been replicated by other groups using both glucose metabolism measurements with PET and even less sophisticated measurement techniques such as regional cerebral blood flow (rCBF) measurements with single photon emission computed tomography (rCBF SPECT). Our previous rCBF SPECT study demonstrated significantly decreased rCBF in the posterior cingulate gyri and precunei bilaterally in MCI subjects as compared with controls at least 2 years before they met a clinical diagnosis of AD (Kogure et al., 2000). We also reported a diagnostic value of reduced rCBF in the posterior cingulate cortex (PCC) to assist in discriminating between normal subjects and MCI subjects who later developed AD (Imabayashi et al., 2004). Furthermore, a PET study demonstrated hypometabolism of the PCC in young subjects with a high genetic risk of developing AD (Reiman et al., 2004). These results suggest that functional neuroimaging techniques such as PET and SPECT may be promising techniques for the preclinical diagnosis of AD.

However, MCI is a heterogeneous diagnostic category comprised of individuals with a variety of clinical outcomes (Petersen et al., 2001). As such, only a longitudinal study comparing MCI subjects who convert to AD at follow-up (converters) with MCI subjects who do not convert at follow-up (non-converters) is appropriate to determine the predictive value of initial neuroimaging for progression of MCI to AD. Only a few longitudinal studies have been published so far (Celsis et al., 1997; Arnaiz et al., 2001; Huang et al., 2002; Chetelat et al., 2003; Drzezga et al., 2003; Mosconi et al., 2004). These studies have suggested that reduced glucose metabolism in the right temporo-parietal cortex or reduced rCBF and glucose metabolism in the PCC might be good predictors of progression to AD.

On the other hand, morphological magnetic resonance imaging (MRI) studies have demonstrated that higher atrophy rates in the medial temporal regions such as the entorhinal cortex and hippocampus may be good predictors of conversion to AD (Jack et al., 1999; Mungas et al., 2002; Nestor et al., 2004). However, such serial MR studies require at least a 1-year follow-up period to predict AD conversion. As with functional imaging studies, the predictive value of morphological MR studies has not been yet clarified.

The present retrospective cohort study assessed initial rCBF SPECT images in a group of amnesic MCI subjects consisting of AD converters and non-converters who were followed clinically for 3 years. The aim of the present study was to find highly specific and sensitive rCBF changes capable of discriminating between MCI subjects who eventually develop AD from those who do not convert to AD, as early as possible. We also demonstrated the predictive value of the initial rCBF SPECT studies in MCI subjects.

Methods

Subjects

The characteristics of the subjects who participated in this study are summarized in Table 1. We retrospectively studied 82 individuals (40 men and 42 women) with MCI who visited our memory clinic with a chief complaint of memory disturbance. Six MCI subjects (3 men and 3 women) dropped out and therefore their outcomes were unknown. Analyses therefore included 76 MCI subjects (37 men and 39 women) and 57 age- and gender-matched control subjects. All subjects were free of depression as operationalized as a score less than 8 on the Hamilton Depression Scale (Hamilton, 1960). MCI was diagnosed using the criteria proposed by Mayo Clinic Alzheimer's Disease Research Center. Recently, the criteria of MCI was modified (Pertersen, 2004), but when our study was conducted, the criteria required: (1) memory complaint by patient, family, or physician; (2) normal activities of daily living; (3) normal global cognitive function; (4) objective impairment in memory or in one other area of cognitive function as evident by scores >1.5 SD below the age appropriate mean; (5) CDR score (Hughes et al., 1982) of 0.5; and (6) absence of dementia.

MCI subjects ranged in age from 48 to 86 years with a mean ± standard deviation (SD) of 69.0 ± 8.6 years. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score ranged from 24 to 29 (mean ± SD 26.5 ± 1.6) at the initial visit. During the subsequent follow-up period of 3 years, 52 patients showed progressive cognitive decline and eventually fulfilled the diagnosis

Table 1
The characteristics of subjects

	MCI (M:F = 37:39)			Results of ANOVA	
	Controls (M:F = 30:27)	Non-converters (M:F = 12:12)	Converters (M:F = 25:27)	*F* value	*P* value
Age	70.4 ± 7.3	68.7 ± 7.6	69.2 ± 9.1	0.5	0.6
Education in years	12.2 ± 2.9	12.2 ± 3.1	12.0 ± 3.1	0.1	0.9
MMSE	28.8 ± 1.5	27.0 ± 1.3*	26.2 ± 1.7*	38.7	<0.001
MMSE (about after 3 years)		26.1 ± 1.4*	19.1 ± 4.3*****	126.1	<0.001
Digit span					
Forward	5.3 ± 1.0	5.6 ± 1.0	5.4 ± 1.0	0.5	0.6
Backward	4.1 ± 0.8	4.2 ± 0.8	4.1 ± 1.0	0.2	0.8
List learning (10 words)					
Delayed recall (30 min)	7.9 ± 1.2	3.7 ± 3.6*	0.9 ± 2.0*****	117	<0.001
Story recall (15 elements)					
Delayed (30 min)	7.9 ± 2.5	0.87 ± 1.72*	0.9 ± 1.72*	101.8	<0.001
Rey–Osterrieth complex figure test					
Delayed recall (30 min)	14.47 ± 6.31	4.28 ± 3.76*	2.9 ± 6.93***	85.3	<0.001

Note. Data are mean ± SD in controls (n = 57) or MCI (n = 76).

* Scores of MCI are significantly lower than those of controls, $P < 0.05$ (Bonferroni correction for multiple comparison).

** Scores of the converters are significantly lower than those of non-converters, $P < 0.05$ (Bonferroni correction for multiple comparison).

*** Scores of the converters are significantly lower than those of non-converters, $P < 0.001$ (Bonferroni correction for multiple independent comparisons).

**** Scores of the follow up MMSE are significantly lower than those of the initial MMSE, $P < 0.05$ (paired t test).

of probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA) (McKhann et al., 1984). Twenty-four of the 76 MCI subjects still did not fulfill the criteria for dementia according to DSM-IV (American Psychiatric Association, 1994) during the follow-up period. Of these participants, 40 converters and 12 non-converters completed follow-up rCBF SPECT studies at the end of the 3-year follow-up period.

Fifty-seven individuals (30 men and 27 women; age 56–86 years, mean ± SD 70.4 ± 7.3 years) did not have memory impairment or cognitive disorders and were assigned to the normal control group. Specifically, their performances were within normal limits (<1 SD) both on the Wechsler Memory Scale-Revised and on the Wechsler Adult Intelligence Scale-Revised, and their MMSE score ranged from 25 to 30 (mean ± SD 28.8 ± 1.5). None of these control subjects manifested cognitive changes during the follow-up period of more than 3 years. The control group did not differ significantly in age or education from the MCI group.

The local ethics committee approved this study for both healthy volunteers and MCI subjects, all of whom gave their informed consent to participate. All subjects were right-handed and screened by questionnaire regarding medical history and excluded if they had neurological, psychiatric, or medical conditions that could potentially affect the central nervous system, such as substance abuse or dependence, atypical headache, head trauma with loss of consciousness, asymptomatic or symptomatic cerebral infarction detected by T2-weighted MRI, hypertension, chronic lung disease, kidney disease, chronic hepatic disease, cancer, or diabetes mellitus.

SPECT imaging

Before the SPECT scan was performed, all subjects had an intravenous line established. They were injected while lying supine with eyes closed in a dimly lit quiet room. Each subject received an intravenous injection of 600 MBq of technetium-99 m ethyl cysteinate dimer (99 mTc-ECD). Ten minutes after the injection of 99 mTc-ECD, brain SPECT was performed using three-head rotating gamma cameras (Multispect3; Siemens Medical Systems, Inc., Hoffman Estates, IL) equipped with high-resolution fan-beam collimators. For each camera, projection data were obtained in a 128 × 128 format for 24 angles at 50 s per angle. A Shepp and Logan Hanning filter was used for SPECT image reconstruction at 0.7 cycle/cm. Attenuation correction was performed using Chang's method.

