

In the PFC of Tg601 mice, progressive morphological changes including axonal swelling and spheroids, histopathological correlates of disrupted axonal transport, were observed. The rat PFC consists of cytoarchitecturally and functionally distinct areas located over the medial, orbital, and insular surfaces of the rostral cerebral hemispheres. The medial PFC and orbitofrontal cortex are involved in both cognitive and emotion functions whereas the insular cortex is primarily a viscerosensory region (Schoenbaum et al., 2003; Uylings et al., 2003). Wheat germ agglutinin conjugated with horseradish peroxidase (WGA-HRP) tracer injections into the Acb in the rat predominantly labeled populations of neurons located in layers II, V, and VI of the medial PFC and in layer V of the orbital cortex (Gabbott et al., 2005). Since, in Tg601 mice, axonal dilatations were mainly observed in layers V and VI but not in layer I or III in the medial PFC and the orbital cortex, we postulate that the disruption of axonal transport of the PFC–Acb pathway may have occurred in Tg601 mice.

Tau multimer (140 kDa) was present in the soluble fraction of Tg601 brain tissue and increased with aging, although Tg601 showed neither insoluble tau nor NFTs. We speculate that this may represent tau dimer consisting of two “55 kDa” tau monomers. In rTg4510 and JNPL3 mice, two forms of multimers (140 kDa and 170 kDa) were described (Berger et al., 2007). The authors speculated that tau 140 represented dimers consisting of two “55 kDa” while tau 170 contained two “64 kDa” and they also suggested the tau 140 multimers were the earliest pathological species. “64 kDa” tau has been considered to represent insoluble tau and NFTs in rTg4510 and JNPL3 mice (Berger et al., 2007; Sahara et al., 2002). Since, in Tg601 mice, NFTs did not appear at 20 months, “170 kDa” tau multimer might not emerge. Generally, tau Tg mice overexpressing wild-type tau did not form NFTs unless the mice reached a very old age (Andorfer et al., 2003; Brion et al., 1999; Gotz et al., 1995; Ishihara et al., 1999, 2001; Kimura et al., 2007; Probst et al., 2000; Spittaels et al., 1999). Tg601 demonstrated, for the first time, the presence of soluble tau multimer among tau Tg mice overexpressing wild-type tau. In vitro heparin-induced assembly of recombinant tau revealed that an increase of tau multimer was observed prior to the detection of increased thioflavin T fluorescence signals (Sahara et al., 2007). Increasing evidence suggests that NFT per se might be dissociated with neuronal dysfunction and the other species that occur during NFT formation (Santacruz et al., 2005; Spires et al., 2006) might cause synaptic dysfunction (Polydoro et al., 2009). Soluble tau multimer may be necessary to reach filamentous structure and may cause behavioral dysfunction in tau Tg mice.

Tg601 mice may be a unique model for FTLD because decreased anxiety behavior is reminiscent of a characteristic symptom, disinhibition, which frequently occurs in patients with FTLD. Moreover, observation of decreased Y-maze spontaneous alternation is potentially consistent with the idea that the animals have impaired working memory and resection of prefrontal cortex of the mice leads to impaired spontaneous alternation in Y-maze test (Mogensen and Divac, 1993). Since, immunohistochemically, Tg601 mice displayed axonal dilatations in the prefrontal cortex, we postulate that Tg601 could be a model of FTLD. Recently, the Acb has been described as being involved in the disease of FTLD. Voxel-based morphometry of MRI was performed for patients with a clinical diagnosis of FTLD (Zamboni et al., 2008) and this analysis demonstrated that the severity of disinhibition was correlated with atrophy in the right Acb. The Acb plays a key role in limbic circuits that are responsible for motivated, goal-directed behaviors (Morgane et al., 2005). These findings support the notion that the PFC–Acb projection is involved in FTLD, which is consistent with our result for Tg601 mice.

Patients with FTLD have shown memory impairment, although a predominant feature is change in personal and social behaviors often associated with disinhibition (Lee et al., 2001). The Tg601 mice present with impairment in spatial learning and memory without decreased glucose metabolism in the entorhinal cortex, hippocampus,

and the piriform cortex. This result could be due to the synapse loss in the Acb as the Acb is involved in consolidation of information necessary for spatial learning (Sargolini et al., 2003). THY-tau 22 mouse model, which expresses tau mutated at sites G272V and P301S, also showed both decreased anxiety in the EPM and impaired learning in the MWM (Schindowski et al., 2006). The authors described decreased hippocampal synaptic transmission but not the function of amygdala or prefrontal cortex. V337M tau Tgs also demonstrated increased time spent in open arms in the EPM, although this was not accompanied by impaired spatial learning in the MWT (Tanemura et al., 2002). They also showed decreased hippocampal activity.

