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Increased binding of peripheral benzodiazepine receptor in mild cognitive impairment–dementia converters measured by positron emission tomography with [^{11}C]DAA1106

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ABSTRACT

Subjects with mild cognitive impairment (MCI) have "prodromal or incipient" dementia with neuropathological changes. Peripheral benzodiazepine receptor (PBR) binding was shown to reflect activated microglia, one of the predictive biomarkers of conversion to dementia. We sought to evaluate PBR binding in MCI subjects using positron emission tomography (PET). PET scans with [^{11}C]DAA1106, a potent and selective ligand for PBR, were performed on seven MCI subjects, 10 patients with Alzheimer's disease (AD) and 10 age-matched control subjects. PBR binding in the regions of interest was quantified by binding potential (BP). Five MCI subjects were clinically followed for 5 years after their initial PET scans. [^{11}C]DAA1106 binding to PBR was significantly increased in widespread areas in MCI subjects when compared to healthy controls. We found no significant difference in BP between MCI and AD patients. MCI subjects with [^{11}C]DAA1106 binding values higher than the control mean +0.5 standard deviation (S.D.) developed dementia within 5 years. Our finding of higher DAA binding in MCI subjects indicated that microglial activation may occur before the onset of dementia. In vivo detection of microglial activation may provide useful prognostic information with respect to stratifying MCI subjects at increased risk of dementia.

1. Introduction

Mild cognitive impairment (MCI) refers to the syndromes of cognitive impairment beyond that expected with normal aging, but that do not fulfill the criteria for dementia. A recent neuropathological study in subjects with MCI reported that the majority had "prodromal or incipient" dementia with pathological changes (Petersen, 2004; Petersen et al., 2006). Subjects with MCI are therefore at increased risk of developing dementia. However, not all subjects with MCI will progress to dementia, and longitudinal studies have focused on identifying predictive biomarkers of conversion to dementia, including neuropsychological, neuroimaging, and cerebral spinal fluid (CSF) markers.

Local glial response including activation of microglia is expected to be one of the predictive biomarkers of conversion to dementia. Its involvement in the process of deposition or degradation of amyloid has been suggested (Cummings et al., 1992; Frackowiak et al., 1992; Wisniewski et al., 1992; el Hachimi and Foncin, 1994). The release of various cytokines and cytotoxic molecules from microglia was believed to result in secondary tissue damage (Barger and Harmon, 1997; Tan et al., 1999). The visualization of activated glial cells in the brain by positron emission tomography (PET) or single photon emission computed tomography (SPECT) was considered useful for investigating the role of the activation of glial cells in the disease process. Peripheral benzodiazepine receptors (PBR) were reported to reflect neuronal injury and inflammatory lesions in the brain by the increased expression of the number of binding sites in glial cells including activated microglia and reactive astrocytes, as previously indicated by autoradiography of Alzheimer's disease (AD) (Diorio et al., 1991; Kuhlmann and Guilarte, 2000).

[^{11}C]PK11195 and [^{123}I]iodo-PK11195 are widely used to visualize PBR in the brain, and especially for the evaluation of lesions, by PET and SPECT, respectively (Hashimoto et al., 1989; Dumont et al., 1999). The binding of these ligands was reported to be increased in stroke regions (Sette et al., 1993; Gerhard et al., 2005; Price et al., 2006), plaques of multiple sclerosis (Banati et al., 2000; Debruyne et al., 2002) and epileptic foci (Goerres et al., 2001). These reports suggested the diagnostic value of PBR binding. Increased binding of [^{11}C]PK11195 and [^{123}I]iodo-PK11195 in the limbic and cortical

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regions has also been reported in patients with AD and other neurodegenerative disorders including frontotemporal dementia and Parkinson disease (Cagnin et al., 2001; Versijpt et al., 2003). One recent study showed microglial activation in approximately 50% of MCI subjects (Okello et al., 2009).

Several novel PBR radioligand candidates have recently been developed, and a number of them are in various phases of pre-clinical and clinical testing, including [^{18}F]PBR06, [^{11}C]PBR28, [^{11}C]DPA713, [^{18}F]DPA 714 and [^{11}C]vinpocetine (Gulyás et al., 2005; Fujita et al., 2008; Chauveau et al., 2009; Fujimura et al., 2009). (*N*-5-fluoro-2-phenoxyphenyl)-*N*-(2,5-dimethoxyl-benzyl) acetamide (DAA1106) is a potent and selective ligand for PBR, with a different structure from other PBR compounds such as PK11195 and Ro5-4864 (Chaki et al., 1999; Okuyama et al., 1999). [^{11}C]DAA1106 binding was markedly inhibited by unlabeled DAA1106 and PK11195 in the monkey brain, suggesting that most of the [^{11}C]DAA1106 binding represents specific binding (Maeda et al., 2004). The radiolabeled metabolite of [^{11}C] DAA1106 was more polar than [^{11}C]DAA1106, and did not cross the blood–brain barrier (BBB) in mice (Zhang et al., 2003).

In a previous study of in vitro autoradiography of radio-iodinated analogues of DAA1106 on human post-mortem brain slices of AD patients and age-matched controls, specific binding in several brain structures in AD was shown to be significantly higher (Gulyás et al., 2009). In our previous study, we showed that [^{11}C]DAA1106 provides a sensitive tool for the determination of pathological changes in the living human brain. In a comparison of healthy controls and AD patients, we showed a widespread increase of PBR binding measured with [^{11}C]DAA1106 in the brain of AD patients (Yasuno et al., 2008).

The objective of the present study is to quantify PBR in the brain of MCI subjects using [^{11}C]DAA1106. MCI subjects have been clinically followed for 5 years after their initial PET scans.

2. Materials and methods

2.1. Subjects with MCI, AD and controls

Subjects fulfilling Petersen's criteria for MCI (Petersen, 2004) were recruited from the outpatient units of university-affiliated psychiatric hospitals and the psychiatric divisions of general hospitals. MCI subjects have to meet the following criteria: cognitive complaint, cognitive function not normal for age, decline in cognition, essentially normal functional activities, and no dementia. The patients with MCI were further classified into one of the following four MCI subtypes: 1) single-domain amnestic MCI, if the impairment was only in the memory domain; 2) multiple-domain amnestic MCI, if the impairment was in the memory domain plus one or more other domains; 3) single-domain nonamnestic MCI, if the impairment was only in the non-memory domain with relative preservation of memory; and 4) multiple-domain nonamnestic MCI, if the impairment was in more than one domain with relative preservation of memory. Demographic and clinical data of the participants are presented in Table 1. We studied seven subjects with MCI (three women, four men) between 52 and 78 years old (67.1 ± 10.7 yrs; mean ± standard deviation (S.D.)).

The patients with AD were recruited from the outpatient units of university-affiliated psychiatric hospitals and the psychiatric divisions of general hospitals. The diagnosis of probable AD was made in accordance with criteria defined by the Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition (DSM-IV) and the guidelines of the National Institute of Neurological Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINDS-AIREN) (McKhann et al., 1984). The healthy subjects were recruited among those participating in a community-based prospective cohort study performed in Ibaragi prefecture in Japan. Demographic and clinical data of the participants are presented in Table 1. We studied 10 healthy controls (three women, seven men) between 55 and 73 years old (67.9 ± 5.0 yrs) and 10 AD patients (five women, five men) between 58 and 79 years old (70.2 ± 7.4 yrs).

All individuals were seen by experienced geriatric psychiatrists or neurologists, and general medical or neurological disease was ruled out by extensive general medical screening, neurological assessment, and brain magnetic resonance imaging (MRI). Subjects were excluded if they showed any major structural abnormalities or signs of major vascular pathology on MRI, such as status post-infarction, extensive leukoencephalopathy, intracerebral aneurysm or arteriovenous malformation. National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia were used to exclude relevant ischemic processes causing cognitive impairment in the patients (Roman et al., 1993).

The subjects were physically active and did not have a past or current history of mood, anxiety, or psychotic disorders or of substance abuse or dependence, based on screening interviews of the subjects and/or their caregivers. Subjects with recreational alcohol (≤2 drinks per day; 1 drink corresponding to approximately to 125 ml of wine, 330 ml of beer or 30 ml of hard liquor) and/or nicotine use (≤20 cigarettes per day) not meeting the criteria for dependence of the DSM-IV were allowed to participate in the study.

Table 1
Participant characteristics.