Statistical parametric mapping

Images were analyzed with the statistical parametric mapping software SPM99 (Wellcome Department of Cognitive Neurology, UK). Using a template for Tc-99 m ECD template, the SPECT data were transformed into a standard stereotaxic space (MNI). The spatial normalization algorithm of SPM99 was used for linear and non-linear transformation (basis function: 8 × 9 × 8: iteration: 16). A Gaussian filter (12 mm full width at half maximum) was used to smooth each image. The effect of global differences in CBF between scans was removed by proportional scaling with the threshold at 60% of whole brain activity. Using MRIcro (www.mricro.com), we checked the mask image for statistical analysis and verified that medial temporal regions including the parahippocampal gyrus and hippocampus were encompassed in the analysis. To test hypotheses about regional population effects, data were analyzed by analysis of variance (ANOVA) using the full monthly option. For this F test, we used an alpha value of 0.001 as our level of significance to correct for multiple comparisons. Group comparisons were also done using t tests within the ANOVA design matrix (uncorrected $P < 0.001$ and cluster extent $K > 100$ voxels, small volume correction (SVC) for correction of multiple comparisons). There were twice as many converters as non-converters raising the concern that the SPECT abnormalities in the former might be influenced by statistical power. Therefore, we randomly subdivided AD converters into 2 groups where the group size was matched to that of non-converters. Then, two-sample t tests between non-converters and each group of AD converters were done (uncorrected $P < 0.001$). The resulting sets of t values constituted the statistical parametric maps {SPM (t)}. Anatomic localization was identified using both MNI coordinates and Talairach coordinates obtained from M. Brett's transformations (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) and were presented as Talairach coordinates (Talairach and Tournoux, 1988).

Logistic regression model

To evaluate the predictive value of rCBF change observed in the initial rCBF SPECT, we used as independent variables (X1) Z scores for the mean adjusted rCBF value at the significant clusters obtained from the SPM (t) map in the group comparison (AD converter vs. Non-converter) for the logistic regression model:

$$Y = b0 + b1*X1$$

where Y is the logit transformation of the probability P. The logit transformation of the probability of a value is defined as:

$$Y = \log(P/(1-P))$$

where P is the probability of conversion from MCI to AD.

The mean value of the adjusted rCBF in each cluster of each subject was extracted using the Marsbar program (http// www.marsbar.sourceforge.net/), then the Z score was calculated using the following formula: Z score = (mean adjusted rCBF value in the control group minus individual value of adjusted rCBF value)/SD of rCBF value in the control group. The logistic regression model analysis was performed using Statistical Package for the Social Sciences (SPSS, Japan Co., Tokyo, Japan). Because the neuropsychological test scores of converters were significantly lower than those of non-converters (especially on delayed recall of list learning and delayed recall of Rey–Osterrieth Complex Figure Test), we also evaluated the predictive value of those scores at the initial visit using logistic regression analysis.

Results

Conversion rate

In our study, 52 of 82 individuals with MCI converted to AD during the 3-year follow-up period. The annual conversion rate of MCI to AD was approximately 21.14%.

Group comparisons

The ANOVA analysis [SPM (F), $P < 0.001$, corrected for multiple comparisons with family-wise alpha < 0.05] revealed a significant difference among groups in the bilateral precunei (Brodmann area [BA] 7), the posterior cingulate cortices (PCC, BA31, peak $x, y, z = 0, -47, 32$, F value = 35.93), the right inferior parietal lobule (BA40, peak $x, y, z = 46, -64, 44$, F value = 25.23) and the left angular gyrus (BA39, peak $x, y, z = -42, -60, 38$, F value = 16.77) (Fig. 1a). In comparison with controls, AD converters demonstrated reduced blood flow in the bilateral parahippocampal gyri, precunei, PCC, bilateral parietal association areas, and the right middle temporal gyrus (Fig. 1b, Table 2). Non-converters also demonstrated significant reduction of rCBF in the PCC and the right caudate nucleus when compared to controls (Fig. 1c, Table 2). Importantly, significant differences in the bilateral precunei and parietal association areas were found between converters and non-converters (Fig. 1d, Table 2).

Group comparisons of subdivided groups of converters and the non-converters

As compared to non-converters, the first group of 26 converters showed significantly decreased rCBF in the right inferior parietal lobule (Talairach coordinate: 46, −64, 47, t value: 3.82, cluster size: 115) and the left angular gyrus (Talairach coordinate: −40, −58, 36, t value: 4.45, cluster size: 127) (Fig. 2 left). The essentially same result was found in the comparison between non-converters and the second group of 26 converters (Right IPL: Talairach coordinate: 53, −58, 42, t value: 3.65, cluster size: 44; Left angular gyrus: Talairach coordinate: −40, −57, 34, t value: 4.81, cluster size: 180) (Fig. 2, right). We could not find reduced rCBF in the precunei at $P < 0.001$; however, reduction in the precunei was detected at a lenient statistical threshold ($P < 0.005$ without multiple comparisons) in each group comparison (data were not shown).

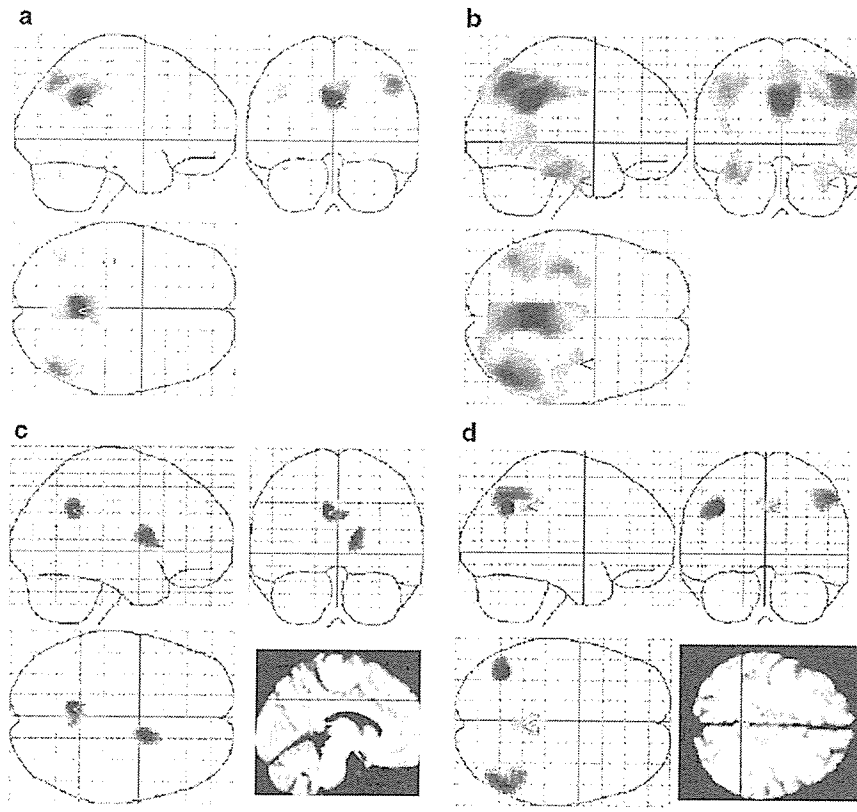

Fig. 1. Results of group comparisons. (a) The SPM {F} is displayed in a standard format as a maximum-intensity projection viewed from the right, the back, and the top of the brain. The anatomical space corresponds to the atlas of Talairach and Tournoux. Representation in stereotaxic space of regions with significantly differences between groups (corrected $P < 0.05$) was demonstrated. The ANOVA demonstrated a significant difference among groups in the bilateral precunei, the posterior cingulate cortices, the right inferior parietal lobule, and the left angular gyrus. (b) The SPM is displayed in a standard format as a maximum-intensity projection of regions with significantly decreased rCBF in converters compared with the control group [$P < 0.001$, corrected by small volume correction (SVC)]. The converters demonstrated reduced blood flow in the bilateral parahippocampal gyri, precunei, PCC, bilateral parietal association areas, and the right middle temporal gyrus. (c) The SPM is displayed in a standard format as a maximum-intensity projection of regions with significantly decreased rCBF in non-converters compared with the control group ($P < 0.001$, corrected by SVC). Non-converters demonstrated significant reduction of rCBF in the PCC and the right caudate nucleus. (d) The SPM is displayed in a standard format as a maximum-intensity projection of regions with significantly decreased rCBF in converters compared with non-converters ($P < 0.001$, corrected by SVC). The converters showed a significant reduction of rCBF in the bilateral precunei and parietal association areas.

