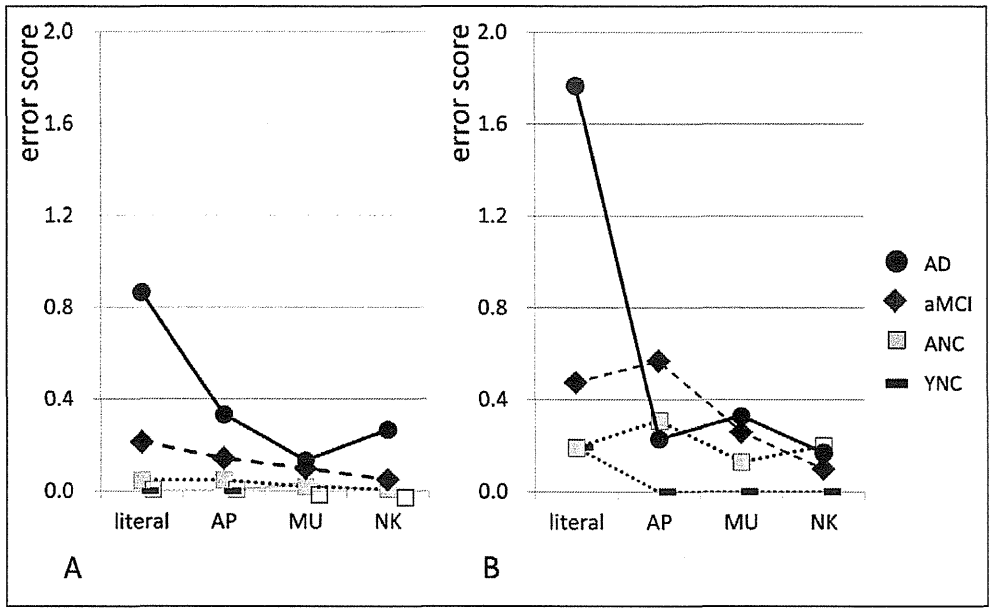

Figure 2. Error patterns. Error patterns of metaphor (A) and sarcasm (B). Significant differences among groups were observed in literal errors in both metaphor and sarcasm and the other 4 patterns of error were not significantly different among groups. AD indicates patients with mild Alzheimer's disease in clinical dementia rating 1; aMCI, amnestic mild cognitive impairment; ANC, aged normal controls; YNC, young normal controls; literal, literal interpretation; AP, answers associated with part of the sentence; MU, misunderstanding of the sentence; NK, not knowing.

significantly lower in ANC than in YNC, whereas no difference was observed in metaphor comprehension. Empirical developmental studies of normal children have found that metaphors are comprehended at an earlier age than ironies.[4] One factor critical for understanding verbal irony (sarcasm) is an individual's ability to attribute appropriate second-order ToM.[4] The success of the second-order ToM task emerges at around age 5 or 6[25] and it has been revealed that age-related decline occurred directly in the second-order ToM and indirectly in the first-order ToM.[26] The influence of difference in difficulty level could not be ruled out. Colston and Gibbs have shown that it takes healthy adults longer to read ironic than metaphoric statements, which suggests that irony (sarcasm) processing requires more cognitive load than metaphor processing.[5]

Age-related decline in metaphor comprehension was not shown in the present study. The deterioration was reported in the early stage of AD by a study that did not include the participants with MCI,[16-18] and the present study showed that comprehension begins to decline even during aMCI, the prodromal stage of AD.

Another issue was with the comprehension of conventional metaphor. In the present study, conventional metaphor comprehension was deteriorated as well as nonconventional novel expressions, as shown in previous studies.[16,17] However, Amanzio et al reported the deficits in nonconventional novel metaphors, while no impairment was observed in conventional metaphors.[18] The study assumed that conventional metaphors might be interpreted automatically through frequent usage, whereas novel metaphors recruited ToM processes. However, the patients might tend to avoid complicated pragmatic wording and without usage in everyday speech, conventional metaphors could recruit ToM processes as novel metaphors.