Subjects	Age	Sex	Disease duration (years)	MMSE score	ADAS-cog score	CDR	Drug
MCI							
1	52	M	2	30	2	0.5	None
2	57	M	3	30	5	0.5	None
3	61	M	2	29	6	0.5	None
4	68	F	3	29	5	0.5	None
5	76	F	1	27	4	0.5	None
6	78	F	2	28	5	0.5	None
7	78	M	3	27	5	0.5	None
AD							
1	58	F	3	16	18	2	None
2	61	M	1	24	15	1	None
3	63	F	2	22	16	1	Donepezil (5 mg), 1 year
4	67	M	1	20	20	1	None
5	73	F	1	24	15	1	None
6	73	M	1	22	11	1	Donepezil (5 mg), 1 year
7	74	F	2	18	24	1	None
8	76	M	2	20	12	1	None
9	78	F	3	22	14	1	None
10	79	M	2	18	22	1	Donepezil (5 mg), 2 years
Controls							
1	55	F	–	30	4	0	None
2	67	M	–	30	3	0	None
3	67	F	–	30	2	0	None
4	67	M	–	30	2	0	None
5	68	M	–	30	3	0	None
6	70	M	–	30	3	0	None
7	70	F	–	28	7	0	None
8	71	M	–	29	4	0	None
9	71	M	–	30	3	0	None
10	73	M	–	30	7	0	None

MMSE = Mini-Mental State Examination, ADAS-cog = Alzheimer Disease Assessment Scale–cognitive subscale, CDR = clinical dementia rating.

All subjects were assessed with the clinical dementia rating (CDR) scale, in which we used a structured-interview protocol and assessed a patient's cognitive and functional performance in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Morris, 1993). The CDR scale of all MCI subjects was 0.5. All patients with AD had mild to moderate disease (CDR 1 = mild, CDR 2 = moderate). The Mini-Mental State Examination (MMSE) and Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-cog) were also used.

The onset of MCI and AD was defined as the time when the earliest cognitive change was noticed by responsible caregivers, with the duration of MCI and AD ranging from 1 to 3 years. Three patients had received donepezil (5 mg) medication for 1–2 years at the time of the PET scans. None of the other subjects, except these three patients, was taking any other psychotropic medications.

The MMSE scores of the MCI subjects ranged from 27 to 30 (28.6 ± 1.3), while those of controls ranged from 29 to 30 (29.7 ± 0.7) and AD patients from 16 to 24 (20.6 ± 2.7). ADAS-cog scores of MCI subjects ranged from 2 to 6 (4.6 ± 1.3), while those of controls ranged from 3 to 7 (3.8 ± 1.8) and AD patients from 11 to 24 (16.7 ± 4.2).

This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. After complete explanation of the study, written informed consent was obtained from all participants.

2.2. Neuropsychological evaluation

Extensive neuropsychological evaluations were performed for all subjects before the PET scans (Table 2). Five amnesic MCI subjects (MCI subjects 1, 3–6) showed abnormality of memory test scores (scores < controls' mean − 1.5 S.D.) (MCI vs. controls' mean: Wechsler Memory Scale–Revised (WMS-R) logical memory immediate, 14.6 ± 7.4 vs.22.4 ± 4.9; WMS-R logical memory delayed, 7.0 ± 3.9 vs. 17.3 ± 4.9), while the other two non-amnesic MCI subjects (MCI subjects 2 and 7) showed no memory disturbance (MCI vs. controls' mean: WMS-R logical memory immediate, 22.0 ± 1.4 vs. 22.4 ± 4.9;

WMS-R logical memory delayed, 18.5±3.5 vs. 17.3±4.9), but did show abnormality of parts A and B of the Trail Making Test (time(s)>control mean +1.5 S.D.) (MCI vs. controls' mean: Trail Making A, 180.5±17.7 vs.109.6±16.4; Trail Making B, 242.0±19.8 vs. 150.2±21.4). Two single domain amnesic MCI subjects (MCI 1, 3) showed only memory disturbance, while the other amnesic MCI subjects (MCI 4–6) had multiple domains of cognitive decline. All AD patients showed cognitive declines of multiple domains (AD vs. controls' mean: Rey–Osterrieth figure copy, 23.4±12.7 vs. 35.5±0.8; Rey–Osterrieth immediate recall, 1.6±2.1 vs. 22.7±7.1; WMS-R logical memory immediate, 5.6±4.4 vs. 22.4±4.9; WMS-R logical memory delayed, 0.7±1.8 vs. 17.3±4.9).

2.3. Clinical follow-up of MCI subjects

Five MCI subjects (MCI 2–6) were followed for 5 years at Tsukuba University Hospital after their DAA-PET scans, and four of these (MCI, 2, 4–6) had clinically converted to dementia. One non-amnesic MCI subject (MCI 2) had converted to dementia with Lewy bodies (DLB), and multiple domain amnesic MCI subjects (MCI 4–6) had converted to AD. One single domain amnesic MCI continued to fulfill the criteria for the diagnosis of MCI (MCI 3) (Table 2).

2.4. Image acquisition and analysis

PET scans were performed once for each subject using ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA), which provides 63 planes and a 15.5-cm axial field of view. A transmission scan with a ^{68}GE–^{68}GA source was followed by a 90-min dynamic scan (20 s*9, 60 s*5, 120 s*4, 240 s*11, and 300 s*6) with a bolus injection of 218 to 396 (360±32) MBq of [^{11}C]DAA1106. [^{11}C]DAA1106 was prepared as described previously (Zhang et al., 2003). The specific radioactivities were 11 to 88 (45.0±17.9) GBq/μmol at the time of injection. There was no significant difference in specific radioactivity among controls, MCI subjects and AD patients (47.6±16.3 for controls, 41.2±13.7 for MCI subjects and 43.2±22.4 for patients). Radioactivity was measured in three-dimensional mode and the data were reconstructed using a Hanning filter with a cut-off frequency of 0.4 (full width at half maximum=7.5 mm).

To obtain the arterial input function, an automated blood sampling system was used for continuous (counts/second) blood radioactivity measurements during the first 12 min of PET measurement (Eriksson et al., 1988). At the same time, arterial blood samples were taken manually and their radioactivity concentration was measured 13 times during the initial 3 min after the injection, eight times during the next 17 min, and once every 10 min until the end of the scan. The parent ligand, separated from the total radioactive compound, was measured as previously described (Ikoma et al., 2007). Unchanged [^{11}C]DAA1106 represented 95±2%, 47±4%, and 19±6% of total plasma activity in controls, 95±2%, 49±9%, and 21±5% in MCI subjects and 94±2%, 50±9%, and 20±6% in AD patients at 5, 20, and 60 min, respectively, and the plasma activity of the parent ligand peaked at 1 min and then decreased to less than 10% of the peak by 5 min. There was no difference in the ratio of parent ligand to total plasma radioactivity among controls, MCI subjects and AD patients. Plasma activity of the parent ligand also showed no difference among controls, MCI subjects and AD patients.

T1-weighted MRI of the brain was acquired with Philips Intera, 1.5T (Philips Medical Systems, Best, Netherlands). The scan parameters were 1-mm thick 3D T1 images with a transverse plane (Repetition Time (TE) / Echo Time (TE)=22/9.2 ms, flip angle=30°, matrix=128*128, field of view (FOV)=256*256).

Radioactivity concentration in 11 brain regions (dorsolateral prefrontal cortex, medial prefrontal cortex, lateral temporal cortex, parietal cortex, occipital cortex, anterior cingulate cortex, posterior cingulate cortex, striatum, thalamus, medial temporal region, and cerebellum) was obtained with a template-based method for defining volumes of interest (VOIs) (Yasuno et al., 2002). Briefly, this template-based method consisted of two major

Table 2
Neuropsychological test results of MCI subjects, AD patients and controls.