The phenotype of Tg601 mice was different from that of WTau-Tg, which we previously described (Kimura et al., 2007), although wild-type human tau (2N4R) was expressed under the CAMKII $\alpha$  promoter in both of these mice. WTau-Tg mice showed hyperphosphorylated tau in parahippocampal cortex and impaired place learning while Tg601 mice displayed decreased anxiety. In Tg601 mice, the total protein level of the transgenic tau in the cortex was almost the same as that of the striatum, while WTau-Tg showed higher expression of transgenic tau in the striatum than in the cortex. In the striatum of Tg601 mice, transgenic tau may be more hyperphosphorylated than in WTau-Tg mice. Polydoro and colleagues described that tau pathology may underlie an age-dependent learning impairment through disruption of synaptic function and our results support this idea. Furthermore, we also demonstrated that hyperphosphorylated tau at PHF-1 epitope and oligomeric soluble tau, not insoluble filamentous tau, may cause synapse loss.

## Conclusion

We generated a four-repeat (4R) tauopathy model mouse that exhibited synapse loss in the Acb and axonopathy in the PFC. We postulate that hyperphosphorylated tau at PHF-1 epitope in the striatum may cause synapse loss in the Acb. In the brain of sporadic 4R tauopathies including PSP, CBD, and AGD, phosphorylated tau pathologies were observed in the subcortical nuclei. Altered distribution pattern of soluble hyperphosphorylated tau may contribute to region-specific neurodegeneration, which occurs in various tauopathies.

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Original Research Article

# Different Characteristics of Cognitive Impairment in Elderly Schizophrenia and Alzheimer's Disease in the Mild Cognitive Impairment Stage

Hiroaki Kazui<sup>a</sup> Tetsuhiko Yoshida<sup>a,b</sup> Masahiko Takaya<sup>a</sup> Hiromichi Sugiyama<sup>a</sup>  
Daisuke Yamamoto<sup>a</sup> Yumiko Kito<sup>a,c</sup> Tamiki Wada<sup>a</sup> Keiko Nomura<sup>a</sup> Yuka Yasuda<sup>a</sup>  
Hidenaga Yamamori<sup>a</sup> Kazutaka Ohi<sup>a</sup> Motoyuki Fukumoto<sup>a</sup> Naomi Iike<sup>a</sup>  
Masao Iwase<sup>a</sup> Takashi Morihara<sup>a</sup> Shinji Tagami<sup>a</sup> Eku Shimosegawa<sup>d</sup>  
Jun Hatazawa<sup>d</sup> Yoshiyuki Ikeda<sup>e</sup> Eiichi Uchida<sup>e</sup> Toshihisa Tanaka<sup>a</sup> Takashi Kudo<sup>a</sup>  
Ryota Hashimoto<sup>a,f</sup> Masatoshi Takeda<sup>a</sup>

<sup>a</sup>Psychiatry, Department of Integrated Medicine, Division of Internal Medicine, Osaka University Graduate School of Medicine, <sup>b</sup>Department of Psychiatry, National Hospital Organization Osaka National Hospital, <sup>c</sup>Department of Psychiatry, Nissay Hospital, <sup>d</sup>Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine, <sup>e</sup>Department of Radiology, Uchida Clinic, and <sup>f</sup>Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Kanazawa University and Hamamatsu University School of Medicine, Osaka, Japan

## Key Words

Alzheimer's disease · Attention deficit · Delayed recall · Executive function · Recent memory · Three-dimensional stereotactic surface projections · Voxel-based specific region analysis · Working memory

## Abstract

We compared indices of the revised version of the Wechsler Memory Scale (WMS-R) and scaled scores of the five subtests of the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in 30 elderly schizophrenia (ES) patients and 25 Alzheimer's disease (AD) patients in the amnesic mild cognitive impairment (aMCI) stage (AD-aMCI). In the WMS-R, attention/concentration was rated lower and delayed recall was rated higher in ES than in AD-aMCI, although general memory was comparable in the two groups. In WAIS-R, digit symbol substitution, similarity, picture completion, and block design scores were significantly lower in ES than in AD-aMCI, but the information scores were comparable between the two groups. Delayed recall and

Hiroaki Kazui, MD, PhD

Psychiatry, Department of Integrated Medicine, Division of Internal Medicine  
Osaka University Graduate School of Medicine, D3 2-2 Yamadaoka, Suita-City  
Osaka 565-0871 (Japan)  
Tel. +81 66 879 3051, Fax +81 66 879 3059, E-Mail kazui@psy.med.osaka-u.ac.jp

forgetfulness were less impaired, and attention, working memory and executive function were more impaired in ES than in AD-aMCI. These results should help clinicians to distinguish ES combined with AD-aMCI from ES alone.