Deficits of AD were characterized by literal interpretation; concerning error patterns, group differences were observed only in the pattern of literal interpretation. Decline of inhibition could be related to choosing literal interpretation. Metaphor and sarcasm comprehension requires contextual coherence judgment, as literal interpretation can be taken out of context. It has been proposed that both the literal and the nonliteral meaning are activated concurrently and the inappropriate meaning is inhibited by the context.[27-31] However, patients with AD had difficulty suppressing inappropriate literal interpretation, which is concurrently activated.[32,33] Literal interpretation of metaphor causes misunderstanding and that of sarcasm could be more problematic. In sarcastic expression, the speakers say the opposite of what they mean[15] and thus the patients with AD may interpret the utterance as admiration, which would be opposite to the speakers' intention. Such misinterpretation would result in social miscommunication.

Miscommunication between patients and caregivers could lead to behavioral and psychological symptoms of dementia (BPSD) in patients and distress in caregivers.[34-37] Therefore, caregivers' understanding of decreased communication abilities in patients may reduce BPSD and caregiver distress.[38,39]

As a limitation, the groups of the present study were not matched for age and education. Based on the results of the present study, further study is required with a larger group of participants for consideration of clinical relevance.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Relative preservation of the recognition of positive facial expression "happiness" in Alzheimer disease

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ABSTRACT

Background: Positivity recognition bias has been reported for facial expression as well as memory and visual stimuli in aged individuals, whereas emotional facial recognition in Alzheimer disease (AD) patients is controversial, with possible involvement of confounding factors such as deficits in spatial processing of non-emotional facial features and in verbal processing to express emotions. Thus, we examined whether recognition of positive facial expressions was preserved in AD patients, by adapting a new method that eliminated the influences of these confounding factors.

Methods: Sensitivity of six basic facial expressions (happiness, sadness, surprise, anger, disgust, and fear) was evaluated in 12 outpatients with mild AD, 17 aged normal controls (ANC), and 25 young normal controls (YNC). To eliminate the factors related to non-emotional facial features, averaged faces were prepared as stimuli. To eliminate the factors related to verbal processing, the participants were required to match the images of stimulus and answer, avoiding the use of verbal labels.

Results: In recognition of happiness, there was no difference in sensitivity between YNC and ANC, and between ANC and AD patients. AD patients were less sensitive than ANC in recognition of sadness, surprise, and anger. ANC were less sensitive than YNC in recognition of surprise, anger, and disgust. Within the AD patient group, sensitivity of happiness was significantly higher than those of the other five expressions.

Conclusions: In AD patient, recognition of happiness was relatively preserved; recognition of happiness was most sensitive and was preserved against the influences of age and disease.

Key words: dementia, Alzheimer disease, emotional face recognition, positivity bias, aging, happiness, social interaction, morphing technology

Introduction

Deficits in the recognition of emotional facial expressions might lead to behavioral disturbances that often accompany Alzheimer disease (AD), and behavioral features are more distressing than cognitive deficits for caregivers of patients with AD (Donaldson *et al.*, 1998). Facial expressions are universally identified into six basic expressions: happiness, sadness, surprise, anger, disgust, and fear (Ekman *et al.*, 1971). The human face conveys non-verbal information about emotional states, the recognition of which is critical for appropriate social behavior.

In aged individuals, positivity recognition bias has been reported for facial expression (Mather and Carstensen, 2003; 2005). The positivity recognition bias was well-studied with memory; aged individuals remember a larger quantity of positive events than negative ones, and show more emotionally positive memory distortion for autobiographical information than younger adults do (Mather and Carstensen, 2005). Such positivity bias in aged individuals has been consistently reproduced in experimental settings of various recognition modalities such as emotional facial recognition and visual stimuli as well as memory (Mather and Carstensen, 2003; 2005; Kapucu *et al.*, 2008; Spaniol *et al.*, 2008). However, studies on emotional facial recognition in AD

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patients have produced various results. First, it is controversial whether facial recognition itself is declined or not; some studies reported preserved ability of emotional facial recognition (Bucks *et al.*, 2004; Luzzi *et al.*, 2007; Guaita *et al.*, 2009; Yamaguchi *et al.*, 2012), whereas others reported impairments (Spoletini *et al.*, 2008; Bediou *et al.*, 2009; Drapeau *et al.*, 2009). It is also controversial whether there were differences in the recognition of various emotions. Some studies reported no difference (Bucks *et al.*, 2004; Luzzi *et al.*, 2007), whereas others reported differences, e.g. selective impairment was reported in labeling the facial expression of sadness (Hargrave *et al*, 2002), and recognition of happy facial expressions was reported to be relatively preserved in comparison with angry facial expressions (Yamaguchi *et al.*, 2012). It was also reported that the most identified emotion was happiness among seven facial expressions (six basic expressions and boredom) in the moderate and severe stage of dementia (Guaita *et al.*, 2009).