Subjects	MCI subtype	Conversion to dementia within 5-year follow-up	Period of examinations to dementia onset (years)	Rey–Osterrieth figure copy	Rey–Osterrieth figure immediate recall	WMS-R logical memory immediate recall	WMS-R logical memory delayed recall	Trail Making Test: time (s) part A	Trail Making Test: time (s) part B
MCI									
1	Single domain amnesic	Not followed	–	36	29	5[a]	4[a]	108	150
2	Non-amnesic	DLB	4	36	20.5	23	16	168[a]	228[a]
3	Single domain amnesic	Nonconverter	–	36	33.5	10[a]	5[a]	94	121
4	Multiple domain amnesic	AD	2	33[a]	18.5	15	9[a]	133	221[a]
5	Multiple domain amnesic	AD	3	34	14	19	4[a]	140	240[a]
6	Multiple domain amnesic	AD	1	36	8[a]	24	13	195[a]	280[a]
7	Non-amnesic	Not followed	–	36	32	21	21	193[a]	256[a]
AD									
1	–	–	–	10[a]	0[a]	1[a]	0[a]	Incomplete	Incomplete
2	–	–	–	33[a]	0[a]	5[a]	0[a]	302[a]	498[a]
3	–	–	–	27[a]	1.5[a]	4[a]	0[a]	250[a]	Incomplete
4	–	–	–	7.5[a]	0[a]	10[a]	0[a]	Incomplete	Incomplete
5	–	–	–	30[a]	4[a]	12[a]	6[a]	597[a]	Incomplete
6	–	–	–	36	5.5[a]	13[a]	0[a]	115[a]	287[a]
7	–	–	–	4.5[a]	0[a]	0[a]	0[a]	Incomplete	Incomplete
8	–	–	–	34.5	4[a]	4[a]	0[a]	320[a]	577[a]
9	–	–	–	9.5[a]	3[a]	7[a]	2[a]	Incomplete	Incomplete
10	–	–	–	36	0[a]	2[a]	0[a]	238[a]	478[a]
Controls									
1	–	–	–	36	28.5	23	16	111	109
2	–	–	–	36	18	25	16	85	130
3	–	–	–	36	19.5	22	12	107	158
4	–	–	–	35.5	33.5	18	17	102	169
5	–	–	–	36	27.5	26	20	112	154
6	–	–	–	36	27.5	18	17	135	178
7	–	–	–	34	14	15	12	110	150
8	–	–	–	36	28	19	13	130	170
9	–	–	–	34	13	29	27	85	130
10	–	–	–	35.5	17.5	29	23	119	154

WMS-R=Wechsler Memory Scale–Revised.
[a] 1.5 S.D. greater or smaller than control mean values.

steps: the first involved the spatial transformation of a template of a VOI on gray matter regions from a standard MRI to an individual MRI, and the second refined the transformed VOI to the individual segmented gray matter of the MRI using the intensity characteristics of these images. The finally refined VOIs on gray matter regions were linearly transformed with the parameters obtained from the coregistration of the individual MRIs to PET images. Manual correction was also applied to VOIs of the striatum thalamus. The VOI of the total measured region was also obtained by combining all measured brain regions.

Activity was shown as % standardized uptake value (%SUV), which was normalized for injected dose and body weight. %SUV = (% injected activity/cm^3 tissue) * (g body weight) (Yasuno et al., 2007). Mean %SUV images were acquired between 30 and 90 min after injection of [^{11}C]*DAA1106 in a typical example of an aged normal subject* and MCI and AD patients (Fig. 2).

Regional time-activity data were analyzed with two-tissue compartment models (2-TCM) (Cunningham and Lammertsma, 1995) using the metabolite-corrected plasma input function. Rate constants were estimated by weighted least squares and the Marquardt optimizer. For each region, K_1, k_2, k_3, k_4 and blood volume were estimated by 2-TCM. Binding potential (BP) was calculated as k_3/k_4 in 2-TCM in this analysis. In our previous study, BP of [^{11}C]DAA1106 was estimated most reliably by 2-TCM (Ikoma et al., 2007) using PMOD (PMOD Technologies, Zurich, Switzerland). However, because of the high noise level with a voxel level analysis of 2-TCM, we were unable to make representative BP maps with compartmental modeling (Ikoma et al., 2007). BP values of each of the healthy controls, MCI subjects and AD patients are shown in Table 3 and Fig. 1.

Statistical analysis was performed using SPSS for Windows 16.0 (SPSS Japan Inc., Tokyo, Japan). Group differences in the values of K_1–k_4 parameters, binding potential and VOI volume of the measured regions were evaluated by multivariate analysis of variance (MANOVA). When a significant group difference was shown with MANOVA, serial one-way analysis of variance (ANOVA) was performed to specify group differences in each measured region. Follow-up *t*-tests were performed to specify group-wise difference of BP and volumes between MCI and control, MCI and AD, and AD and control. All statistical tests were two-tailed and reported at $\alpha < 0.05$.

3. Results

The mean values of K_1–k_4 parameters across measured regions in controls, MCI subjects and AD patients were 0.053 ± 0.005, 0.064 ± 0.005 and 0.049 ± 0.005 for K_1, 0.073 ± 0.003, 0.092 ± 0.005 and 0.080 ± 0.005 for k_2, 0.048 ± 0.002, 0.059 ± 0.004 and 0.053 ± 0.004 for k_3 values, and 0.011 ± 0.001, 0.011 ± 0.001 and 0.010 ± 0.001 for k_4, respectively. For K_1–k_4 values, MANOVA of each value for groups showed no significant main effect of groups.

Mean BP values of MCI subjects and AD patients were higher than those of controls in all measured regions (Table 3). There was no relationship between age and [^{11}C]DAA1106 binding in any of the measured regions in each group within their age ranges. There was no relationship in each group between the scores of ADAS/MMSE and neuropsychological tests and BP values in any of the measured regions by Pearson's correlation analysis.

MANOVA of BP value for MCI, AD and controls showed a significant main effect of groups. ANOVA of BP values for groups showed a significant effect of groups on regional BPs in 6 of 11 regions. Follow-up unpaired *t* tests revealed that BP values of MCI subjects were significantly higher in the cerebellum, medial prefrontal cortex, parietal cortex, lateral temporal cortex, anterior cingulate cortex, and striatum ($p < 0.05$). After correction for multiple comparisons among MCI, AD and controls, the difference of BP remained significant in the lateral temporal cortex, parietal cortex, anterior cingulate cortex and striatum ($p < 0.05/3$).

We also found significant increases of BP in AD patients compared to controls in the cerebellum, medial prefrontal cortex, parietal cortex, lateral temporal cortex, anterior cingulate cortex, and striatum ($p < 0.05$). After the correction of multiple comparisons among MCI, AD and controls, the difference of BP was significant in these regions except the cerebellum ($p < 0.05/3$). We found no significant difference of regional BPs between MCI and AD patients (Table 3).

ANOVA of BP values of total measured regions for groups showed a significant effect of groups, and follow-up unpaired *t* tests revealed that BPs of MCI and AD patients were significantly higher when compared to controls (Table 3).

[^{11}C]DAA1106 binding of the whole measured region was increased in six of seven (77%) MCI subjects (>control mean + 0.5 S.D.) (Fig. 1). Five of these seven subjects were followed for 5 years after their PET study, and three of them (MCI 4–6) had converted to AD and one to dementia with Lewy bodies (MCI-2). One subject whose DAA binding was lowest and less than the control mean + 0.5 S.D. continued to fulfill the criteria for a diagnosis of MCI (MCI 3) (Table 2, Fig. 1).

MANOVA of VOI volumes for MCI, AD and control subjects showed a significant main effect of groups. ANOVA of VOI volumes showed a significant effect of groups on regional volumes in 4 of 11 regions. Follow-up unpaired *t* tests revealed that the volumes of VOIs of MCI were significantly smaller than those of controls in the lateral temporal cortex and posterior cingulate cortex ($p < 0.05$). After correction for multiple comparisons among MCI, AD and control subjects, the difference of the volume of the VOI was significant in the lateral temporal cortex ($p < 0.05/3$). VOIs of AD patients were significantly smaller than those of controls in the lateral temporal cortex, posterior cingulate cortex, thalamus and medial temporal region. After the correction of multiple comparisons among MCI, AD and controls, the difference of the volumes of VOIs was significant in the lateral temporal cortex, posterior cingulate cortex and medial temporal region ($p < 0.05/3$). We found no significant difference of regional VOI volumes between MCI and AD patients (Table 4).

ANOVA of VOI volumes of the total measured regions for groups showed a significant effect of groups, and follow-up unpaired *t* tests revealed that volumes of MCI and AD patients were significantly smaller when compared to controls (Table 4).

4. Discussion

In this study, [^{11}C]DAA1106 binding to PBR was significantly increased in widespread regions in MCI subjects when compared to healthy controls. Providing that the affinity of radiotracer to PBRs did not differ between the groups, our finding might be attributable to the higher number of PBRs in these brain regions, which may reflect mainly the activated glial cells. The present findings of increased PBR signals in MCI subjects are in line with the findings with [^{11}C]PK11195 (Cagnin et al., 2001; Okello et al., 2009). We found no significant difference of [^{11}C]DAA1106 binding between MCI subjects and AD patients. There was no clear difference in the pattern of DAA1106 uptake between MCI and AD. Two MCI subjects showed higher BP in several regions when compared to AD patients.