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## Introduction

Schizophrenia is a common psychiatric disease with onset usually occurring during adolescence or early adulthood. Recently, new atypical antipsychotic drugs for schizophrenia have been developed, and social systems to support schizophrenia patients have been established. As a result, schizophrenia patients are now living longer than they used to [1], and the number of elderly schizophrenia (ES) patients is increasing. The number of Alzheimer's disease (AD) patients has also increased due to the rapid aging of society. Although the incidence of AD rises with age, AD also occurs in younger patients; the prevalence rate of AD in people aged  $\leq 64$  years is 0.12 cases per 1,000 people (<http://www.mhlw.go.jp/houdou/2009/03/h0319-2.html>; Japanese Ministry of Health, Labor and Welfare). Therefore, there are many ES patients who also have AD, and their number is supposed to be increasing. In clinical settings, there is a growing need to differentiate between age-related and AD-related cognitive impairment in patients who have developed schizophrenia in adolescence or middle age.

Because some clinical characteristics of schizophrenia and AD are similar, differentiation between ES and AD can be difficult. Neuropsychiatric symptoms, such as apathy, poverty of speech, and delusional thinking, are common in both types of patients. Neuroimaging studies have shown volume loss in the hippocampus [2] and in the frontal lobe [3] in schizophrenia, and similar losses have been observed in AD [4]. Furthermore, patients with schizophrenia are impaired in various domains of cognition, such as memory, working memory, and executive function [5]. These symptoms are also observed in patients with AD.

Acetylcholine esterase inhibitors have been developed for the treatment of AD. Although administration of these agents does not result in a radical improvement of symptoms, their early administration can improve the prognosis of AD patients [6]. In addition, disease-modifying drugs for AD are now being developed. Thus, early diagnosis and early initiation of treatment are important in AD patients. One method to identify early AD with a high probability is the measurement of amnesic mild cognitive impairment (aMCI), which is a syndrome characterized by memory performance below the age norm, while intellectual functioning and activities of daily living are otherwise unimpaired [7]. A substantial proportion of patients with aMCI later develop clinically diagnosable AD [7]. In order to treat early-stage ES patients who have AD in the aMCI stage (AD-aMCI) for AD, it is necessary to differentiate between ES combined with AD, and ES alone. As a first step toward this goal, in this study, we clarified the degree of cognitive impairment in patients with ES compared to patients with AD-aMCI.

## Methods

### *Subjects*

All patients in this study were recruited from the Department of Neuropsychiatry of the Osaka University Medical Hospital, which includes Schizophrenia and Neuropsychological Clinics. At both clinics, patients underwent standard neuropsychological examinations as well as routine laboratory tests and cranial magnetic resonance imaging (MRI). Single pho-

**Table 1.** Comparison of characteristics of the ES and AD-aMCI groups with and without WAIS-R

Characteristics	ES group		p value	AD-aMCI group		p value
	with WAIS-R	without WAIS-R		with WAIS-R	without WAIS-R	
Sex, male/female	5/9	10/6	0.14	7/6	7/5	0.57
Age, years	56.6 ± 5.5	57.1 ± 5.7	0.79	72.6 ± 6.0	70.2 ± 9.5	0.44
Education, years	13.1 ± 2.6	13.3 ± 2.2	0.79	13.7 ± 3.3	13.4 ± 1.8	0.8
MMSE total score	–	–	–	26.1 ± 1.9	27.0 ± 2.1	0.27
WMS-R GM index	81.3 ± 15.5	79.1 ± 17.0	0.75	80.5 ± 13.1	74.9 ± 6.1	0.19
WMS-R AC index	84.8 ± 10.3	94.8 ± 16.0	0.09	99.8 ± 11.1	97.3 ± 12.7	0.59
WMS-R DR index	75.9 ± 15.9	76.6 ± 18.4	0.92	61.5 ± 9.7	55.8 ± 6.5	0.1

ton emission computed tomography (SPECT) was performed on patients with aMCI at the Neuropsychological Clinic. The clinical and investigative data were collected in a standardized manner and were entered into each registry. In this study, we selected patients with ES and patients with AD-aMCI who met the inclusion criteria mentioned below for each group from the registry. In the Schizophrenia Clinic, we began using the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in March 2004 and then switched to the third version of the WAIS (WAIS-III) in October 2006. In the Neuropsychological Clinic, we began using five subtests of the WAIS-R in September 2002 and switched to five subtests of the WAIS-III in February 2009. In this study, we selected patients who were evaluated with the WAIS-R, because few patients with AD-aMCI were evaluated with the WAIS-III and then followed up until they reached the dementia stage. The revised version of the Wechsler Memory Scale (WMS-R) has been used in both clinics as a memory test because the third version of the WMS (WMS-III) is not standardized and cannot be used in Japan. In both clinics, the WMS-R was usually used before the WAIS-R. However, in some cases, there was no opportunity to use the WAIS-R.