Table 2
Results of group comparisons and paired *t* tests

Region	BA	Coordinates			*K*	Corrected *P* value (with small volume correction)	*t* value
		x	*y*	*z*			
Controls > AD converters							
Bilateral precuneus, and PCC	BA31						
	B7	2	−45	32	6794	<0.001	8.46
R IPL	BA40	46	−64	44	6794	<0.001	6.95
L Angular gyrus, IPL	BA39	−42	−60	38	1301	<0.001	5.24
L PHG	BA20,36	−38	−22	−17	771	<0.001	5.36
R PHG	BA20,36	34	−15	−19	535	0.005	3.97
R Middle temporal gyrus	BA21	63	−37	−8	535	0.008	4.25
Controls > MCI non-converters							
L PCC	BA31	−8	−49	34	231	<0.001	4.83
R PCC	BA31	4	−47	30	231	0.003	3.81
R Caudate nucleus		14	6	11	158	<0.001	4.63
MCI non-converters > AD converters							
R IPL	BA40	51	−58	45	653	0.001	4.49
L Angular gyrus	BA39	−38	−58	36	368	<0.001	5.21
L Precuneus	BA7	−6	−35	42	140	0.014	3.34
R Precuneus	BA7	2	−45	43	140	0.009	3.51

BA: Brodmann area, IPL: inferior parietal lobule, PCC: posterior cingulate cortex, PHG: Parahippocampal gyrus.

The predictive value of rCBF changes observed at initial SPECT and scores of neuropsychological tests

Given the results of the group comparisons, we hypothesized that rCBF changes in the precuneus and the parietal association areas would be good predictors of progression from MCI to AD in individuals with MCI. Using the *Z* score of each region (Fig. 3) for each MCI subject, we determined the predictive value of the initial rCBF SPECT using a logistic regression analysis. Table 3 shows the results of the logistic regression analysis. We found that higher *Z* scores in the left angular area (Wald $\chi^2 = 11.1$, $df = 1$, $P = 0.001$, odds ratio [OR] 2.174, 95% confidence interval [CI] = 1.38–3.43), right inferior parietal lobule (Wald $\chi^2 = 10.7$, $df = 1$, $P = 0.001$, OR 2.13, 95% CI = 1.35–3.35), and the precuneus (Wald $\chi^2 = 10.13$, $df = 1$, $P = 0.001$, OR 2.417, 95% CI = 1.4–4.16) were good predictors of progression from MCI to AD (Table 3). A cutoff value of 0.5, which best divided the converter and non-converters, provided high sensitivity (82–90%) and adequate overall accuracy (68–73%) in each region (Table 3).

In contrast, lower scores on delayed recall of list learning (Wald $\chi^2 = 8.369$, $df = 1$, $P = 0.004$, odds ratio [OR] 1.413, 95% confidence interval [CI] = 1.118–1.786) and lower scores on delayed recall of the Rey–Osterrieth Complex Figure Test (ROCFT) (Wald $\chi^2 = 7.092$, $df = 1$, $P = 0.008$, OR 1.167, 95% CI = 1.042–1.308) had lower predictive values than those of the rCBF changes observed in SPECT studies. A cutoff value of 0.5, which best divided the converters and non-converters, revealed similar sensitivity (90.3% for word leaning and 86.2% for ROCFT,

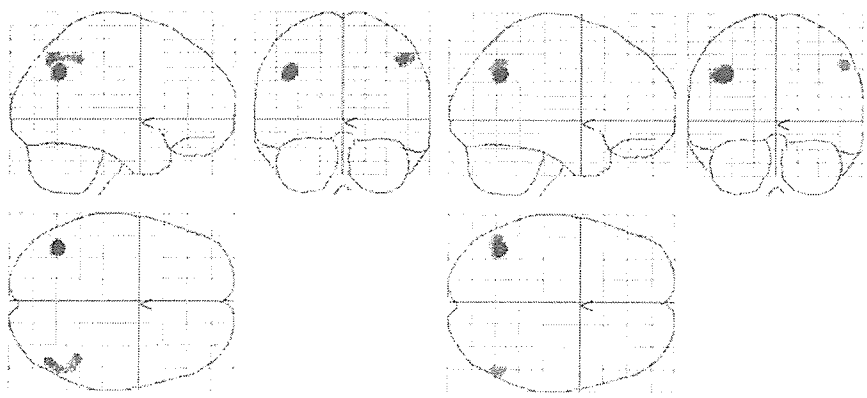

Fig. 2. Results of group comparisons of subdivided groups of converters and the non-converters. The SPM is displayed in a standard format as MIP of regions with significantly decreased in rCBF in converters compared with non-converters (uncorrected $P < 0.001$). Fifty-two converters were randomly divided two groups. Then, two-sample *t* tests between non-converters and each group of AD converters were done. Left: The first group of converters showed a significantly decreased rCBF in the left angular gyrus and the right inferior parietal lobule. Right: The second group of converters also showed essentially the same result.

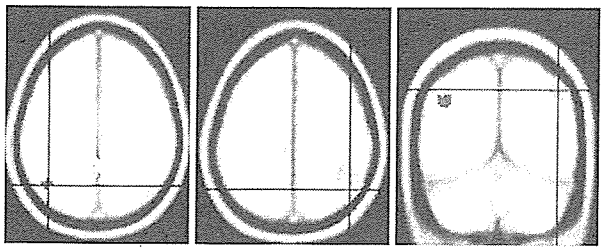

Fig. 3. Regions of interest (ROIs) for the logistic regression model. Red: The ROI for the *Z* score in the left angular gyrus. Yellow: The ROI for the *Z* score in the bilateral precunei. Green: The ROI for the *Z* score in the right inferior parietal lobule.

respectively) and overall accuracy (69.8% for word leaning and 78% for ROCFT respectively) to the sensitivity and accuracy associated with the rCBF changes observed in the initial SPECT (Table 3).

Discussion

The conversion rate

The annual conversion rate of MCI to AD in the current study was 21.14%, which is higher than that observed in other cohorts of MCI subjects (Bruscoli and Lovestone, 2004). A recent review of conversion studies reported that the overall rate of conversion was 10%, but that large differences existed between studies (Bruscoli and Lovestone, 2004). The single most important variable accounting for between-study heterogeneity was the source of subjects, with self-selected clinic attendees having the highest conversion rate (Bruscoli and Lovestone, 2004). In our study, all individuals with MCI were outpatients that attended a memory clinic, and therefore the high conversion rate in the study is not surprising.

Different rCBF changes between converters and non-converters and the predictive value of initial SPECT study

In this study, converters displayed a significant reduction of rCBF in the precuneus and bilateral parietal association areas when compared to non-converters. Although the sample size of converters was larger than that of non-converters, the results of group comparisons with randomly re-sampling the converters in cohorts where the sample sizes were matched to that of non-converters demonstrated essentially the same results. The fact indicated that the greater extent of rCBF abnormalities in converters was not influenced by statistical power. Importantly, we also found that reduction of rCBF in these areas is a good predictor of conversion from MCI to AD. Performance on measures of delayed recall of word learning and ROCFT also showed relatively high discriminative ability, although these scores had lower odds ratios than those associated with reduction of rCBF. These results demonstrate the utility of rCBF SPECT for the prediction of AD conversion. Previous functional neuroimaging studies in very early AD and MCI have consistently demonstrated dysfunction in the PCC and cinguloparietal transitional area or precuneus (Minoshima et al., 1997; Kogure et al., 2000; Imabayashi et al., 2004). A recent PET study showed that the retrosplenial PCC was the only abnormality common to all MCI individuals (Nestor et al., 2003a,b). However, our data suggest that reduced rCBF in the parietal association areas and precuneus are better predictors than PCC hypoperfusion. Indeed, the comparison between the controls and non-converters also demonstrated a significant reduction of rCBF in the PCC. We consider that hypoperfusion in the temporo-parietal regions could be more advanced signs of AD pathology and may precede manifestation of clinical symptoms of AD, and therefore they were better predictors of early conversion. A recent longitudinal FDG-PET study reported similar results to those of the present study: a high predictive value of reduced FDG uptake in the parietal association areas and a lower predictive value of that in the PCC (Chetelat et al., 2003). Mosconi et al. also reported that converters demonstrated reduced glucose metabolism in the inferior parietal cortex as compared with non-converters (Mosconi et al., 2004). Although Nestor's study emphasized the importance of functional abnormality of the retrosplenial cortex in MCI subjects, they also reported that MCI subjects with additional hypometabolism in the parietal association areas converted to AD during the follow-up period (Nestor et al., 2003). These results in conjunction with the current results strongly demonstrate the high predictive value of functional abnormality in the parietal association areas. Furthermore, these results are consistent with the results of a postmortem study of tau pathology in aging and AD (Delacourte et al., 1999). According to Delacourte's study, neurofibrillary degeneration (NFD) with paired helical filaments (PHF)-tau was systematically present in varying amounts in the hippocampal region of non-demented aged subjects, whereas tau pathology in the angular gyrus (BA39) and dorsolateral prefrontal cortex (BA9) was found in all AD patients