It has been reported that Aβ can activate microglia (Tan et al., 1999, 2002; Wyss-Coray, 2006). In our recent studies of tau model mice using [^{18}F]FEDAA1106 and [^{11}C]Ac-5216, microglial PBR expression was linked to neurotoxic tau pathology (Yoshiyama et al., 2007; Ji et al., 2008; Maeda et al., 2011). However, our observation of elevated PBR binding in widespread areas of MCI and AD brains showed the emergence of reactive microglia and astrocytes in widespread areas,

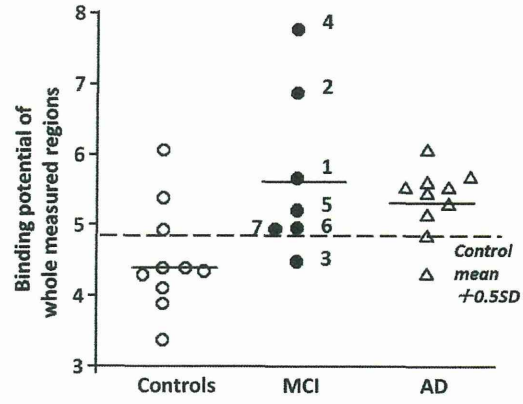

Fig. 1. [^{11}C]DAA1106 BP of healthy controls, MCI subjects and patients with AD in the total measured regions. The plots of the individual MCI subjects are indicated by the numbers shown in Tables 1 and 2. Mean BP values in these regions were significantly higher in MCI subjects and AD patients than in control subjects.

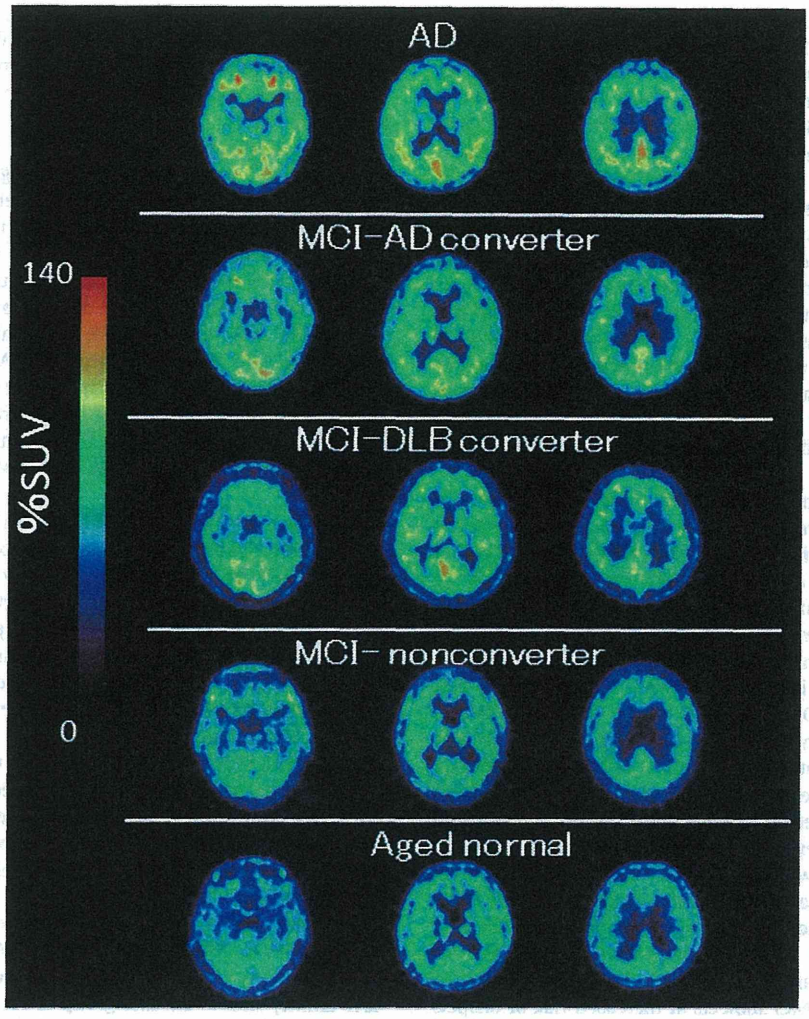

Fig. 2. Mean %SUV images between 30 and 90 min after injection of [^{11}C]DAA1106 of AD, MCI–AD converter, MCI–DLB converter, MCI-nonconverter and an aged normal subject.

Table 3
Comparison of binding potential (BP) values between MCI subjects, AD patients and controls.

	BP values (mean ± S.D.)[a]			Analysis of variance		*t* test					
						MCI vs. control (d.f. = 15)		MCI vs. AD (d.f. = 15)		AD vs. control (d.f. = 18)	
Region	Controls (n = 10)	MCI (n = 7)	AD (n = 10)	F (d.f. = 2, 24)	p	t Score	p	t Score	p	t Score	p
Cerebellum	4.63 ± 0.97	6.01 ± 1.32	5.38 ± 0.56	4.50	0.02[b]	2.51	0.02[c]	0.19	0.19	2.14	0.05[c]
Lateral prefrontal cortex	4.57 ± 0.81	5.54 ± 1.17	5.23 ± 0.50	3.21	0.05	2.05	0.06	0.46	0.46	2.21	0.04
Medial prefrontal cortex	4.42 ± 0.78	6.04 ± 1.85	5.58 ± 0.67	4.91	0.02[b]	2.49	0.03[c]	0.48	0.48	3.58	0.002[c,d]
Parietal cortex	4.39 ± 0.69	5.58 ± 1.05	5.23 ± 0.60	5.63	0.01[b]	2.83	0.01[c,d]	0.40	0.40	2.93	0.009[c,d]
Lateral temporal cortex	4.57 ± 0.70	5.96 ± 1.19	5.60 ± 0.55	7.06	0.004[b]	3.03	0.008[c,d]	0.42	0.42	3.64	0.002 [c,d]
Occipital cortex	4.49 ± 0.82	5.50 ± 1.22	5.16 ± 0.56	3.15	0.06	2.07	0.06	0.44	0.44	2.14	0.05
Anterior cingulate cortex	4.44 ± 0.82	5.67 ± 1.04	5.90 ± 1.20	5.57	0.01[b]	2.72	0.01[c,d]	0.69	0.69	3.16	0.005[c,d]
Posterior cingulate cortex	4.43 ± 1.34	5.49 ± 0.96	5.00 ± 0.78	2.11	0.14	1.79	0.09	0.27	0.27	1.17	0.26
Striatum	4.09 ± 0.63	5.07 ± 0.72	4.84 ± 0.59	5.77	0.009 [b]	2.97	0.01[c,d]	0.50	0.50	2.77	0.01[c,d]
Thalamus	5.54 ± 1.35	6.48 ± 1.65	5.94 ± 1.31	0.89	0.43	1.28	0.22	0.47	0.47	0.67	0.51
Medial temporal region	4.70 ± 0.98	5.90 ± 1.56	5.53 ± 0.91	2.57	0.10	1.94	0.07	0.55	0.55	1.96	0.07
Whole measured regions[e]	4.52 ± 0.76	5.70 ± 1.19	5.35 ± 0.49	4.88	0.02[b]	2.50	0.02[c]	0.84	0.41	2.89	0.01[c,d]

[a] Multivariate analysis of variance revealed a significant main effect of groups (Wilks's lambda = 0.11; F = 2.54, d.f. = 22, 28, p = 0.01).
[b] Analysis of variance showed a significant effect of groups on regional BP values.
[c] Follow-up t test revealed significant difference at p<0.05.
[d] Follow-up t test revealed significant difference at p<0.016 (0.05/3) under the consideration of multiple comparisons among controls, MCI and AD patients.
[e] VOI of whole measured regions was obtained by combining all measured regions.

including the striatum and cerebellum and was not spatially linked to depositions of Aβ and tau fibrils. One possible explanation of the broad extent of glial activation is that it is attributable to stimuli by circulating soluble Aβ oligomers and their related immunomediators in the disease process. Soluble Aβ oligomer is considered to be a more deleterious substance that can activate microglia and stimulate secretion of cytokines (Tan et al., 1999, 2002; Wyss-Coray, 2006).

Recent study showed a significant negative correlation between microglial activation and Aβ accumulation in the posterior cingulate cortex, suggesting that microglial activity increases at an early stage of soluble Aβ production and subsides during the phase when neurodegeneration is predominant with large insoluble Aβ fibril deposits (Yokokura et al., 2011). Our finding of a similar or higher level of PBR signals in MCI subjects when compared to AD patients is in line with this previous study, and indicated that microglial activation can occur before the onset of clinical symptoms of dementia, and may be informative in predicting the presence of the early stage of the disease process.

During clinical follow-up, all of the subjects whose DAA binding was higher than the control mean + 0.5 S.D. developed dementia within 5 years. One MCI subject, whose DAA binding was less than the control mean + 0.5 S.D., continued to fulfill the criteria for the diagnosis of MCI for 5 years after the PET scan. This finding suggested that in vivo detection of microglial activation may provide useful prognostic information with respect to stratifying MCI subjects at increased risk of dementia. It is less clear at what stage microglial activation, as detectable by DAA-PET, plateaus in any given patient during the clinical transition from MCI to dementia. However, all subjects who developed dementia showed similar or higher DAA binding during 1–4 years before the onset of dementia. This suggested that the MCI–dementia converter might have reached a plateau of microglial activation at least several years before the onset of dementia.