#### ES Group

Thirty patients with schizophrenia (15 women and 15 men) were selected from the Schizophrenia Clinic registry. The mean age of the patients was  $56.9 \pm 5.5$  years, and the mean years of education were  $13.2 \pm 2.3$ . All subjects in the ES group (1) met the criteria for schizophrenia based on the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR); (2) were aged  $\geq 50$  years [8]; (3) showed first symptoms of schizophrenia before 65 years of age; (4) had been evaluated by either the WMS-R or the WAIS-R; (5) had no other neurological disease, and (6) had no evidence of focal brain lesions on MRI. Of the 30 patients, 14 were given the WAIS-R (group with WAIS-R) and the other 16 were not given the WAIS-R (group without WAIS-R). There were no significant differences in gender, age, education, or WMS-R indices between the ES groups with and without WAIS-R (table 1). Other demographic data on the ES group are summarized in table 2. Mean duration of hospitalization was short, although mean duration of disease was long. Many patients received atypical antipsychotic drugs at the time of neuropsychological assessment in this study. There were no significant differences between the groups with and without WAIS-R in any of the items except for the positive/negative symptom scores of the Positive and Negative Syndrome Scale (PANSS). Both PANSS scores were higher in the group without WAIS-R than in the group with WAIS-R. Four of the 30 patients with ES were not given the WMS-R.

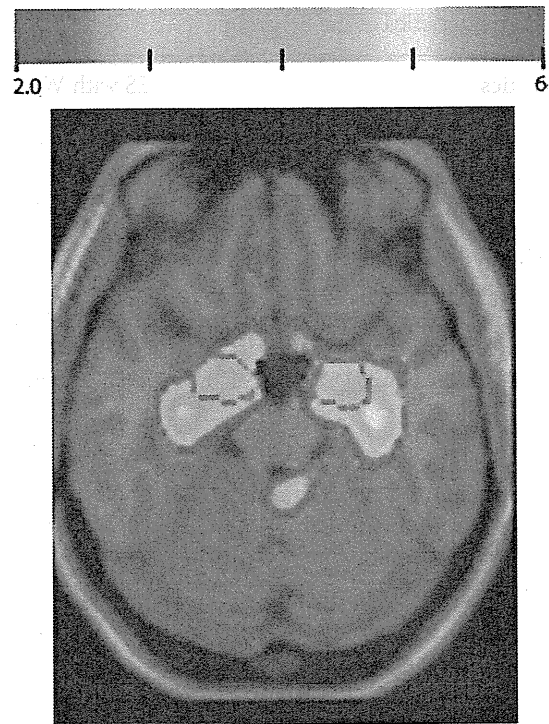
**Table 2.** Characteristics of the ES group

Characteristics	ES with WAIS-R mean ± SD	ES without WAIS-R mean ± SD	p value	Total mean ± SD (range)
Age of disease onset, years	32.3 ± 12.0	30.1 ± 12.3	0.64	31.1 ± 12.0 (19.0–61.0)
Duration of untreated psychosis, years	3.6 ± 6.5	4.1 ± 8.4	0.87	3.9 ± 7.5 (0–26)
Duration of disease, years	23.8 ± 11.7	27.4 ± 10.7	0.41	25.8 ± 11.1 (1–45)
Total duration of hospitalization, months	14.0 ± 12.2	9.7 ± 19.6	0.56	11.4 ± 16.8 (0–72)
Daily dose of antipsychotic drugs (chlorpromazine equivalent), mg	554.7 ± 283.6	469.1 ± 387.6	0.5	509.0 ± 340.0 (0.0–1,300.0)
Daily dose of atypical antipsychotic drugs (chlorpromazine equivalent), mg	485.7 ± 306.6	318.8 ± 379.9	0.2	396.7 ± 352.0 (0.0–1,300.0)
PANSS score				
Positive symptoms	12.3 ± 4.6	16.3 ± 4.4	0.03	14.5 ± 4.8 (5–28)
Negative symptoms	12.3 ± 3.2	18.3 ± 6.5	0.01	15.5 ± 6.0 (7–30)
Overall severity in the Drug-Induced Extra- Pyramidal Symptoms Scale (n = 21)	0.90 ± 1.9	0.86 ± 0.7	0.94	0.88 ± 1.3 (0–6)