Table 3
Results of logistic regression model

	Odds ratio	95% CI	*P* value	Sensitivity (%)	Overall accuracy (%)
SPECT imaging test					
Regions					
L Angular gyrus	2.174	1.38–3.43	<0.001	82	68
R IPL	2.130	1.35–3.35	<0.001	90	73.3
Precuneus	2.417	1.40–4.161	<0.001	88	73.3
Neuropsychological test					
List learning (delayed recall)	1.413	1.118–1.786	0.004	90.3	69.8
Rey–Osterrieth complex figure test (delayed recall)	1.167	1.042–1.308	0.008	86.2	78

CI: confidence interval, IPL: inferior parietal lobule.

(Delacourte et al., 1999). The data support the notion that functional abnormality in the parietal association areas should be a *better predictor* of AD conversion. However, two longitudinal studies (Huang et al., 2002; Drzezga et al., 2003) suggested high predictive value of functional abnormality in the PCC; further study will be needed to clarify the predictive value of the functional abnormality in the PCC.

Unexpectedly, we found decreased rCBF in the right caudate nucleus in comparing controls and non-converters. A recent voxel-based volumetric MR study (Frisoni et al., 2002) revealed reduced gray matter volume of caudate nucleus in mild AD; however, we have no good explanation or hypothesis about this finding at the present moment.

Reduction of rCBF in the parahippocampal gyrus in converters

In this study, we found reduced parahippocampal rCBF in converters. Numerous structural MRI studies have demonstrated that progressive atrophy of the parahippocampal area including the entorhinal cortex is a sensitive marker for detecting and predicting AD (Chetelat and Baron, 2003; Korf et al., 2004; Nestor et al., 2004). In this study, we did not apply a partial volume effect (PVE) correction for SPECT imaging; therefore, one could argue that reduced rCBF in the parahippocampal area could be explained by partial volume effect. We agree that PVE partially contributes to the results of our study. However, an atrophy-corrected FDG-PET study demonstrated hippocampal hypometabolism in AD and MCI and the study's authors concluded that metabolism reductions exceed volume losses in MCI (De Santi et al., 2001). Other studies with MRI-guided FDG-PET also demonstrated hypometabolism of the limbic systems (de Leon et al., 2001; Nestor et al., 2003a,b) including the entorhinal cortex in MCI.

Limitations of this study

The first limitation of this study is that we did not evaluate the cross-validity of the predictive value of the SPECT findings using split-half reliability due to the limited number of non-converters. To conclude the usefulness of rCBF SPECT in predicting AD conversion, our data should be replicated in other cohorts. In this context, our data may be considered to be preliminary rather than conclusive. However, other studies conducted by different research groups using a different imaging method (FDG-PET) reported similar results to those of the present study (Chetelat et al., 2003), and we believe that our predictive model should be reliable.

Second, we did not perform the correction of partial volume effects (PVE) for SPECT images. We agree that PVE could partially contribute to the results of the present study. Even so, the predictive value of rCBF patterns identified in this study still has diagnostic value. From a diagnostic point of view, atrophy-related hypoperfusion is a consequence of AD pathology and might improve the detection of early functional abnormalities.

Finally, some may argue that a 3-year follow-up is not long enough. We agree that it remains a possibility that some of the non-converters would develop AD during a longer observation period, because the logistic model cannot be certain that someone will not convert AD after the follow-up period. However, we can still distinguish rapid converters from slow converters or slow decliners using the initial SPECT study. The results suggest that the initial SPECT study can discriminate between rapid decliners and slow decliners. Such discrimination is important for both therapeutic and research purposes.

Conclusion

We demonstrated that the rCBF reductions in the parietal association areas and the precunei are a good predictor of progression from MCI to AD. The data suggest that the initial rCBF SPECT in individuals with MCI could be a promising method to accurately predict who would meet diagnostic criteria for AD in the next 3 years.

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Activation of A1 and A2 noradrenergic neurons in response to running in the rat

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Abstract

Since running accompanied with blood lactate accumulation stimulates the release of adrenocorticotropic hormone (ACTH), running above the lactate threshold (LT) acts as stress (running stress). To examine whether A1/A2 noradrenergic neurons that project to the hypothalamus activate under running stress, c-Fos immunohistochemistry was used to compare the effects of running with or without stress response on A1/A2 noradrenergic neurons. Blood lactate and plasma ACTH concentrations significantly increased in the running stress group, but not in the running without stress response and control groups, confirming different physiological impacts between different intensity of running with or without stress. Running stress markedly increased c-Fos accumulation in the A1/A2 noradrenergic neurons. Running without stress response also induced a significant increase in c-Fos expression in the A1/A2 noradrenergic neurons, and the percentage of the increase was smaller than that of running stress. The extent of c-Fos expression in the A1/A2 noradrenergic neurons correlates with exercise intensity, signifying that this neuronal activation is running speed-dependent. We thus suggest that A1/A2 noradrenergic neurons are activated in response to not only running stress, but also to other physiological running, enhanced by non-stressful running. These findings will be helpful in studies of specific neurocircuits and in identifying their functions in response to running at different intensities.

Keywords: A1/A2; Running stress; Noradrenaline; Hypothalamic paraventricular nucleus; Lactate threshold; Rat

Exercise at around the lactate threshold (LT) produces a variety of physiological and psychological effects on the body [13,26] and thus it has been widely used as a beneficial tool for preventing or ameliorating lifestyle-related diseases in the clinical field. However, the effects of this intensity of exercise on brain function have yet to be determined. The LT is a work rate at which the steady state of blood lactate accumulation breaks down [28] and the plasma adrenocorticotropic hormone concentration begins to increase notably during graded running [6,12,18]. Since it is well known that ACTH release is a marker of stress [15], acute running can act as one kind of stress, termed running stress, if it persists above the LT. We would like to know what brain regulatory mechanisms underlie running stress just above the LT since it would add greatly to our understanding of the mechanisms behind the variety of physio-/psychological benefits produced by exercise around the LT.

Little is known about the regulating mechanism underlying running stress, although we have previously delineated anatomical activation of the parvocellular part of the hypothalamic paraventricular nucleus (pPVN) during running stress using our rat treadmill running model [20,25]. We further attempted to determine the nuclei or neuropeptides that regulate ACTH release during running stress via pPVN activation. The A1 and the A2 noradrenergic (NA) neurons that project to the pPVN are prime candidates for the regulation of running stress, since these noradrenergic neurons play a crucial role in other ACTH releases induced by stress, such as hypoxia [23], hemorrhage [3] and swimming stress [22]. However, it is very odd that no one has examined whether NA neurons in the A1/A2 are responsive to running stress, despite considerable physiological changes

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including stress response and sympathetic activation, being generally observed during exercise around LT. Thus, the aim of this study is to clarify whether running stress activates NA neurons; and if so, if it can be hypothesized that this activation will occur only during exercise above the LT. To address this, we investigated whether running stress activates NA neurons in the A1/A2 by examining the expression of Fos protein, an immediate early gene product, in NA neurons in the A1/A2.

Male Wistar rats (250–300 g) were housed four per cage and kept on a 12-h light:12-h dark cycle with standard laboratory feed and water *ad libitum*. Body weight was measured daily. All the procedures used were in accordance with the NIH Guidelines for Ethical Care of Experimental Animals and were approved by the University of Tsukuba's Experimental Animal Use Committee.