In our follow-up study, we found that one of the MCI subjects had developed dementia with Lewy bodies, indicating that the intracellular accumulation of α-synuclein might also influence glial PBR upregulation at an early stage of neurodegeneration. This means that PBR imaging is a sensitive and useful tool for prognostic information with respect to stratifying MCI subjects at increased risk of unspecified species of dementia at an early stage. However, there is no difference in the pattern of DAA1106 uptake between AD converters and dementia with Lewy bodies converters, and we cannot predict the outcome of MCI with PBR imaging. It may be possible to stratify MCI subjects at increased risk of dementia by PBR imaging, and then specific pathological examinations such as amyloid imaging could be applied for predicting the outcome of MCI in the high-risk group shown with PBR imaging.

Several confounding factors need to be considered. Firstly, patients with AD may have decreased regional cerebral blood flow. However, the K_1 values (ratio of delivery) of [^{11}C]DAA1106 were very small, indicating small values for the capillary permeability-surface area product. Thus, delivery of [^{11}C]DAA1106 is independent from cerebral blood flow. Further, BP values calculated as k_3/k_4 in 2-TCM are independent from the delivery or cerebral blood flow.

Secondly, VOI volumes were significantly smaller in some measured regions in the MCI subjects and AD patients compared with healthy controls (Table 4). Although there is a possibility that the smaller VOI volumes affect the appearance of the higher uptake of [^{11}C]DAA1106 in AD patients, this effect was mainly expressed by K_1 values, and its effect on k_3/k_4 in 2-TCM is thought to be relatively small.

Thirdly, a sizable amount of [^{11}C]DAA1106 binding was displaceable by cold ligand in normal primate brains (Maeda et al., 2004). This may not be simply explainable by the localization of PBR in microglia, and implies the need for determination of the cellular source of PBR signals in both healthy and pathological conditions. Following neurotoxic injuries of rodent brains, substantial levels of PBR expression have been detected in astrocytes by autoradiographic and immunohistochemical assays (Chen et al., 2004; Chen and Guilarte, 2006; Maeda et al., 2007; Rojas et al., 2007). This may suggest that PBR expression is not confined to macrophages, monocytes and microglia, all of which are considered to be derived from mesoderm, but is inducible in nervous tissue cells of neuroepithelial origin. Thus, PBR ligand binding in normal human subjects may also arise from astrocytes and other non-microglial elements, and could be altered in response to AD pathology.

Fourthly, recent study showed that several novel PBR ligands including PBR06, PBR28, DPA713, and DAA1106 bind to a single class of high-affinity sites in one group of subjects, to a single class of low-affinity sites in another group of subjects, and to two distinct affinities in a third group of subjects (Owen et al., 2011). The presence of differing affinities in the general population complicates the quantitative assessment of PET data, because differences in PBR

Table 4
Comparison of volume of VOIs between MCI subjects, AD patients and controls.

Region	Volume of VOIs (cm^3) (mean ± S.D.)[a]			Analysis of variance		*t* test					
						MCI vs. control (d.f. = 15)		MCI vs. AD (d.f. = 15)		AD vs. control (d.f. = 18)	
	Controls (n = 10)	MCI (n = 7)	AD (n = 10)	F (d.f. = 2, 24)	p	t Score	p	t Score	p	t Score	p
Cerebellum	21.8 ± 4.1	19.8 ± 2.6	22.8 ± 3.5	1.45	0.25	1.17	0.26	1.91	0.08	0.55	0.59
Dorsolateral prefrontal cortex	93.4 ± 10.0	88.0 ± 10.5	91.8 ± 12.8	0.49	0.62	1.08	0.30	0.64	0.53	0.32	0.75
Medial prefrontal cortex	26.3 ± 1.8	24.6 ± 2.4	24.5 ± 2.9	1.67	0.21	1.65	0.12	0.10	0.92	1.67	0.11
Parietal cortex	74.7 ± 7.3	69.1 ± 9.7	67.4 ± 5.8	2.54	0.10	1.35	0.20	0.46	0.65	2.48	0.02
Lateral temporal cortex	85.4 ± 6.4	74.6 ± 8.8	78.0 ± 6.1	5.58	0.01[b]	2.96	0.01[c,d]	0.94	0.36	2.68	0.01[c,d]
Occipital cortex	67.6 ± 12.4	57.1 ± 11.5	58.3 ± 5.9	2.95	0.07	1.78	0.10	0.30	0.77	2.14	0.05
Anterior cingulate cortex	11.5 ± 1.3	10.3 ± 1.7	10.3 ± 1.1	2.66	0.09	1.65	0.12	0.09	0.93	2.34	0.03
Posterior cingulate cortex	11.1 ± 1.4	9.1 ± 1.8	9.5 ± 0.8	5.78	0.009[b]	2.60	0.02[c]	0.64	0.53	3.22	0.005[c,d]
Striatum	18.6 ± 1.9	19.4 ± 1.6	17.4 ± 1.9	2.45	0.11	0.86	0.40	2.21	0.04	1.38	0.18
Thalamus	10.8 ± 1.6	10.9 ± 1.6	9.3 ± 1.0	4.05	0.03[b]	0.08	0.94	2.58	0.02	2.61	0.02[c]
Medial temporal region	25.4 ± 2.9	23.0 ± 3.4	21.0 ± 2.3	6.18	0.007[b]	1.59	0.13	1.46	0.17	3.81	0.001[c,d]
Whole measured regions[e]	446.7 ± 24.6	411.1 ± 26.6	405.8 ± 38.7	5.25	0.01[b]	2.68	0.02[c]	0.33	0.74	3.11	0.006[c,d]

[a] Multivariate analysis of variance revealed a significant main effect of groups (Wilks's lambda = 0.16; F = 1.95, d.f. = 22, 28, p = 0.04).
[b] Analysis of variance showed a significant effect of groups on regional BP values.
[c] Follow-up t test revealed significant difference at p<0.016 (0.05/3).
[d] Follow-up t test revealed significant difference at p<0.016 (0.05/3) under the consideration of multiple comparisons among controls, MCI and AD patients.
[e] VOI of total measured regions was obtained by combining all measured regions.

radioligand signal cannot be safely interpreted as differences in target density.

In conclusion, [^{11}C]DAA1106 binding to PBR was significantly increased in widespread areas in MCI subjects in comparison to healthy controls. Our finding of similar or higher levels of DAA binding in our MCI subjects when compared to AD patients indicated that microglial activation could occur before the onset of clinical symptoms of dementia, and provide a rationale for assessing microglial activation in subjects with MCI. In vivo detection of microglial activation may provide useful prognostic information with respect to stratifying MCI subjects at increased risk of dementia. However, the number of subjects in the present study was relatively small, and the results should be regarded as preliminary. Future work using a more sensitive ligand, such as [^{11}C]AC-5216 (Maeda et al., 2011), with larger patient populations will be necessary.

Disclosures for authors

All authors declare no proprietary interest or any conflict of interest related to this study.

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REVIEW ARTICLE

Multicentre population-based dementia prevalence survey in Japan: a preliminary report

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Key words: *community-based survey, dementia, mild cognitive impairment, prevalence.*

Abstract

Community-based surveys were performed in seven rural areas in Japan to investigate the prevalence of dementia and illnesses causing dementia. A total of 5431 elderly subjects were selected based on census data from 1 October 2009. In total, 3394 participants were examined (participation rate: 62.5%), and 768 dementia cases and 529 mild cognitive impairment cases were identified. Of the illnesses causing dementia, Alzheimer's disease was the most frequent (67.4%), followed by vascular dementia (18.9%), dementia with Lewy body disease (4.6%), mixed dementia (4.2%) and other illnesses. The prevalence of dementia according to 5-year age strata between 65 and 99 years was 5.8–77.7% among the participants. The prevalence of dementia in this study was higher than in previous reports in Japan and other countries. To verify the upward trend of dementia prevalence and its background factors, we have scheduled surveys for three other urban areas in 2011–2012.

INTRODUCTION

In Japan, life expectancy is now higher than in any other country, and society has been ageing with remarkable speed. In 2008, the Japanese government declared that the country needed a new strategy to ensure the welfare of people living in this era of increased longevity and low birth rates, and it launched a 'The Project for the Well-Being of Individuals with Dementia and Their Caregivers'. Briefly, this project aims to improve medical treatment for dementia and the quality of life for patients and their caregivers.[1] The government has also stated the need for a survey to accurately determine the prevalence of dementia based on established dementia diagnostic criteria and present conditions of daily life. Such data are needed to ensure that services provided cover the needs of patients and their family caregivers in Japan. Herein, we investigated the prevalence of dementia and illnesses causing dementia as well as the status of medical and social services use among elderly Japanese subjects.