#### AD-aMCI Group

Twenty-five AD-aMCI patients were selected from the Neuropsychological Clinic registry. The number of males exceeded the number of females (14 males and 11 females). The mean age of the patients was  $71.4 \pm 7.8$  years, the mean years of education were  $13.6 \pm 2.6$ , and the mean MMSE score was  $26.5 \pm 2.0$ . All subjects in the AD-aMCI group met the criteria for aMCI, which included (1) a memory complaint documented by the patient or another source; (2) a score in the story A recall task in the logical memory II subtest of WMS-R which is less than the age-corrected and education-corrected cutoff score; (3) a score of  $\geq 24$  on the MMSE; (4) a total Clinical Dementia Rating (CDR) score of 0.5 and a memory CDR score  $>0$ ; (5) normal basic and instrumental activities of daily living evaluated with Lawton's Physical Self-Maintenance Scale and Instrumental Activities of Daily Living Scale [9], and (6) no symptoms of dementia based on a clinical examination and an extensive interview with a knowledgeable informant. All subjects in this group also (7) had been evaluated by either the WMS-R or the short form of the Japanese version of the WAIS-R, (8) had no other neurological disease, and (9) had no evidence of focal brain lesions on MRI. To confirm that the aMCI patients had AD in the preclinical stage, at least one of the following three criteria had to be fulfilled: (1) atrophy in the entorhinal cortex on MRI, (2) hypoperfusion in the posterior cingulate cortex (PCC) and precuneus on SPECT, or (3) progression to AD during annual follow-ups. Progression to AD was defined as meeting the criteria of the National Institute of Neurological Disease and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD and a total CDR score of  $\geq 1.0$ .

Progression to AD from aMCI during the subsequent follow-ups (up to 8 years) was confirmed in 17 of the 25 patients. Nineteen of the 25 AD-aMCI patients received three-dimensional spoiled gradient echo MRI, which identified atrophy in the entorhinal cortex in 13 of the 19 patients. Twenty-three of the 25 AD-aMCI patients received N-isopropyl-p-[ $^{123}\text{I}$ ]-iodoamphetamine ( $^{123}\text{I}$ -IMP)-SPECT, and hypoperfusion in either the PCC or precuneus was identified in 12 of the 23 AD-aMCI patients. One patient was recruited due to abnormality on the MRI and 7 patients were recruited due to abnormality on SPECT. Of the 25 patients, 13 were given the five subtests of the WAIS-R (group with WAIS-R) but the other 12 were not (group without WAIS-R). There were no significant differences in gender, age, education,



**Fig. 1.** Z-score map overlaid on an MRI template of a representative patient with AD-aMCI made with VSRAD. This patient was included in the study because of the presence of significant atrophy in the entorhinal cortices on MRI. Parts of the colored areas are in the areas circumscribed by purple lines, indicating significant atrophy in the entorhinal cortices. Purple lines indicate the bilateral entorhinal cortices. Colored areas on MRI are those with a Z-score  $>2$  (significant atrophy). Color bar indicates Z-score.

MMSE score or WMS-R indices between the two groups with and without WAIS-R (table 1). All AD-aMCI patients were administered the WMS-R.