The controversy may be partly due to confounding factors. Some studies have suggested involvement of confounding factors such as deficits in spatial processing of non-emotional facial features and in verbal processing to express emotions (Cadieux *et al.*, 1997; Burnham *et al.*, 2004). The deficits shown in the experiments could be due to the decline of the spatial recognition and/or verbal processing, which were prominent in AD. Thus, in the present study, we demonstrated characteristics of emotional face recognition in AD patients, by adapting a new method that eliminated the influences of these confounding factors to reveal whether the recognition of positive expressions is relatively preserved in AD.

Methods

Participants

The participants were 12 outpatients with mild AD in Clinical Dementia Rating scale (CDR) 1, 17 aged normal control (ANC), and 25 young normal control (YNC). Participants were limited to mild AD patients to eliminate the influence of difficulties of understandings of the rules. The exclusion criteria were: prosopagnosia, psychiatric diseases, delirium, and verbal incomprehension including aphasia. Those who had weak in eyesight were also excluded; all the participants could distinguish a 2-pixel gap (0.58 mm) on a 15″ monitor screen of Landolt ring from 70 cm away. Subjects were diagnosed based on the criteria for AD by NINCDS-ADRDA (Dubois *et al.*, 2007). Scores over 7 on the Japanese version of the Short Form of the Geriatric Depression Scale (Yesavage *et al.*, 1982) were also excluded because depressive tendencies could affect facial recognition. The Ethics Board of the Gunma University School of Health Sciences approved all procedures (No. 21-26), and written informed consent was obtained from all the participants.

Stimuli

Six hundred colored face images of six basic emotional expressions (happiness, surprise, anger, sadness, fear, and disgust) were used. To eliminate confounding factors related to individual difference in non-emotional facial features and ways to express emotions, we used standardized photos of four Japanese women (one neutral and six basic expression photos for each person) in database DB99 (Advanced Telecommunications Research Institute International, Inc. Nara, Japan); facial features and expressions of non-Japanese individuals could be confounding factors for Japanese. Then we made "averaged faces", which canceled individual differences. We prepared one neutral and six emotional expression (100% expression faces) averaged faces by morphing photos of four women. For grading the ability, we prepared photos of 1%–99% intermediate expression levels of each emotion by morphing neutral and 100% expression faces with weight. In this way, the images of 600 emotional averaged faces were prepared; e.g. 38% happy image was made by morphing the 100% happy image and the neutral image with a ratio of 38–62. Each image was framed by an oval to avoid the influence of hairstyle and clothing.

Experimental setting

The experimental setting is shown in Figure 1A (stimuli were in color in the experimental setting). One of the images of intermediate expression levels was displayed on the monitor of touch panel screen in the left, and six small faces of 100% expression were displayed on the right. To eliminate the confounding factor of verbal processing, the participants were required to answer by touching the 100% face that corresponded to the expression of intermediate face. Using the choice of faces instead of verbal labels, even those who had difficulties in verbal processing could answer the question.

The sensitivity of expression was measured using staircase method. The orders of six expressions were randomized using a computer program, and the first stimulus was 100% expression faces in each expression. In each expression respectively, if the response was correct, the level of stimuli increased in the next trial (ex. 38%–35% expression face).