METHODS

Seven areas were chosen for this study, and a sample of 5431 elderly subjects was selected based on the census data from 1 October 2009 (Fig. 1). This study was approved by the ethical committees from the following institutions: the University of Tsukuba

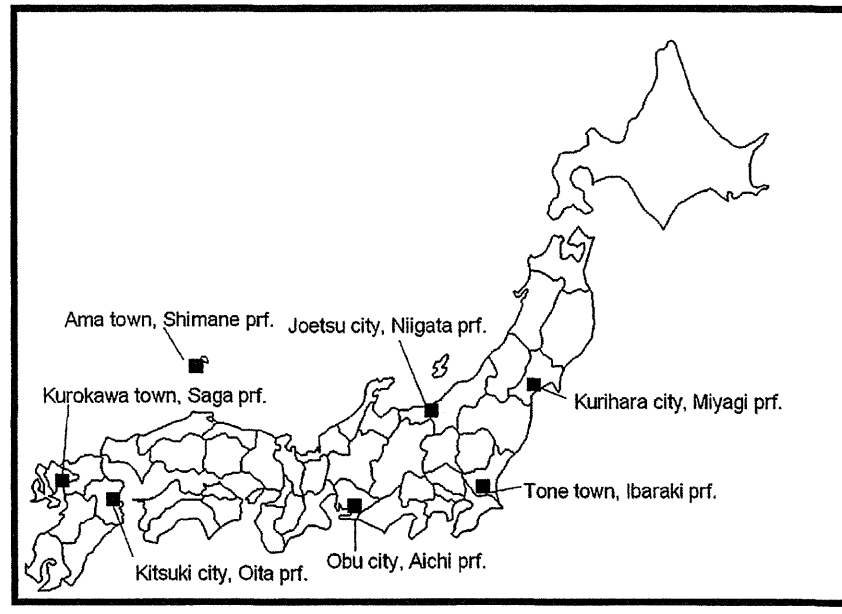

Figure 1 Study areas.

(Tsukuba, Japan), Tohoku University (Sendai, Japan), Niigata College of Nursing (Joetsu, Japan), National Center for Geriatrics and Gerontology (Obu, Japan), Tottori University (Yoango, Japan), Fukuoka University (Fukuoka, Japan), and Saga University (Saga, Japan).

Cases were compiled between November 2009 and September 2010. Principally, a three-phased survey was carried out in each area. For those who could not attend group assessments, a door-to-door survey was also conducted.

Phase 1 included a home visit and interview with participants and their families. During phase 2, basic data, including demographics were checked, and participants underwent a series of physical examinations and blood sampling. Participants then underwent screening examinations that included the Mini-Mental State Examination (cut-off point = 26/27) for cognitive screening,[2] Clinical Dementia Rating (cut off = 0.5) for global function assessment,[3] and 'logical memory A' from the Wechsler Memory Scale-Revised for memory assessment.[4] The screening examination assessments during phase 2 were conducted by psychology students studying for their doctorates who had been trained for the present study.

Only participants who scored below the cut-off point on at least one test in phase 2 proceeded to phase 3. To detect possible false-negatives, we randomly selected 10% of subjects who scored above the cut-off point on the three exams in phase 2 and entered them in phase 3 as well.

During phase 3, experienced neuropsychiatrists conducted the following tests: psychiatric interviews and physical examinations using the Geriatric Depression Scale-Short Form,[5] the Psychogeriatric Assessment Scales,[6] and some tests used in the Japanese Alzheimer's Disease Neuroimaging Initiative.[7] In addition, we asked all participants to undergo electroencephalograms and magnetic resonance imaging of the brain.

We used the Diagnostic and Statistical Manual of Mental Disorders, third edition-revised, for the diagnosis of dementia.[8] We used the National Institute of Neurological Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for the diagnosis of Alzheimer's disease and the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences for vascular dementia.[9,10] We used the revised criteria for the clinical diagnosis of dementia with Lewy bodies and the Lund-Manchester diagnostic criteria for frontotemporal lober degeneration.[11,12] In addition, we defined mild cognitive impairment based on the criteria of the Japanese Alzheimer's Disease Neuroimaging Initiative, which comes from Petersen's mild cognitive impairment criteria.[13]

Table 1 Patient demographics in each area

	Total	Tone	Joetsu	Obu	Ama	Kitsuki	Kurokawa	Kurihara
Total population (*n*)	420 801	17 401	204 193	84 366	2 434	32 706	1 806	77 895
Population ≥65 years of age (*n*)	108 721	4 644	53 474	14 481	926	10 102	464	24 630
Population ≥65 years of age (%)	23.7†	26.7	26.2	17.2	38.0	30.9	25.7	31.6
Candidates (*n*)	5431	899	980	770	924	833	556	473
Death/transfer	213	43	60	65	19	3	23	–
Participants (*n* (%men))	3 418 (45.7)	612 (46.1)	516 (50.8)	462 (52.8)	723 (40.9)	439 (50.1)	437 (35.9)	229 (41.9)
Participation rate (%)	66.7†	71.5	52.7	65.5	80.3	52.6	82.6	48.4
Age, mean ± SD (year)	78.7 ± 8.7	79.1 ± 8.8	81.1 ± 9.8	80.6 ± 9.7	77.3 ± 7.8	79.5 ± 9.1	76.7 ± 7.2	–
Education, mean ± SD (year)	9.7 ± 2.5	10.3 ± 2.9	9.4 ± 2.5	8.4 ± 1.8	9.7 ± 2.2	10. 3 ± 2.5	8.9 ± 1.8	–
Living situation (%)								
Alone	11.8	7.4	9.5	9.3	20.7	12.5	8.2	–
With family	78.8	81.5	80.8	90.3	68.6	72.1	83.3	–
Hospitalized	0.7	1.3	0.4	0.0	0.0	1.6	1.4	–
Institutionalized	6.5	9.6	8.6	0.2	2.4	12.6	6.6	–
Others	0.2	0.0	0.8	0.0	0.0	0.0	0.2	–
Mild cognitive impairment cases	539	140	84	103	98	49	65	–
Dementia cases	768	160	136	137	148	100	63	24
Diagnosis of dementia (%)								
Alzheimer disease	67.4	67.5	52.4	95.1	72.2	73.0	57.4	–
Vascular dementia	18.9	19.4	28.6	0.0	12.4	20.0	21.3	–
Dementia with Lewy bodies	4.6	4.4	1.9	0.0	10.3	3.0	6.4	–
Frontotemporal lober degeneration	1.1	0.6	1.9	0.0	0.0	2.0	2.1	–
Alcohol-related dementia	0.5	0.6	1.0	0.0	0.0	0.0	2.1	–
Mixed dementia	4.2	2.5	14.3	4.9	0.0	0.0	4.3	–
Others	3.3	5.0	0.0	0.0	5.2	2.0	6.4	–

†Mean for seven areas.

RESULTS

Table 1 shows the demographics of study subjects. The participation rates in the areas surveyed ranged from 48.4% to 82.6%, and 3418 participants were examined in total. The mean age and years of education were 78.7 years and 9.7 years, respectively, for six areas. Almost 80% of all participants lived at home with their family. A total of 768 dementia cases and 529 mild cognitive impairment cases were identified.

The peak in the number of dementia cases occurred in subjects aged 90–94 years old in both sexes (Fig. 2). Of the illnesses causing dementia, Alzheimer's disease was the most frequent (67.4%), followed by vascular dementia (18.9%), dementia with Lewy bodies (4.6%), mixed dementia (4.2%), and other illnesses (Table 1). The prevalence of dementia according to 5-year age strata between 65 and 99 years was 5.8–77.7% (Fig. 3).

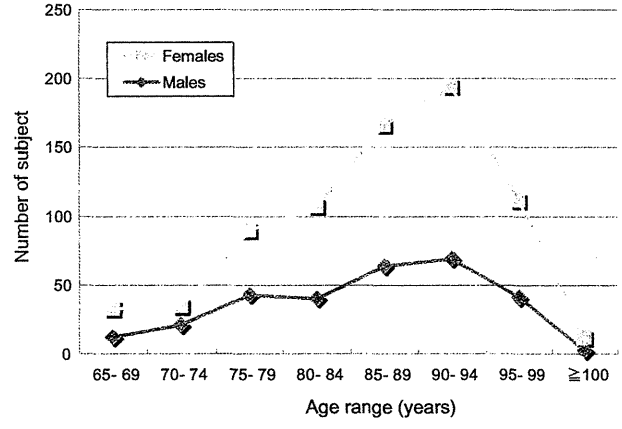

Figure 2 Number of dementia cases by age and sex (*n* = 744).