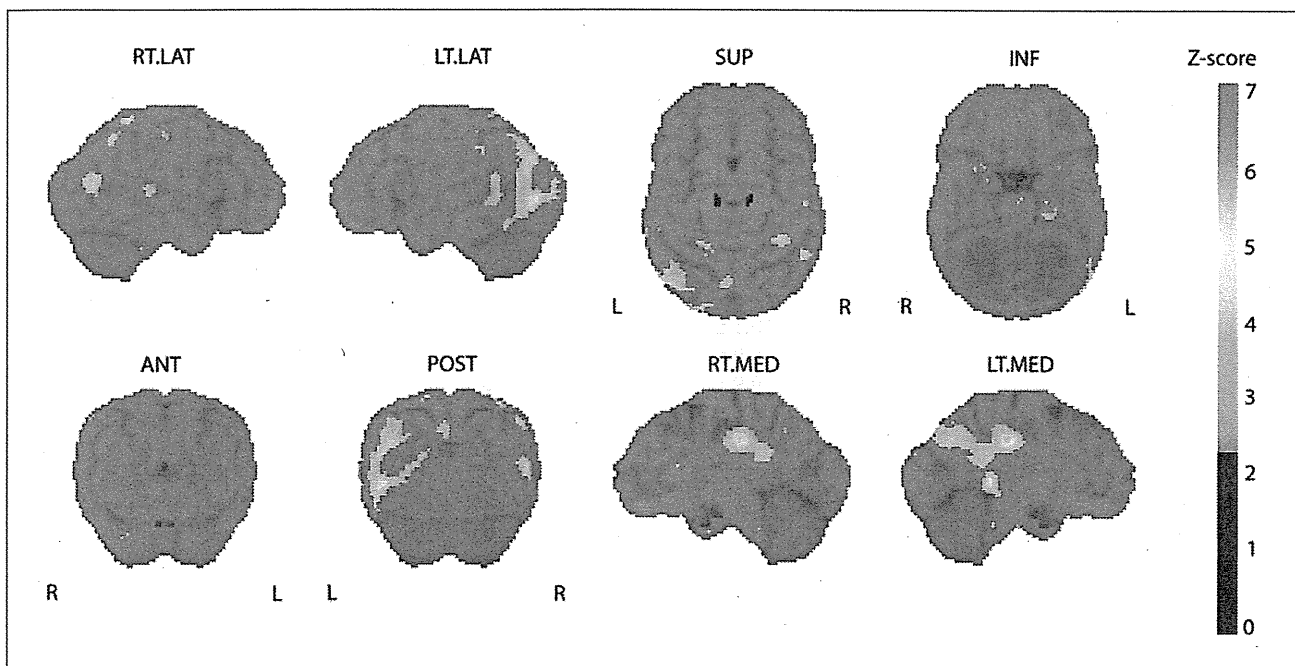
#### *Comparison of Demographic Data in the ES and the AD-aMCI Groups*

There was no significant difference between the ES and the AD-aMCI groups in terms of sex ( $p = 0.48$ ,  $\chi^2$  test) or education ( $p = 0.71$ , t test). However, the ES group was significantly younger than the AD-aMCI group ( $p < 0.001$ , t test).

#### *MRI and SPECT Criteria for the AD-aMCI Group*

MRI was performed on a 1.5-tesla system (Signa Excite HD 12x; General Electric Medical Systems, Milwaukee, Wisc., USA). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections that covered the whole calvarium. The operating parameters were as follows: field of view = 240 mm, matrix =  $256 \times 256$ ,  $124 \times 1.40$  mm contiguous sections, TR = 12.55 ms, TE = 4.20 ms, and flip angle =  $15^\circ$ . The three-dimensional T1-weighted MRI data of the patients were analyzed with the voxel-based specific region analysis for AD (VSRAD) [10] (fig. 1). VSRAD contained the MRI data of normal control subjects with a wide age range and could automatically compare the gray matter intensities of the MRI data on a voxel-by-voxel basis between an aMCI patient and age-comparable normal control subjects after a series of steps including segmentation, anatomical standardization and smoothing using Statistical Parametric Mapping 2002 (SPM2; Wellcome Department of Imaging Neuroscience, London, UK). The Z-score is calculated on a voxel-by-voxel basis as  $(I_s - I_c)/SD$  where  $I_s$  and  $I_c$  are the gray matter intensities of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the gray matter intensities of the normal control subjects. The region of interest was set to the entorhinal cortex in the VSRAD software. Atrophy corresponding to a Z-score  $>2.0$  in the entorhinal cortex was used as a criterion for AD in the VSRAD method.





**Fig. 2.** Z-score map of a representative patient with AD-aMCI made with 3D-SSP. This patient was included in the study because of the presence of hypoperfusion in the PCC and precuneus on SPECT. Colored areas contain PCC and precuneus. Colored areas with significant rCBF reduction with a Z-score of  $>2.32$  were overlaid on original surface images from eight views. Color bar indicates Z-score. RT.LAT = Right lateral; LT.LAT = left lateral; SUP = superior; INF = inferior; ANT = anterior; POST = posterior; RT.MED = right medial; LT.MED = left medial.

$^{123}\text{I}$ -IMP-SPECT was performed with a SPECT scanner (SPECT-2000H; Hitachi Medical Co., Tokyo, Japan) and a four-head rotating gamma camera. SPECT data were analyzed using three-dimensional stereotactic surface projection (3D-SSP) software [11] (fig. 2). 3D-SSP contained  $^{123}\text{I}$ -IMP-SPECT data of normal control subjects with a wide age range and could automatically compare the regional cerebral blood flow (rCBF) between an aMCI patient and age-comparable normal control subjects. The peak cortical values of the SPECT data were projected back and assigned to the original surface images from eight views on a pixel-by-pixel basis. Z-score was calculated on a pixel-by-pixel basis as  $(I_s - I_c)/SD$  where  $I_s$  and  $I_c$  are the rCBFs of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the rCBF of the normal control subjects. Areas with a Z-score  $>2.32$  (the significance level of the Z-score) were overlaid on original surface images from eight views. With the computer program Stereotactic Extraction Estimation (SEE) we determined which gyri included the regions with a Z-score  $>2.32$  [12]. In SEE, the percentage of areas with a Z-score  $>2.32$  in each gyrus was calculated and the percentage was called the 'extent'. The presence of areas of hypoperfusion, in which both the Z-score was  $>2.32$  and the extent was  $>10\%$  [13] in either the PCC or precuneus, was used as the inclusion criteria for AD in the aMCI stage.