The protocols for the training and the exercise tests were the same as in our previous study [20]. Briefly, rats were initially trained to run 5 days/week for 2 weeks with a graded increase in the speed and duration for 30 m/min/day on a treadmill (KN-73 Natsume, Tokyo, Japan), before they were subjected to an exercise test. This test consisted of running at 15 m/min or 25 m/min a 0° incline for 30 min. The control rats were put on the treadmill without running for 30 min. All exercise tests were performed between 8:00 and 11:30 a.m. to eliminate the effect of basal glucocorticoid level, which is known to increase during the dark phase. After completion of the test, the animals were withdrawn blood from previously inserted jugular catherter for measurements of blood lactate and plasma ACTH concentrations. Blood lactate was measured using an automated glucose-lactate analyzer (2300 Stat Plus, YSI, OH, USA). Plasma samples were obtained by centrifugation and stored at −30 °C until measurement. Plasma concentrations of ACTH were measured using commercially available kits (ICN Biomedicals, Costa Mesa, CA) with a detection limit of <4 pg/ml. The coefficient of intra-assay variation was 7.2%. For immunohistochemistry, the animals were returned to their home cage. A hundred twenty minutes after the initiation of the test, they were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and perfused first with saline and then with 5% acrolein in 0.1 M phosphate buffer (PB, pH 7.4). The brains were quickly removed and immersed for more than 24 h in PB containing 30% sucrose. Frozen serial frontal sections (40 μm thick) of the brain were made using a cryomicrotome. The sections were then processed for immunohistochemistry.

A sensitive immunohistochemical method of that employs a free-floating technique was used as previously described [20]. Briefly, the cryosections were washed with PB and immersed sequentially in the following solutions: (1) 0.5% sodium metaperiodate in PB for 20 min, (2) 1% sodium borohydride in PB for 20 min, (3) 1% normal goat serum and 0.2% Triton X-100 in PB (GPB) for 1 h, (4) a rabbit polyclonal antibody against Fos protein (Oncogene, Boston, MA, USA, diluted 1:48,000) in GPB for 24 h, (5) biotin-conjugated donkey antirabbit IgG (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, diluted 1:400) in GPB for 2 h, and (6) avidin-biotinylated HRP-complex (ABC, Vector Laboratories, Inc., Burlingame, CA) for 30 min. Fos immunoreactivity was then visualized as a black nuclear precipitate by means of a glucose oxidase-based nickel-intensified diaminobenzidine (Nickel-DAB) procedure.

After staining the Fos protein with Nickel-DAB, the free-floating sections were first washed with 0.1 M acetate buffer (pH 6.0) and then incubated for 24 h with a rabbit polyclonal antibody against tyrosine hydroxylase (Chemicon, Temecula, CA, USA, diluted 1:5000) in GPB. The sections were treated with biotin-conjugated donkey antimouse IgG (Santa Cruz Biotechnology, Inc.) diluted 1:400 in GPB for 2 h, then further incubated with avidin-biotinylated HRP-complex (ABC, Vector Laboratories, Inc.) for 30 min. Finally, the sections were visualized as a brown cytoplasmic precipitate using a diaminobenzidine procedure. Sections incubated without primary antibodies remained virtually free of immunolabeling. After processing, the sections were mounted and examined by light microscopy. The C1/C2 regions are mainly located in the rostral part of the area postrema (AP) [11], whereas the A1/A2 regions are localized more in the caudal part than C1/C2 [10], so we divided both the C1/C2 and the A1/A2 region into rostral and caudal parts to AP. The two to three sections containing the A1/A2 (−13.7 to −13.1 mm from the bregma) and the parvocellular part of the paraventricular nucleus (pPVN) (−1.9 mm from the bregma) that most closely matched the Paxinos and Watson [17] rat brain stereotaxic atlas and our previous study [20] were counted for each animal. All Fos- and/or TH-positive cells in both sides of each nuclear area were counted by staff blind to treatment. To avoid double counting, only neurons with a complete nucleus were counted.

All data shown are expressed as mean ± S.E. The comparisons between different groups were performed using one-way ANOVA followed by *Scheffé's post hoc* test. Brain areas showing between-group variations with $p < 0.05$ were regarded as statistically significant.

Concentrations of blood lactate after 30 min of running were 1.58 ± 0.08 mmol/l in the controls ($n = 4$), 1.71 ± 0.08 mmol/l in the below-LT running ($n = 5$), and 3.34 ± 0.06 mmol/l in the supra-LT running group ($n = 5$). Running-induced increase in plasma ACTH concentrations in the control ($n = 4$), below-LT ($n = 5$), and supra-LT running groups ($n = 5$) were 108 ± 17, 177 ± 52 and 473 ± 77 pg/ml, respectively. Values are expressed as mean ± S.E. These absolute values were consistent with our previous results [21]. Blood lactate and plasma ACTH concentrations significantly increased in supra-LT running groups compared to controls and below-LT running groups (one-way ANOVA followed by *Scheffé's post hoc* test, $p < 0.01$ versus control and below-LT running groups). The photomicrographs in Fig. 1 show TH- and/or Fos-ir cell labeling in the A1/A2 (Fig. 1A–F), and Fos-ir cell labeling in the pPVN (Fig. 1G–I) in supra/below-LT running and control animals. In the A1/A2, as revealed in the quantitative data, labeling is minimal in the controls (Fig. 1A and D). Increased running speed increased the number of TH/Fos-ir cells in both nuclei. Supra-LT running markedly increased the cell number of TH/Fos-ir cells in both the A1 cell group (Fig. 1C) and the A2 cell group (Fig. 1F) as expected. It is of interest that below-LT running also increased the cell number of TH/Fos-ir cells in both the A1 cell group (Fig. 1B) and the A2 cell group (Fig. 1E),

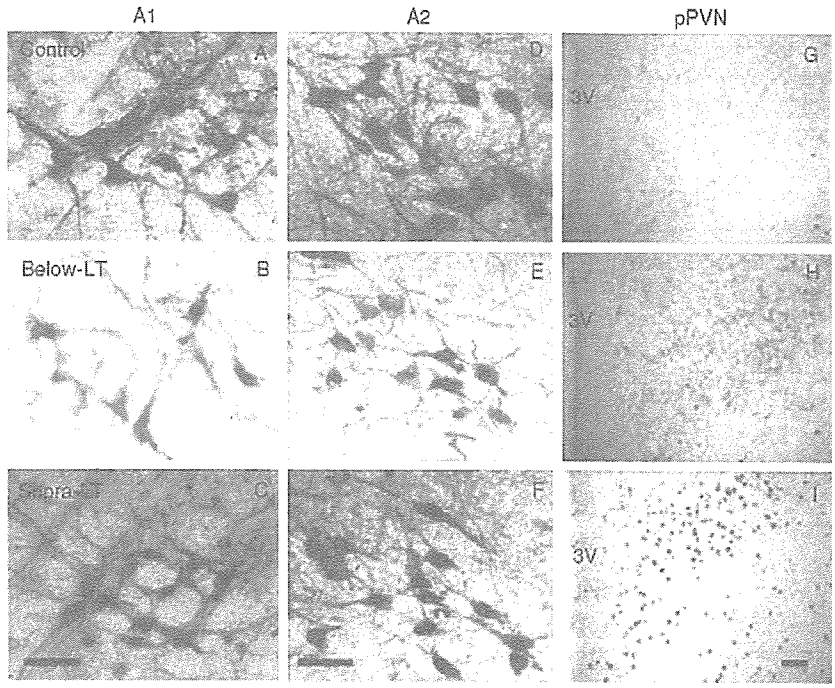

Fig. 1. Photomicrographs show double immunostaining with TH/Fos-ir and Fos-ir cells in the A1 (A–C), A2 (D–F) and the pPVN (G–I) of rats subjected to treadmill running at 0 m/min (controls: A, D and G), 15 m/min (below-LT running: B, E and H), and 25 m/min (supra-LT running: C, F and I). TH/Fos-ir cells were gradually labeled in response to the exercise intensity, whereas Fos-ir cells were remarkably labeled only Supra-LT running in the pPVN. TH-ir cells and Fos-ir cells were stained brown and black, respectively. Scale bars = 50 μm.

although the extent of accumulation was smaller than that for supra-LT running. Supporting our previous study [21], supra-LT (Fig. 1I) running markedly increased the number of Fos-ir cells in the pPVN, whereas control (Fig. 1G) and below-LT (Fig. 1H) running increased them to a lesser extent. The percentage of c-Fos expression in the TH-ir cells of the A1 and the A2 cell groups significantly increased according to running speed. The increased percentages of TH/Fos-ir cells were statistically different among the control, below-LT, and supra-LT running groups (one-way ANOVA followed by *Scheffé's post hoc* test, $p < 0.01$) (Fig. 2A). The number of Fos-ir cells in the pPVN was significantly higher than those in the below-LT and the control groups (one-way ANOVA followed by *Scheffé's post hoc* test, $p < 0.01$ versus control and below-LT running groups) (Fig. 2B).