DISCUSSION

The prevalence of dementia in this study was higher than in previous reports in Japan.[12] There are several

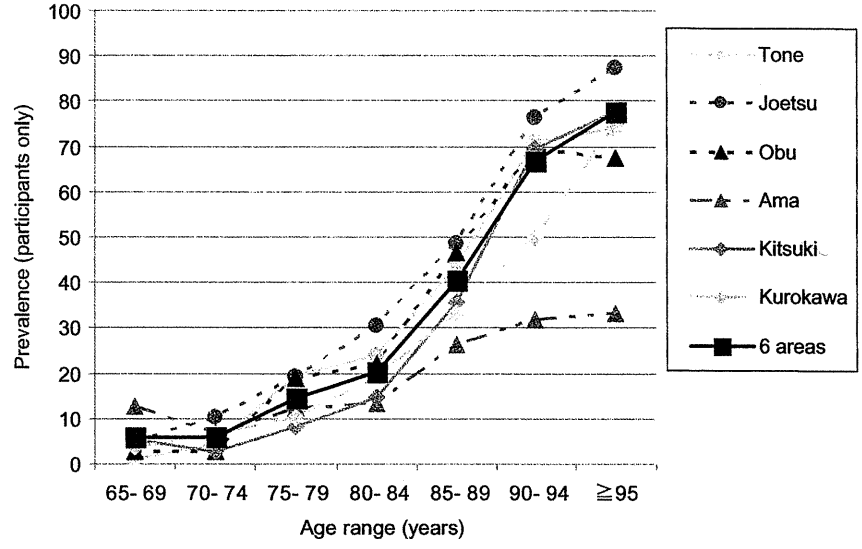

Figure 3 Prevalence of dementia for six areas (participants only). These rates were calculated without adjusting for sampling rate and participation rate.

possible reasons for our results. The main reason is the increasing number of subjects in the elderly population, in particular, the 'oldest old' group.[14] It is well known that ageing is the most influential risk factor for developing dementia, and in Japan, life expectancy has been rising; Japanese women have the longest life expectancy worldwide. The rise in life expectancy may have contributed to the increased prevalence of dementia, including Alzheimer's disease. Another possible reason is that early detection of mild dementia has improved. As a result, very mild dementia cases that might have been overlooked 20 years ago can now be detected.

A limitation of the current study is that the accuracy of these diagnoses could not be confirmed by neuropathological examination. To investigate the upward trend in dementia prevalence and its background factors, we have scheduled surveys for three other urban areas in 2011–2012.

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RESEARCH ARTICLE

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ApoE4 is not associated with depression when mild cognitive impairment is considered

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Objective: The aim of the study was to examine the relationship between apolipoprotein E4 allele (ApoE4) and depression among an older Japanese population. Mild cognitive impairment (MCI) was taken into consideration.

Methods: This is a community-based cross-sectional study. We assessed the mood and cognitive function of Japanese community-dwelling individuals aged 65 years or older. In the first phase of the study, we evaluated the mood and cognitive function. In the second phase, face-to-face structured interviews were conducted. Individuals with dementia and other mental diseases were excluded on the basis of a consensus meeting of psychiatrists and neuropsychologists; 738 subjects with full data were included in the analyses. We subdivided depression into major depressive episode (MDE) and depressive symptoms cases (DSCs). DSC was defined as a score of 6 or more on the Geriatric Depression Scale but not having a diagnosis of MDE. The relationship between depression (MDE and DSC) and ApoE4 was examined by multivariate logistic regression.

Results: The adjusted odds ratio (OR) of ApoE4 on DSC was not significant (OR = 0.82, 95%CI = 0.48–1.39, $p < 0.46$). Sex (OR = 2.53, 95%CI = 1.33–4.79, $p < 0.01$), MCI (1.95, 1.21–3.14, $p < 0.01$), years of education (0.87, 0.79–0.95, $p < 0.01$), and Nishimura's activities of daily living scores (0.75, 0.63–0.89, $p < 0.01$) significantly correlated with prevalence of DSC. There were no significant risk factors for MDE.

Conclusion: Apolipoprotein E4 allele contributed to neither DSC nor MDE. The association of MCI with ApoE4 and DSC suggested that MCI is a confounder for the association between ApoE4 and DSC.

Key words: apolipoprotein E4 allele; depression; mild cognitive impairment; older people
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Introduction

The most challenging issues in the field of geriatric psychiatry include depression and various forms of dementia, such as Alzheimer's disease (AD). Several risk factors for depressive symptoms and depressive disorders in the older people have been pointed out by previous studies: number of chronic diseases (Bisschop *et al.*, 2004; Braam *et al.*, 2005; Schoevers *et al.*, 2005), poor health status (Copeland *et al.*, 1999; Gazmararian *et al.*, 2000), functional limitation (Blumstein *et al.*, 2004; Horowitz *et al.*, 2005; Jorm *et al.*, 2005), stressful life events (Kraaij and de Wilde, 2001; Oldehinkel *et al.*, 2003), and lower education (Beekman *et al.*, 2001; Jang *et al.*, 2002; Azar *et al.*, 2005).

Apolipoprotein E4 allele (ApoE4) is known as one of the most influential risk factors for AD. Additionally, a number of researchers have reported that ApoE4 is also a risk factor for depression (Krishnan *et al.*, 1996; Rigaud *et al.*, 2001; Yen *et al.*, 2007). However, among the older people, the role of ApoE4 has been controversial for more than a decade.

Using clinic-based data, Krishnan *et al.* (1996) studied 42 older people with depression and found that the proportion of ApoE3/4 carriers was significantly higher for late-onset depression compared with early-onset depression. Another study examining 140 patients with depression revealed that the presence of ApoE4 was significantly associated with late-onset depression (Rigaud *et al.*, 2001).

On the other hand, a clinic-based study by Ohara *et al.* (1999) included 134 clinic patients with depression; they found no association between early-onset or late-onset depressive disorders and ApoE4.

As for community-based studies, Bonger *et al.* (2009) investigated the association between a subtype of depression and impaired cognitive performance with ApoE4. They used data from 305 older subjects with depression who were seen in primary care offices in the Baltimore area; however, they failed to confirm an association. Harwood *et al.* (1999) used the Hamilton Depression Rating Scale to investigate a possible association between depressive symptoms and ApoE4 among 506 community-residing older subjects who were screened for cognitive impairment, but they failed to find an association. In a large retrospective study, Surtees *et al.* (2009) used data from 17 507 subjects but found no association between ApoE genotypes and a recent (within the past year) or chronic major depressive disorder.

Among community-based studies, only Yen *et al.* (2007) found that ApoE4 significantly enhanced the risk of depression. However, they assessed depressive symptoms by using a questionnaire, and the details of clinical data for depression were not included.

Although such previous studies provided much informative knowledge, the number of the subjects was generally small except for the study by Surtees *et al.* (2009) (Krishnan *et al.*, 1996; Ohara *et al.*, 1999; Rigaud *et al.*, 2001; Bonger *et al.*, 2009). Some of the studies dealt with major depression (Krishnan *et al.*, 1996; Ohara *et al.*, 1999; Rigaud *et al.*, 2001; Surtees *et al.*, 2009), whereas others focused on depressive symptoms (Harwood *et al.*, 1999; Yen *et al.*, 2007; Bonger *et al.*, 2009). Additionally, interviews to confirm the psychiatric diagnosis by psychiatrists were not performed in the community-based studies (Harwood *et al.*, 1999; Yen *et al.*, 2007; Bonger *et al.*, 2009; Surtees *et al.*, 2009).

During the last decade, a number of attempts have been made to detect a distinct state of abnormal cognition that does not amount to dementia but is distinguishable from normal cognitive decline associated with aging. We use the term "mild cognitive impairment" (MCI) to describe such a transitional status. Petersen *et al.* (1999) has provided the most frequently used definition of MCI. However, thus far, few epidemiological studies have used the parameters of MCI when looking at depression. In previous studies, overlooking MCI might have affected the results. In fact, Harwood *et al.* (1999) reported that mood disturbances were not associated with ApoE4 but more with memory complaints. We examined methods of cognitive assessment and presence or absence of MCI diagnosis from the previous studies described earlier (Table 1). Although the previous studies excluded those who had a diagnosis of dementia from the analysis, many of the studies used only screening tests such as the Mini-mental State Examination, and none of them made MCI diagnosis based on its recent definition.

We have conducted a community-based investigation of depression and dementia since 2001 in Tone Town, Ibaraki, Japan. As a part of this study, we examined the relationship between ApoE4 and depression. We took MCI into consideration and limitations of previous studies as described earlier.