#### Assessment of Cognitive Functions

The attention/concentration (AC) index in the WMS-R was used for measuring attention and working memory, the general memory (GM) index was used for recent memory, and the delayed recall (DR) index for delayed memory. For each index, the normal range is

**Table 3.** Cognitive impairment in ES and AD-aMCI patients

Test/subtest	ES group	AD-aMCI group	p value
<i>WMS-R</i>			
GM index	80.0 ± 16.2	77.8 ± 10.5	0.58
AC index	91.0 ± 14.7	98.6 ± 11.7	0.046
DR index	76.3 ± 17.2	58.8 ± 8.6	<0.001
GM-DR	3.6 ± 10.7	19.9 ± 8.6	<0.001
<i>WAIS-R</i>			
Information	10.1 ± 3.7	11.2 ± 2.8	0.37
Digit symbol substitution	8.0 ± 2.7	11.6 ± 2.3	<0.001
Similarity	9.9 ± 3.2	12.5 ± 2.2	0.024
Picture completion	8.5 ± 4.0	11.2 ± 1.8	0.037
Block design	8.4 ± 2.7	11.5 ± 1.9	0.0018

between 80 and 120 and the mean index of normal subjects is 100. We also defined a new index equal to the GM index minus the DR index (GM-DR), which is a measure of the degree of forgetfulness.

For the WAIS-R, five test data were used in this study. Four of the five subtests were information, digit symbol substitution, similarities, and picture completion, which were selected according to the manual of the short form of the Japanese version of the WAIS-R [14]. Another was a block design to evaluate visuoconstructive function directly, as this dysfunction is a common symptom in AD patients. In each age-corrected score of the subtest, the normal range is between 7 and 13 and the mean score of normal subjects is 10.

#### *Statistical Analyses*

Age-corrected scores of both the WMS-R and the five subtests of the WAIS-R were compared between the two groups using a t test. The significance level was set at  $p < 0.05$ .

## **Results**

### *Results of the WMS-R*

In this study, the mean GM indices in the two groups were around the lower limit of the normal range, and the mean AC indices in ES and AD-aMCI were normal (table 3). The mean DR index of ES was slightly below the normal range, but the mean DR index of AD-aMCI appeared to be significantly lower. The GM indices of the two groups were comparable. The AC index was significantly lower and the DR index was significantly higher in ES than in AD-aMCI. The difference in the GM and DR scores (GM-DR), which is a measure of the degree of forgetfulness, was significantly lower in ES than in AD-aMCI.

### *Results of the Five Subtests of the WAIS-R*

The mean scores of all the subtests of the WAIS-R in this study in both groups were within the normal range (table 3). The information scores of the two groups were comparable, but scores of the digit symbol substitution, similarity, picture completion, and block design subtests were significantly lower in ES than in AD-aMCI.

## Discussion

We could not confirm that all AD-aMCI patients in this study developed AD to the dementia stage. However, we were able to select aMCI patients that had AD-specific findings on MRI or SPECT in this study. Pathological abnormalities related to AD, neurofibrillary tangles and neuronal loss, were found to be present in the entorhinal cortex of AD in aMCI stage [15], leading to atrophy in the region on MRI [16]. Because the entorhinal cortex is functionally connected to the PCC [17], the reduction of rCBF in the PCC was probably caused by the abnormal pathology in the entorhinal cortex. In addition, atrophy in the entorhinal cortex on MRI [18] and reduction of rCBF in the PCC and precuneus on SPECT [19] predict progression from MCI to AD. We used two reliable and user-independent statistical image-analyzing methods, VSRAD and 3D-SSP, to detect AD-specific abnormalities in the MR and SPECT images.