The running protocol in this study consisted of both below- and supra-LT running, which are typical exercise intensities that induce different metabolic and cardiovascular responses to running, as conclusively established in humans [1] and rats [2,24]. In our running model used in this study, rats subjected to running at supra-LT showed a significant increase in plasma ACTH levels and osmolality together with blood lactate levels, while rats in the below-LT running group did not [20,25]. Indeed, the fact that blood lactate and plasma ACTH concentrations and the number of Fos-ir cells in the pPVN were significantly elevated in the supra-LT running group demonstrates the validity and reproducibility of our running model as used in the present study. Our running model consists of two different runs with or without stress response.

TH/Fos-ir cells markedly increased in the A1/A2 at supra-LT running as shown in Figs. 1 and 2. The A1/A2 noradrenergic neurons showed the most prominent activation in supra-LT running, suggesting that these NA neurons play a crucial role in

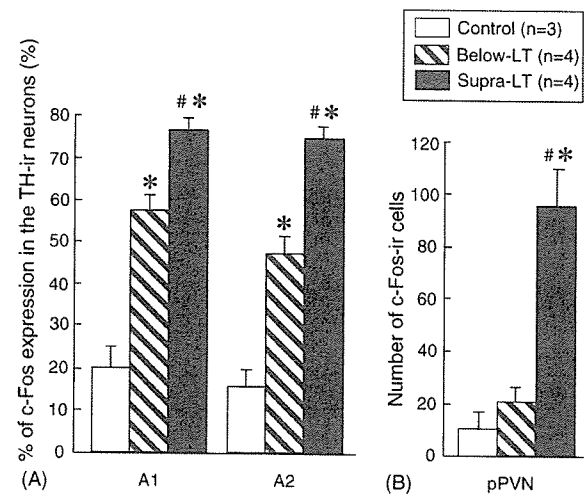

Fig. 2. Percentage of c-Fos expression in TH-ir cells in the A1/A2 (A) and number of Fos-ir cells in the pPVN (B) for the control (open bars), the below-LT (stripe bars) and the supra-LT (filled bars) groups. The supra-LT running markedly increased the number of Fos/TH-ir cells in the A1/A2, and the percentage of c-Fos expression in the TH-ir cells of the A1/A2 significantly increased according to running speed (A). Fos-ir cells in the pPVN significantly increased in supra-LT running (B). Values are mean ± S.E. $^{*}p < 0.05$ vs. control. $^{\#}p < 0.01$ vs. below-LT (*Scheffé's post hoc* tests) ($n = 3$–4).

some physiological events induced by running stress, for example, the pPVN receives dense projections from the A1/A2 [21], and it has been reported that both nuclei involve several stress responses [3,4,16,23], including swimming stress [22]. Furthermore, we delineated anatomical activation of the pPVN where it receives NA innervation during supra-LT running [20], suggesting that the A1/A2 play a provocative role in regulating ACTH release in running stress.

We also have demonstrated that running stress causes plasma hyper-osmolality, resulting in the activation of hypothalamic arginine–vasopressin (AVP) neurons in the pPVN and the SON [20]. Because NA neurons in the A1 enhance responsiveness to plasma hyper-osmolality in the PVN neurosecretory cells [27], activation of hypothalamic AVP neurons during running stress that induces plasma hyper-osmolality might be amplified by these NA neurons.

Unexpectedly, TH/Fos-ir cells in the A1/A2 also showed a significant increase in below-LT running (running without ACTH release), unlike the pPVN. The reason why below-LT running increased TH/Fos-ir cells in the A1/A2 is unclear at present. However, one possible involvement appears to exist. In contrast, only in the stress response induced above the LT did the cardiovascular response increase linearly with running speed [1,24]. Since these areas are generally accepted as being the circulation center in the brain stem [19] and A1/A2 neurons are responsive to different cardiovascular conditions [14], it is possible that A1/A2 are activated in response to the cardiovascular response during below-LT running. It is not known why below-LT running increased TH/Fos-ir cells in the A1/A2 without activation of the pPVN; however, the pPVN may receive GABAergic inhibitory inputs from other brain areas, such as the bed nucleus of the stria terminalis [5,9] or hippocampal formation [8], suggesting involvement of another inhibitory factors that regulate running-induced ACTH release.

The physiological role of activated NA neurons in the A1/A2 could not be determined in this study; however, we first demonstrated anatomical evidence that these neurons are responsive not only to supra-LT running, but also to below-LT running. This is to be expected in regulatory systems that respond to running. Neuroendocrine systems in the hypothamalo-pituitary-adrenal axis and sympathetic nervous system including cardiovascular regulation, act cooperatively to support the increased metabolic demands made by contracting muscles when running speed increases [7]. The A1/A2 noradrenergic neurons may be involved in the regulation of both systems. Further studies are needed, using adrenoreceptor antagonists and agonists or by means of lesion studies, to estimate the physiological contributions of these neurons during running.

In summary, TH-containing neurons in the A1/A2 are linearly activated with exercise intensity. We thus suggest that these neurons are activated in response not only to running stress and other types of stress, but also to other physiological responses enhanced by non-stressful running (running without ACTH release). These findings will be helpful in studies of specific neurocircuits and in identifying their functions in response to running at different intensities.

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研究報告

安心院地区の独居者人における認知症調査結果（第一報）

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はじめに

友人・近隣・親族との接触頻度より地域集団への参加頻度の方が生存率を高め、地域活動への参加は健康障害や死亡の低減に関連するという。従って高齢期には閉じこもることなく、外出し、社会的刺激を受ける生活習慣が重要と考えられている[1]。

独居高齢者数は今後益々の増加が予想されている。独居であるが故に、認知症の発見が遅れ、さらには独居状態で認知症になると介護環境の整備により深刻な対応が求められる。物理的に孤立し、家庭内支援環境を持たない独居高齢者が最後まで自立した生活を維持するには行政のみでなく、コミュニティーレベルでの対応が要求されるが、これに対する施策整備は急務である。特に認知症予防的な意味からも社会全体で、高齢者の社会参加や生き甲斐を創出することの可能な社会基盤を、と

りわけ独居高齢者に向けて、整備していく必要がある。

われわれが都市在住独居高齢者を対象に行った研究では、独居者の日常生活動作（ＡＤＬ）は比較的保たれ、運動能力も高く維持されているが、生活全般の満足度が低く、潜在的に高い割合でうつ状態がみられた[2]。また大都市近郊独居者についての研究では、外出頻度は比較的高く保持されていた。しかし隣近所には外出できるが、一人で遠出はしない者は、精神的身体的虚弱性があり、近隣閉じこもりとも呼べる状態で予防的支援の必要性が指摘された[3]。さらには独居高齢者の生活空間狭小化が死亡に関連すると報告されている[4]。このように様々な視点から独居高齢者の問題点が取り上げられているが、調べ得た範囲で認知症との関連での検討はない。

われわれは3年前から大分県宇佐市安心院町で主として認知症予防の視点からフィールドワークを実施している[5]。この研究活動では認知症早期発見のみならず、その後の治療をも行うための相談業務も取り入れている。その過程の中から、認知症発症独居高齢者への早急な取り組みと認知症予防対策立案の緊急性と重要性を実感した。今回の研究では安心院町安心院地区独居高齢者の悉皆調査により認知症疑いやＡＤＬ障害とうつを有する住民の頻度を求め、行政への提言という意味合いを込めて検討した結果を報告する。