Methods

The present cross-sectional study was conducted in Tone Town, Ibaraki, Japan. This town is located approximately 40 km northeast of central Tokyo and consists of 22 districts. On 1 May 2001, Tone Town had 3083 residents aged 65 years and older. These 3083 inhabitants were considered as potential subjects. The composition of Tone Town was similar to that of Japan's total population in 2001.

The prevalence of depression was estimated using a two-phase design. Seven psychiatrists and eight psychologists, who were trained for this study by the authors, and public health nurses conducted the first phase (screening and clinical evaluation) and the second phase (structured interview and cognitive assessment).

Ethical considerations

The protocol of this study was approved by the ethics committee of the University of Tsukuba (Miyamoto *et al.*, 2009; Sasaki *et al.*, 2009). Eligible subjects gave written informed consent to participate in the study

Table 1 Comparison of the association between ApoE4 and depression

Authors	Year	Country	Setting	Age range, years	*n*	Definition of depression	Cognitive function scale	Diagnosis of MCI (+/−)	Association with ApoE4
Krishnam *et al.*	1996	USA	Clinic	≥58	42	Major depression (DSM-IIIR)	MMSE ≥23	−	Late-onset depression ($p < 0.05$)
Ohara *et al.*	1999	Japan	Clinic		239	Depressive disorder (ICD-10)	MMSE >23	−	No association between ApoE4 and early-onset/late-onset depressive disorder
Harwood *et al.*	1999	USA	Community	≥60	506	Depressive symptoms (HAM-D)	MMSE 27.7 ± 1.9	−	No association between ApoE4 and depressive symptoms
Rigaud *et al.*	2001	France	Clinic		140	Major depression (DSM-IV)	MMSE 29.1 ± 1.0	−	Late-onset depression($p < 0.05$)
Yen *et al.*	2007	Taiwan	Community	65–74	283	Depressive symptoms (TDQ)	SPMSQ (normal, mild, moderate, severe)	−	Severe depression($p < 0.05$)
Bonger *et al.*	2009	USA	Clinic	≥65	305	Depressive symptoms (CES-D, CIDI)	MMSE 27.0 ± 2.8, FAS, HVLT, BTA	−	No association between ApoE4 and depressive symptoms
Surtees *et al.*	2009	UK	Community	41–80	17 507	Past-year or lifetime major depression (HLEQ, DSM-IV)	None/no description	−	No association between ApoE4 and major depression

Values are mean ± SD. MCI, mild cognitive impairment; ApoE4, apolipoprotein E4 allele; MMSE, Mini-mental State Examination; HAM-D, Hamilton Depression Rating Scale; TDQ, Taiwanese Depression Questionnaire; SPMSQ, Short Portable Mental State Questionnaire; CES-D, Center for Epidemiological Studies Depression Scale; CIDI, Composite International Diagnostic Interview; FAS, Controlled Oral Word Association Test; HVLT, Hopkins Verbal Learning Test; BTA, Brief Test of Attention; HLEQ, Health and Life Experiences Questionnaire.

and underwent a screening interview. Participants were assured that all data were confidential, and anonymity was preserved by assigning random numbers to the data sets.

First phase

This study was conducted between December 2001 and April 2002. Before the baseline examination, we sent an invitation letter explaining the objectives of the project to all potential subjects. We also asked local welfare commissioners (persons who are vested with promoting social welfare in each local area) to recommend individual residents for participation in the research. We excluded individuals with whom a local welfare commissioner could not meet and individuals whom we could not contact despite three telephone calls during the week prior to the initial examination (unreachable individuals).

We visited each of the 22 districts once per week and conducted two group screenings in the morning and afternoon. In addition to the group screenings in the 22 districts, we visited 44 individuals who were institutionalized in a long-term care facility and used the same methods described in the succeeding text.

Assessment procedures

Demographics and medical and psychiatric issues. The interview consisted of a structured questionnaire assessing age, sex, education, and medical and psychiatric conditions. Subjects were also asked to provide blood samples for routine testing and genotyping of ApoE (Corder *et al.*, 1993).

Mood status. The interview was followed by the 15-item short version of the Geriatric Depression Scale (GDS) for mood assessment. Those with a score of 6 or higher were considered to have depressive symptoms (Brink *et al.*, 1982).

Perceived memory difficulty. Participants were asked whether they had memory difficulties in general, as well as difficulties in specific areas according to the 19 items of the Détérioration Cognitive Observée (DECO), which was originally developed as an objective assessment for memory difficulty (Ritchie and Fuhrer, 1992). DECO is a Likert scale dealing with changes in behavior (activity level, memory for places, events, procedures and persons, and learning of new skills). The maximum score on the scale is 38, and the minimum score is 0 (with lower scores indicating

a greater decrease in performance). Participants were considered to have memory complaints if they had problems on one or more of the items. This type of test does not involve direct cognitive examination of the older person but has the advantage of indicating degree of change from former level of functioning.

Assessment of activities of daily living. Basic activities of daily living were measured using Nishimura's activities of daily living (N-ADL; Nishimura *et al.*, 1993), which determines the level of independence in five activities: walking/transferring, going outside, dressing/bathing, feeding, and toileting. Responders were considered to be functionally intact if they reported no difficulty on any of the five items of the N-ADL.

Neuropsychological assessment battery. After completing the interview, all participants underwent a group assessment using a set of five tests (5-Cog), which measured the following cognitive domains: attention, memory, visuospatial function, language, and reasoning. The validity and reliability of the tests and the details of the assessment battery have been described elsewhere (Miyamoto *et al.*, 2009; Sasaki *et al.*, 2009).

We evaluated attention by using a Japanese version of a set dependency activity (Sohlberg and Mateer, 1986). To assess memory, we used a category cued recall test (Grober *et al.*, 1988). The Clock Drawing Test, which requires subjects to draw the hands of a clock to depict the time at "ten after eleven" (Freedman *et al.*, 1994), was employed for the assessment of visuospatial function. We examined language ability by using a category fluency test (Soloman and Pendlebury, 1998). To assess abstract reasoning, we employed the similarity subset of the revised Wechsler Adult Intelligence Scale (Wechsler, 1981).

Test–retest reliability of the 5-Cog was confirmed (mean value of Pearson's correlation coefficient was 0.70, $p < 0.01$ for all five tests). We used data from 38 initial participants who were randomly selected; data were collected at a mean interval of 64 days (standard deviation (SD) = 28 days).

Consensus diagnosis of dementia. After each assessment, a group of psychiatrists and neuropsychologists reviewed the functional, medical, neurologic, psychiatric, and neuropsychological data and reached a consensus regarding the presence or the absence of dementia by diagnosis of dementia according to the DSM-IV (American Psychiatric Association, 1994) criteria. Only those who were not diagnosed as having dementia were considered for a diagnosis of MCI.

Mild cognitive impairment diagnostic criteria. Criteria for MCI were retrospectively applied among individuals without dementia after the consensus conference. Consistent with standard criteria for all subtypes of MCI (Petersen and Morris, 2005), those with MCI were required to have the following: (i) a memory complaint (defined previously); (ii) objective impairment in at least one of five cognitive domains (memory, attention, language, visuospatial function, and reasoning) based on the average scores of the neuropsychological measures within that domain and 1.5 SDs cutoff using normative corrections for age, years of education, and sex; (iii) essentially preserved activities of daily living (defined earlier); and (4) no diagnosis of dementia at the consensus conference. We used the following subtypes of MCI: amnestic MCI single, amnestic MCI multiple, non-amnestic MCI single, and non-amnestic MCI multiple (Petersen and Morris, 2005). The classification into the four MCI subtypes was mutually exclusive.

Second phase (structured interview)

To make final diagnoses of depression, we conducted the second phase. For this phase, we invited all of the individuals who had participated in the first phase.

As a result, 738 first-phase participants who fulfilled the following criteria took part in the second phase: no diagnosis of dementia, acceptance of ApoE typing, and no missing data.

Except for the 44 institutionalized people, 881 individuals were not interviewed for the following reasons: diagnosis of dementia, refusal of ApoE typing, missing data, or refusal to participate in the second phase.

The participants of the first phase were interviewed by seven psychiatrists and eight psychologists in a face-to-face interview between April and July 2002. The mean interval between the first phase and the second phase was 62 days (SD = 36 days).

We conducted straightforward interviews with the subjects by using the Psychogeriatric Assessment Scale (PAS), which provides a brief but comprehensive profile of the older individual's mental state (depression, cognitive impairment, and stroke; Jorm *et al.*, 1995). There were three scales derived from an interview with the subject (depression, cognitive impairment, and stroke). In general, the validity and reliability of the PAS has been documented. The depression subscale, in particular, has excellent validity when judged against the clinical diagnosis of MDE based on DSM-III-R criteria (American Psychiatric Association, 1987). The guidelines of PAS