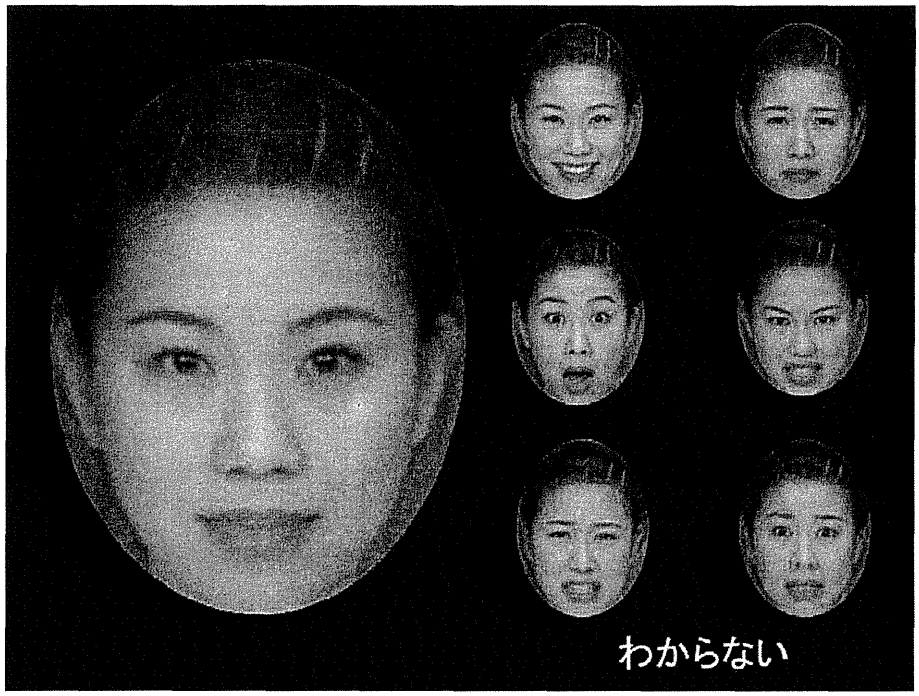

Figure 1. A stimulus shown on the monitor. On the left of the screen, 27% happy face was shown; recognition of 27% happy face corresponded to the sensitivity of 73%, which was the average sensitivity in patients with Alzheimer disease (AD). On the right, six kinds of 100% expressions were shown. The participants were required to choose and tough one of the 100% faces corresponding to the face on the left. The Japanese letters on the right bottom means to have no idea, and they could choose the option.

Alternatively if the participant made an error, the level of stimuli decreased in the subsequent trial. When the sequence was switched from ascending to descending or *vice versa*, the level was recorded as a reversal point score. The levels were changed by 15% until the first reversal point, after that, by 3%. The experiment was continued until the four reversal points were obtained. The average of the third and fourth reversal point scores was used as the sensitivity of the expression. Sensitivity was the difference calculated by subtracting expression level from 100(%); the sensitivity corresponding to 38% expression face was 62. We used the screen of a 15″ touch panel connected to a PC running C++ software based on Windows XP. Before the experimental session, a practice session was conducted. In the practice session, 100% expression images were displayed as stimuli and the participants were confirmed to be capable to match the same expression on the right, where six small faces of 100% expression were displayed as choices. The participants were also required to explain the emotion verbally to confirm that they recognized each emotion.

Statistical analysis

AD patients, ANC, and YNC were compared by using repeated-measured analysis of variance (ANOVA; 3 groups × 6 basic expressions) followed by *post hoc* testing with Bonferroni correction. According to *post hoc* analysis, significantly higher sensitivity in YNC compared with ANC was defined as age effects, and significantly higher sensitivity in ANC compared with AD patients was defined as AD effects. The data were analyzed using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, New York). Significant differences are set for two-tailed $p = 0.05$ for all analyses.

Results

The ages of the participants were 81.1±9.2 years in mild AD, 76.8±3.5 years in ANC, and 18.9±1.1 years in YNC, and there was no significant difference between age of AD patients and that of ANC by two sample *t*-test. Sensitivities of the three groups and comparisons are shown in Figure 2 and Table 1. There was a significant difference among three groups in perception of facial expressions. According to the *post hoc* analysis, both age and AD effects were observed for anger and surprise (anger: age effects $p = 0.031$, AD effects $p < 0.001$; surprise: $p < 0.001$, $p = 0.029$), whereas for happiness and fear, neither age effects nor AD effects were observed (happiness: $p = 0.138$,