対象

安心院町安心院地区に居住する65歳以上高齢者のうち独居老人全員の139名を対象とし、非独居高齢者312名を対照群にした。

方法

平成16年度に公民館で、記憶、注意、言語、視空間認知と類推に着目した設問から構成されている集団的認知機能検査ファイブ・コグ[6]を実施し、同時に手段的ＡＤＬ[7]（ＩＡＤＬ：電話使用、買い物、会の世話係、交通手段、薬の管理、家計管理、申告書作成の7項目）とGeriatric Depression Scale（ＧＤＳ）[8]を用いて評価を行った。公民館に来館できなかった独居者には訪問を行い、そこでの認知機能検査にはＭＭＳＥを用いた。統計学的検定にはt-検定と度数検定としてKolmogorov-Smirnovテストを用いた。この研究は福岡大学医学部倫理委員会の承認を得ている。

結果

表1に対象者の背景と検査結果の平均値（標準偏差）と検定結果を示す。平成16年度に独居と登録されていた139名のうち、113名がこの研究に参加した（80%）。平均年齢は74・5歳で、男性21名、女性86名であった。非参加者は26名で検査拒否や入院中であ

ることが主な理由であった。非独居群は平均年齢74・3歳で男性105名、女性207名であった。教育歴は独居群は9・8年、非独居群が10・4年で有意差はなかった。

表1. 対象者の背景、各検査の平均値（標準偏差）と統計学的解析

	独居者	非独居者	有意差
年齢（才）	74.5(6.4) n=113	74.3(6.3) n=312	
教育歴（年）	9.8(1.7) n=113	10.4(2.1) n=312	
ファイブ・コグ	1.1(1.5) n=79	1.1(1.3) n=312	
GDS	4.6(4.0) n=112	3.3(2.6) n=311	p<0.01
IADL	5.2(1.6) n=111	5.2(1.8) n=311	

表2. 独居者のファイブ・コグ成績（79名）

AACD数	男	女	計
0	6	39	45
1	1	11	12
2	1	8	9
3	0	7	7
4	1	5	6
5	0	0	0
計	9	70	79

表3. 非独居者のファイブ・コグ成績（312名）

AACD数	男	女	計
0	45	92	137
1	33	49	82
2	11	40	51
3	8	15	23
4	4	8	12
5	4	3	7
計	105	207	312

ファイブ・コグの成績（Five-Cog）

Age-associated Cognitive Decline（AACD）[9]でない正常独居者は45名（男6、女39）であり、約57%であった。Mild Cognitive Impairment（MCI）[10]を含む軽度の認知障害を疑わせる者（AACD数が1から2）は21名（27%）で、AACD数3以上（認知症が強く疑われる）は13人（16%）であった。

非独居者群では正常者が137名（44%）、軽度認知障害が133名（44%）で、認知症疑いは42名（13%）

図1. 両群でのファイブ・コグの結果（A、B）とMMSEの得点を加味した結果（C）

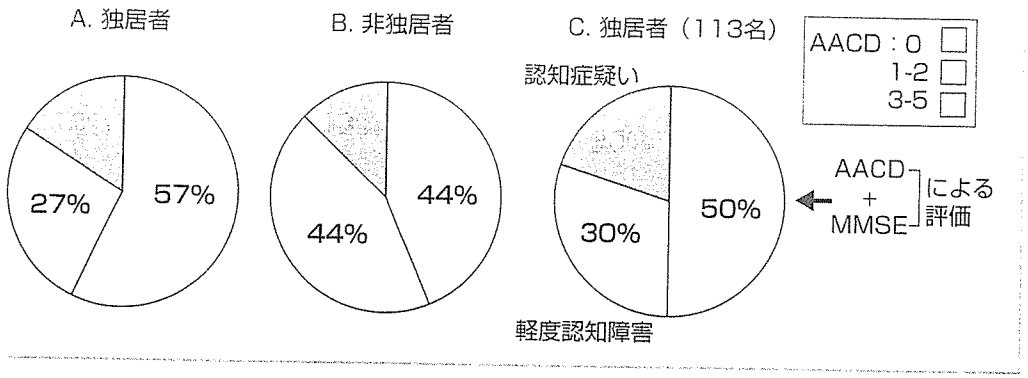

表4. 独居者のMMSE値（34名）

点数	男	女	計
0-19	1	1	2
20-23	2	5	7
24-27	5	8	13
28-30	3	9	12
計	11	23	34

表5. 独居者のIADL値（111名）

点数	男	女	計
0-3	1	18	19
4-6	10	47	57
7	8	27	35
計	19	92	111

表6. 非独居者のIADL値（312名）

点数	男	女	計
0-3	10	50	60
4-6	37	101	138
7	58	56	114
計	105	207	312

表7. 独居者のGDS値（112名）

点数	男	女	計
0-4(正常)	11	56	67
5-9(うつ疑)	6	21	27
10-15(うつ)	2	16	18
計	19	93	112

表8. 非独居者のGDS値（312名）

点数	男	女	計
0-4	80	148	228
5-9	21	53	74
10-15	4	8	10
計	105	207	312

であった。度数検定では両群間には有意差は認めず、独居でも非独居でも認知障害の割合には差がないことが示された。

独居者におけるMMSEの成績（表3）

正常は12名で、軽度障害が13名で認知症疑いが9名に認められた。

ファイブコグとMMSEの独居者群の成績を合わせると113名中正常は57名（50%）、軽度障害は34名（30%）、認知症疑いが22名（20%）であった（図1）。実際には調査できなかった26名中7名が認知症に罹患しているとの報告もあり、これを加えると認知症疑いは29名（24%）になる。

IADL値

7項目のIADLについては、独居者群の111人中35人（32%）は自立（7点）しており、57人（55%）が軽度障害（4-6点）があり、19人（13%）は高度に日常生活が障害されていた（3-0点）（表5）。非独居者群においては自立が114名（37%）、軽度障害が138名（44%）で高度障害が60名（19%）であった（表6）。両群間の平均値には有意差はなかった。またIADLの障害の程度ごとの度数に関して

も両群間で有意差を認めなかった。

うつ

独居者の112名のうち、うつでない者は67名（59%）で、うつの疑いは27名（24%）、うつは18名（17%）であった（表7）。一方非独居者では、312名中それぞれ228名（70%）、74名（24%）と10名（3%）であった（表8）。うつは明らかに独居群に多く、度数検定でも同様の結果であった。また認知症疑いではうつが2名、軽度認知障害では9名で認知障害がない者では7名がうつであった。

考察

この検討の結果、安心院地区の調査に協力していただいた多くの独居高齢者は非独居者と比べて、認知機能やADLでは差はなく、一方でうつの頻度は高かった。この結果はわれわれが4年前に福岡市で行った独居高齢者調査と一致する[9]。今回の認知症に関する調査は一次調査のみで、詳細な二次調査での検討がなされていないため、正確な頻度とはいいがたい。またうつは認知症疑い例のうち2名に認められ、うつが認知症類似状態を引き起こしている可能性もある。

両群とも100%の住民調査ではないため明確には指摘できないが、非独居者群との比較を調査不参加例まで含めたとすると独居者群で24%に対し、非独居では13%と明らかに認知症疑いの割合が独居群で高頻度であり、独居という環境が認知症を生じやすいという可能性も考えられる。この点と関連して注目すべきは、独居群では日常生活遂行能力のみでなく認知機能も十分保たれている元気高齢者が多い一方で、中間的な軽度の認知障害者が少ない傾向がみられたことである。この事実は、軽度障害から明らかな認知障害への移行を、独居環境が早めた結果を意味しているのかもしれない。

うつはアルツハイマー病の危険因子であり、非独居群に比べて明らかに高頻度である独居者にみられたうつやうつ状態に薬物療法などで介入していく必要性と重要性が改めて認識された。独居者は家庭内支援がないために身体的な障害で容易に生活空間の狭小化がもたらせられ、対人的接触頻度はより少なくなり、このような面からも認知障害を引き起こしやすくすると考えられる[10]。