This is the first report to compare cognitive impairment between ES and AD-aMCI. The WMS-R GM indices of the two groups were comparable, indicating a similarity in the impairment of recent memory between the two groups. Some previous studies compared recent memory in ES and AD at the dementia stage. There is some disagreement on whether recent memory is better [20] or worse [21] in ES than in AD in the dementia stage. aMCI is a relatively homogeneous group with respect to memory impairment, because the definition of aMCI includes the degree of memory impairment. However, the severity of recent memory impairment could vary in patients with ES. The ES patients in this study were mild cases, because they could complete the WMS-R or WAIS-R, which are comprehensive tests, and the mean duration of their hospitalization was short. Thus, the recent memory tests in this study indicated that the recent memory scores of ES patients with mild cognitive impairment were comparable with those of AD-aMCI patients, and, therefore, that recent memory was not useful for distinguishing between ES and AD-aMCI.

The fact that the WMS-R GM indices were comparable in the ES and AD-aMCI groups indicates that the two groups in this study had similar degrees of impairment of recent memory. This narrows down the difference between the two groups to differences in other cognitive impairments, such as forgetfulness, and impairments of DR, attention, working memory and executive function. The WMS-R GM-DR scores were lower and the DR scores were higher in ES than in AD-aMCI, indicating that the degree of forgetfulness was less and DR was better in ES. On the other hand, the AC was lower in ES than in AD-aMCI, indicating that ES patients had more impaired attention and working memory than AD-aMCI patients. DR was found to be better in ES patients than in AD patients in the dementia stage [21], and forgetfulness did not increase in ES patients but increased in AD patients in the dementia stage [20]. The present study confirmed that memory after a short while was retained in ES but not in AD. In addition, we found that the retention in ES patients was better than in AD even at the aMCI stage, which should help to distinguish ES from AD in the very early stage.

The hippocampus, parahippocampus, and entorhinal cortex have traditionally been thought of as the principal structures responsible for the consolidation of short-term stores into long-term memory. Significant associations between hippocampal size and memory have not been observed in schizophrenia [22], although size reductions in the hippocampus have been reported in schizophrenia [2]. In addition, memory capabilities were similar to general intellectual abilities in ES [23]. Therefore, damage in the medial temporal lobe may not play an important role in memory impairment in schizophrenia. On the other hand, memory impairment in AD is inversely associated with hippocampal volume [24].

The ES group was more impaired on the digit symbol substitution, similarities, picture completion, and block design subtests of WAIS-R than the AD-aMCI group, and each subtest score in the ES group was below the mean of each score of the general population in this study. Although the block design subtest was used to evaluate visuoconstructive function in

this study, attention and executive function are required to perform the block design subtest [25]. Thus, these findings confirmed that attention, working memory, and executive function are impaired in ES. Previous studies reported that ES patients were impaired in the WAIS-R digit symbol substitution, similarities, picture completion, and block design subtests [21], and in attention, working memory, and executive function [20]. These studies also reported that impairment in these functions were comparable in ES and AD patients in the dementia stage. The differences in cognitive impairment that we found in ES and AD-aMCI deviate from those found in previous studies. This discrepancy may be due to differences in the severity of cognitive impairments in the AD-aMCI patients in this study compared to the AD patients in the dementia stage in previous studies.

Which region of the brain is responsible for the difference in attention, working memory, and executive function in the two groups? Impairments in cognitive function in patients with schizophrenia were found to be related to dysfunction of the prefrontal cortex (PFC) [26]. On the other hand, gray matter loss on MRI [27] and pathological abnormality [28] in the PFC were not observed in AD-aMCI, and gray matter loss on MRI was observed at the time of progression from aMCI to AD [27]. These results suggest that differences in impairment in attention, working memory, and executive function in the two groups probably reflect the difference in impairment in the PFC.

The WAIS-R information scores of the ES and AD-aMCI groups were comparable and within the normal range, being consistent with those of a previous study [29]. Semantic memory may be preserved in ES and AD-aMCI patients because they have less impairment in the inferior and anterior temporal lobe regions, which crucially contribute to semantic cognition [30].

There were some limitations in this study. First, approximately half of the patients in each group were not given the WAIS-R. Second, the ES patients in this study were younger than the AD-aMCI patients, and cognitive function in schizophrenia patients undergoes a marked decline after 65 years of age [8]. Third, we did not control the effects of medication on the cognitive test scores in ES patients. Most ES subjects in this study had received atypical antipsychotic drugs, which might improve cognitive function [31]. These issues should be taken into consideration before the findings are generalized.

In this study, DR and forgetfulness were less impaired in ES than in AD-aMCI, while attention, working memory, and executive function were more impaired in ES than in AD-aMCI. The results of this study should help clinicians to distinguish patients with ES from patients with AD-aMCI and might also give us some clues for distinguishing ES combined with AD-aMCI from ES alone. The next step is to clarify the difference in the characteristics of cognitive impairment in ES combined with AD-aMCI compared to ES alone.

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### Disclosure Statement

The authors declare that they have no conflict of interest.

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