Table 1. Age effects and Alzheimer disease effects

	HAPPINESS	SADNESS	SURPRISE	ANGER	DISGUST	FEAR
†YNC	86.7 ± 14.0	63.1 ± 22.9	81.1 ± 8.9	66.8 ± 15.1	55.5 ± 14.9	55.0 ± 15.3
§*YNC versus ANC*	*0.138*	*0.183*	*<0.001***	*0.031**	*<0.001***	*0.178*
††ANC	76.8 ± 16.8	48.3 ± 25.8	63.9 ± 14.3	55.0 ± 12.3	32.4 ± 19.2	43.9 ± 13.7
¶*ANC versus AD*	*1.000*	*0.048**	*0.029**	*<0.001***	*0.718*	*1.000*
AD	72.8 ± 15.8	25.3 ± 26.0	50.5 ± 18.4	23.4 ± 14.5	25.0 ± 14.6	37.3 ± 28.0

†YNC: young normal controls; ††ANC: aged normal controls; §age effects: significantly higher sensitivity of YNC in comparison with ANC; ¶AD effects: significantly higher sensitivity of ANC in comparison with AD. Both of the age and AD effects were shown by p values of intrasubject *post hoc* analysis with Bonferroni correction of 3 × 6 repeated measured ANOVA (three groups of YNC, ANC, and AD, and six expressions). *$p < 0.05$, **$p < 0.001$.

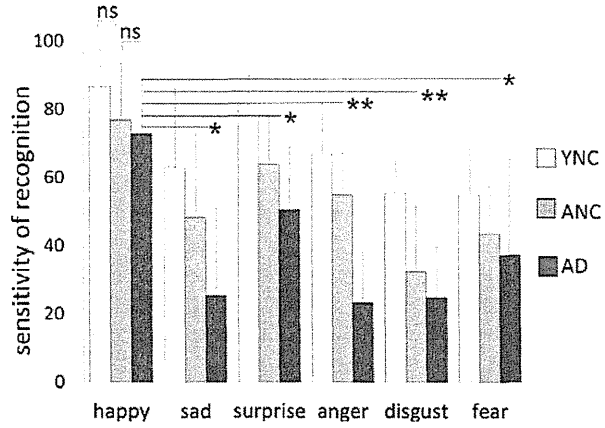

Figure 2. Results of sensitivities of the young normal controls (YNC), the aged normal controls (ANC), and the AD patients. Error bars indicate standard deviation. Regarding recognition of happy and fear faces, there was no significant difference between YNC and ANC, and ANC and AD patients. Regarding recognition of surprise and anger faces, there was significant difference between YNC and ANC, and ANC and AD patients. There was significant difference between ANC and AD in sad face recognition, and between YNC and ANC in disgust recognition. Within AD patients, sensitivity of happy face was significantly higher than that of other expressions. *$p < 0.05$, **$p < 0.001$.

$p = 1.000$; fear: $p = 0.178$, $p = 1.000$). For sadness, AD effects were observed ($p = 0.048$), whereas age effects were not ($p = 0.183$). However, for disgust, age effects were observed ($p < 0.001$), whereas AD effects were not ($p = 0.718$). Within AD patients, sensitivity of happiness was significantly higher than those of the other five expressions, and that of surprise was significantly higher than those of anger and disgust.

Discussion

This study showed that recognition of happy facial expressions was relatively preserved in AD patients. Recognition of happiness was significantly easier than recognition of five other expressions and there were no age effects or AD effects. Regarding negative expressions, age effects were observed in recognition of anger and disgust, and AD effects were observed in recognition of sadness and anger. Surprise had a neutral emotional valence and both effects were observed in surprise recognition.

The results from this study should be reliable because the task used involved a sophisticated matching task that improved on problems in previous studies to cancel confounding factors. In previous experimental settings, participants were required to match the expression of photos of different people. Thus, impairment in the matching could be a result of visuospatial dysfunctions rather than deficits in processing emotions (Ekman *et al.*, 1971). Upon misunderstanding of individual differences in facial features, the participants might fail to extract the emotional implications. The stimuli used in the present study were averaged faces with different emotional valence, where non-emotional features were shared. Thus, differences in features are directly related to emotional differences. Another merit of this matching task was to eliminate the cognitive process to convert perception to abstract verbal expression; abstract thinking and verbal recognition also decline in AD patients. The use of images of Japanese individuals for Japanese participants also eliminated irrelevant cognitive load. Social recognition, including

emotional facial expression, has sociocultural implications, and expression of facial emotions could be influenced by cultural backgrounds (Ekman *et al.*, 1987; Shioiri *et al.*, 1999).