安心院町では認知症調査研究が3年前から始まり、AD前状態も考えられるMCI状態の65歳以上住民の頻度は約5%であった。すなわち約3000人いる高齢者のうち150人が記憶障害を有するMCIと推定される。問題は認知症への移行阻止であり、福岡大学第五内科と町の健康福祉科スタッフが介入する健康クラブ活動が25名の参加者で、1年前から始まった。内容は認知リハビリテーション[12]と運動療法であり、その成果は別誌で報告する。

しかしながら軽度認知障害を有する独居高齢者の参加が得られず、より一層の情宣活動が求められている。地域住民の追跡調査を行ったZunzungenuiら[13]は地区組織の会員であったり、協会の行事に参加したり、老人センターを訪問するなどの社会統合の高い行動をすることが認知機能低下を予防できる可能性を示している。また渡辺らは社会交流のないことが要介護移行により強く関連すると報告した[14]。われわれが提唱している健康クラブ活動は、認知症患者が通所リハビリとして行っているような受け身の活動でなく、参加者一人ひとりの企画力の集積によって創造されたもので、かつ社会的意味合いを保持した活動である。独居高齢者にも積極的に参加しやすい仕組み作りが今後必要であろうし、認知症予防に貢献し、それらは行政・住民・大学一体となって作り上げられるべきだろう。

まとめ

安心院町独居高齢者は全般的にうつの傾向が強く、統計学的には有意ではないが、認知症疑いの割合も高い傾向にあった。認知症予防の観点から積極的なうつの治療と見守りと予防介入事業（安心院町での健康クラブへの参加など）が求められている。

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[原著論文]

非薬物療法による Mild Cognitive Impairment（MCI）から認知症への進行予防効果に関する検討

―― 安心院プロジェクト ――

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抄録

目的：大分県安心院町に居住する65歳以上高齢者のうちMCIと判定された住民を対象に認知症予防活動の効果を検討した．対象：MCIと判定された住民で認知症への進行予防介入に参加した18人を介入群とし，非参加14人を非介入群とした．方法：予防介入前後にファイブ・コグを行い，1年後の認知機能の変化を検討した．予防介入は住民自ら企画した作業療法と運動療法によって行われた．結果：介入の効果を，繰り返し測定のある分散分析において，有意な交互作用効果が見いだせるかどうかで確認した．介入群は非介入群に比べて，記憶と言語の項目で有意な得点の上昇が認められた．非介入群においては記憶と言語では悪化する傾向を認めた．結論：筆者らが企画したMCI住民への非薬物的認知症予防介入は有効であり，多くの住民を対象とした予防活動へと展開できるものと考える．

Key words：Mild Cognitive Impairment（MCI），ファイブ・コグ，非薬物療法，認知症予防介入

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はじめに

2000年4月から開始の介護保険制度は2006年4月から予防重視型システムへと変換される．もちろん認知症予防にも重点がおかれ，さまざまな施策が考えられている．また新たなサービス体系の確立のため地域の特性を生かした多様で柔軟なサービス提供が求められている[12]．こうした点から，認知症の前駆状態とされる軽度認知障害（Mild Cognitive Impairment；MCI）の早期発見と，認知症への進行予防可能な介入の確立は緊急の課題であり，医療費と介護費の抑制という面からも重要なテーマである．

認知症患者に対する非薬物療法の有効性については，これまで数多く検討されている[5,6,8,10,13,14,19,23,27,28,30]．これらの研究はおもに軽度～中等度の認知症患者を対象にしたもので，アルツハイマー病（Alzheimer's disease；AD）の前駆状態とされるMCIに対する有効性について検討したものはきわめて少ない[20,21]．

今回筆者らはMCI状態の住民を地域調査により抽出し，認知症への進行予防のための介入を行い，一定の成果が得られたので報告する．

Ⅰ．対　象

大分県安心院町（現・宇佐市）において2003年6月から2004年11月まで，65歳以上高齢者を対象に一次調査を行った．毎週1回，地区の公民館を巡回し，家族構成や教育歴，疾病の既往歴や日常生活動作障害を聴取し，Geriatric Depression Scale（GDS）[31]によるうつの有無を問診によって評価した．また住民の認知機能評価を集団スクリーニング検査であるファイブ・コグ[3,4,17,22,25,26,29]（記憶，視空間，言語，注意，抽象的思考の5つの認知機能項目によって構成されている）によっ

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て行った．検査後には認知症啓発活動を目的とした教育講演も実施し，こうした活動を含め，一次調査を「いきいき元気教室」と名づけた．

一次調査参加者で，ファイブ・コグの記憶の項目のみ標準より低下していると判定された住民に対して，二次調査として認知症診療を専門とする神経内科医と老年科医による詳細な問診と診察，血液検査，頭部CT，脳血流SPECTおよび詳細な心理検査（表1）を行った．血液検査では，一般的な血算，生化学のほか，ビタミンB_{12}濃度や甲状腺ホルモン濃度の測定が含まれた．

本研究におけるMCIは，1996年のPetersenの定義[24]に基づき，①診察の結果DSM-Ⅳ[2]およびNINCDS-ADRDA[15]の診断基準により認知症がないこと，②自身でもの忘れの訴えがあること，③Clinical Dementia Rating（CDR）[7,18]で0.5と判定されること，④基本的なADLに障害のないこと，⑤ファイブ・コグの成績で記憶は-1SD以下であり，他の4つの認知機能は1SD以内であることとし，二次調査終了時点でこれらの基準に合致した対象者を抽出した．

一次調査終了時，1,251人の地域住民への調査が完了した．対象者のうち，1996年のPetersenの定義に基づくMCIは64人であり，対象者の5.1%であった．この数値は日本で過去に行われた調査結果に一致した[1,9,16]．

詳細な二次調査により明らかに記憶のみが障害され，MCIと判定された住民に対し，認知症への進行予防介入への参加を呼びかけた．介入の趣旨に同意した18人を対象に認知症への進行予防介入を実施し，この18人を介入群とした．一方，介入への参加は希望しないものの1年後の追跡調査への参加を同意した14人を非介入群とした．

介入群の内訳は男性8人，平均年齢74.3 ± 5.6歳（66 ～ 82歳），女性10人，平均年齢73.2 ± 3.8歳（68 ～ 81歳）であり，教育年数は男性9.5 ± 1.5年（8 ～ 12年），女性10.7 ± 2.5年（8 ～ 16年）であった．

非介入群の内訳は，男性8人，平均年齢70.9 ± 6.0歳（65 ～ 81歳），女性6人，平均年齢72.8 ± 4.7歳（69 ～ 81歳）であり，教育年数は男性11.9 ± 3.0年（8 ～ 16年），女性10.2 ± 1.7年（8 ～ 12年）であった．参加者の心理検査の詳細については表1に示す．二次調査で施行した脳血流SPECTでは介入群，非介入群ともに全例において初期ADで認められる，帯状回後部から楔前部の血流低下[11]が認められた．

表1　介入開始前の介入群と非介入群の基礎データ

a. 介入群

変数	N	平均値	標準偏差
性別	18	1.56	0.51
教育年数	18	10.17	2.15
年齢	18	73.67	4.58
記憶	18	6.11	4.24
言語	18	11.67	3.51
抽象的思考	18	7.22	3.00
注意	18	2.80	0.30
視空間	18	865.57	336.25

b. 非介入群

変数	N	平均値	標準偏差
性別	14	1.43	0.51
教育年数	14	11.14	2.63
年齢	14	71.71	5.38
記憶	14	5.86	3.82
言語	14	11.64	2.82
抽象的思考	14	7.36	3.39
注意	14	2.70	0.49
視空間	14	923.17	353.63

Ⅱ．方　法

1．介入群の認知症予防活動

2004年4月から介入群への活動の場として「安心院けんこうクラブ」を設立した．介入内容は参加者が話し合いにより計画を立て実行し，達成感を得ることができるものとした．活動開始時には①使用されていなかった古家をリフォームし，活動の拠点（安心院けんこうクラブ）となるように整備する作業，②栄養士の指導を受けた後，自分たちでメニューを決め，食材の手配から調理までを行う料理教室と③スポーツインストラクターの指導のもとで，踏み台昇降やケア・ビクスなどの運動療法であった．①，②は午前中，③は午後