Adding to canceling confounding factors, another advantage of this method is the precise measurement of the sensitivity by using the intermediate level of expressions. In the often used experimental settings, the participants were required to classify the photos of typical emotional faces (100% in the present study) by emotional expression. According to a meta-analysis of 17 studies on emotion recognition and aging, the average of the stimuli of one emotion was around 7. Concerning happiness recognition, the magnitude of the difference between young and aged subjects is potentially masked by a ceiling effect, with young subjects scoring 98% or better in 15 out of 17 studies (Ruffman *et al.*, 2008). Such ceiling effects could exist in the experiments comparing aged subjects and AD patients, thus more sensitive tests with subtle stimuli are desirable. In the present study, we applied 1%–99% intermediate levels of expression, which enabled precise measures of sensitivity.

After eliminating the confounding factors of deficits in spatial processing of non-emotional facial features and in verbal processing to express emotions, positivity bias in ANC was shown, in that recognition of happiness was spared in comparison with YNC. In AD patients, recognition of happiness was spared in comparison with ANC. Hargrave *et al.* (2002) reported that AD patients showed selective impairment in labeling facial expressions of sadness compared with ANC. The results were not identical, as there were differences in the methods used to eliminate the confounding factors of facial features of different people. Hargrave *et al.* (2002) tried to remove the factors by analysis. The experimental setting involved matching the emotion displayed on the reference face with one of six simultaneously presented alternatives, and all seven photographs were faces of different people. A multivariate analysis of covariance (MANCOVA) model was adapted using each subject's score on the facial identity matching task as a covariate. The advantage of the present study is eliminating the confounding factors at the experimental phase.

The mechanism of positivity recognition bias in aged individuals and AD patients remains unproven. Positivity bias in aged individuals was explained by lifetime perspective motivational changes; as the time perspective is reduced, current emotional goals associated with well-being become more important (Carstensen *et al.*, 1999). Consequently, aged individuals would tend to allocate more cognitive resources to improve emotion regulation, and their information processing was characterized by a positivity bias (Mather and Carstensen, 2005; Mather and Knight, 2005; Brassen *et al.*, 2011). Within this framework, positivity bias in facial emotional recognition could be explained by shifts in attention allocation for positive stimuli (Mather and Carstensen, 2005; Goeleven *et al.*, 2010).

Concerning such allocation of cognitive resources to emotion regulation, capacities of cognitive resources should be considered. Mather and Knight reported that aged individuals with superior cognitive abilities were more likely to exhibit positivity bias (Mather and Knight, 2005). In line with the report, the positivity bias should be reduced in AD patients with cognitive decline. However, the experiment was conducted on memory, and if the allocation occurred only in the remembering phase, and not the memorizing phase, the explanation could not be applied to facial recognition. Goeleven *et al.* (2010) suggested that increased age is associated with reduced allocation of resources to negative stimuli, and the explanation could also be true in AD patients.

The present study showed decreases of negative emotion recognition and relatively preserved positive recognition. Our results are in line with the conclusions based on the meta-analysis of Murphy and Issacowitz, which revealed an age-related decrease of negativity preference as compared to an increased positivity preference (Murphy and Isaacowitz, 2008). The above explanations are still hypotheses, and specifying the interaction between cognitive decline and emotion processing would be a valuable topic for future research.

Regarding study limitations, it is possible that recognizing happy facial expressions was easier, as this was the only positive emotion in the study. The differentiation of the four negative expressions, sadness, anger, disgust, and fear, was more difficult. Thus, the results should be confirmed in an experimental setting using stimuli with three facial expressions: happiness, a negative emotion, and a neutral expression.

This study showed that recognition of happy facial expressions was relatively preserved in AD patients; the results could be generalized to other ethnicity because emotional facial recognition is basically universal. These experimental results may be useful if they are implemented in a way to improve the daily life of AD patients. Caregivers should take advantage of cues from happy facial expressions to provide beneficial care.

Conflict of interest

None.