Methods

Kana pick-out test

In the KPT, the subjects are shown a short story written in Japanese kana characters. The original paper version on which a short story is written in Japanese kana characters was described previously (Inoue *et al.*, 2003). The subjects are required to find as many vowel symbols as possible within two minutes, while understanding the meaning of the story (Kaneko, 1996; Nakatsuka *et al.*, 2003). While reading the story, the subjects circle the vowel symbols with a pencil. If the subjects concentrate only on reading the story, they tend to become careless in finding the symbols. Inversely, if they concentrate on finding the symbols, they tend to forget the substance of the story. Thus, this test assigns two simultaneous tasks: find the vowel symbols and recognize the content of the story (Inoue *et al.*, 2003). The Japanese kana character set consists of 66 phonetic symbols that include five vowels; the story consists of 406 symbols with 61 vowels, so the full score for this test is 61. The lower normal limits of KPT scores are 11 for those in their seventies, 10 for those in their eighties, and 9 for those in their nineties (Kaneko, 1996). In this study, the subjects with low scores on the KPT did not reach the lower limits of normal, and the subjects with high scores on the KPT were required to score higher more than the mean score for their ages (20 for those in their 60s, 18 for those in their 70s, and 16 for those in their 80s) (Kaneko, 1996).

In this study, KPT memory score was also recorded. Two questions to examine whether the subjects remembered the substance of the story were asked, and the memory score was determined according to the following criteria: 10 for two correct answers, 5 for one correct answer (full score was 10).

Subjects

Twenty AD patients with a dementia severity of 0.5 (possible) or 1 (mild) based on the Clinical Dementia Rating (CDR) (Hughes, *et al.*, 1982), whose score on the KPT did not reach the lower limits of normal, were selected from 227 consecutive Japanese patients who were fully examined at the Memory Clinic of Okayama University Hospital, between April 2004 and March 2008. Thereafter, 20 AD patients with high scores on the KPT, matched for age, sex ratio, education, and scores on the Addenbrooke's Cognitive Examination (ACE) (Mathuranath *et al.*, 2000; Yoshida *et al.*, 2010), were also selected.

The inclusion criteria for all participants were: (i) they underwent general physical and neurological examinations and extensive laboratory testing, including thyroid function tests, serum vitamin B12, and syphilis serology; (ii) they took the KPT, Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) and ACE; (iii) underwent brain SPECT as well as head CT and/or head MRI; (iv) they were diagnosed with probable AD according to the NINCDS-ADRDA criteria (McKhann *et al.*, 1984); (v) they had a dementia severity of 0.5 or 1 based on the CDR (Hughes, *et al.*, 1982); and (vi) they or their nearest relatives gave informed written consent. The exclusion criteria were (i) complications from other neurological diseases or illnesses; (ii) history of mental illness or substance abuse prior to the onset of dementia; (iii) any evidence of focal brain lesions on head MRI; (iv) treatment with cholinesterase inhibitors, antipsychotics, antidepressants or anxiolytic drugs; and (v) left-handedness or ambidexterity. The profile of each participant (age, sex, years of education, and disease duration) was recorded, and the CDR score was rated by the chief clinician.

Other instruments

Addenbrooke's Cognitive Examination (ACE) was developed to provide a brief test sensitive to early stage dementia, and is capable of differentiating between dementia subtypes including AD, fronto-temporal dementia, progressive supranuclear palsy and other parkinsonian syndromes (Mathuranath *et al.*, 2000). ACE includes the MMSE but extends it to encompass important areas not covered by the MMSE, such as frontal-executive function and visuospatial skills. ACE has a comparable sensitivity to the Dementia Rating Scale (Bak *et al.*, 2005), a well-established dementia screening tool, widely used in research but not in clinical practice because of its length and difficulty of administration. For this study, we used the Japanese version of ACE described by Yoshida *et al.* (2010). The reliability of the Japanese version of ACE is excellent, and its validity is, to some extent, established (Yoshida *et al.*, 2010).

The Physical Self-Maintenance Scale (PSMS) and the Instrumental Activities of Daily Living scale (IADL) are validated scales for the assessment of activities of daily living (ADL) (Lawton and Brody, 1969; Hokoishi *et al.*, 2001). The PSMS is a six-item scale that rates self-care ability in toileting, feeding, dressing, personal hygiene and grooming, locomotion (physical ambulation), and bathing. The IADL scale assesses patients' ability to perform eight complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundering, mode of transportation, responsibility for medications, and ability to manage finances.

The Neuropsychiatric Inventory (NPI) is a valid and reliable instrument for measuring behavior in dementia (Cummings *et al.*, 1994; Hirono *et al.*, 1997). It is a caregiver-based tool that assesses ten common behaviors in dementia.

Ethics

This study adhered to the 1975 Helsinki Declaration of Human Rights and the study protocol was approved by the Committee of Okayama University Hospital on Human Research. After providing a complete description of the study to the subjects and their relatives, written informed consent was obtained.

Brain perfusion SPECT imaging

All subjects were examined by brain perfusion SPECT. Patients were examined in a comfortable supine position with their eyes closed in quiet surroundings. First, the passage from the heart to the brain was monitored after intravenous administration of 99mTc-ethylcysteinate dimer (ECD, 600 MBq, Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan). Ten minutes after the angiography, SPECT images were obtained using a triple-head, rotating gamma camera interfaced to a minicomputer (GCA9300A/ DI; Toshiba, Tokyo, Japan) equipped with a fanbeam, low-energy, high-resolution collimator. Sixty projection images over a 360° angle in a 128 × 128 matrix were acquired. All images were reconstructed using ramp-filtered back-projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.12 cycles/cm). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

Data analysis

Spatial reprocessing and statistical analysis of images was performed on a voxel-by-voxel basis using Statistical Parametric Mapping 2 (SPM2, Wellcome Department of Imaging Neuroscience, U.K.) running on MATLAB (The Mathworks, Inc). All SPECT images of each subject were normalized to the standard brain of the Montreal Neurological Institute (MNI), and the spatial normalization was performed with 12-parameter affine and non-linear transformations (Friston *et al.*, 1995a; 1995b). The voxel sizes of the reslice option were (2 mm, 2 mm, 2 mm). The non-linear parameter was set at 25 mm cut-off basis functions and 16 iterations. All of the normalized SPECT images were then smoothed with an isotropic gaussian kernel filter (12-mm full-width at half-maximum). To examine the images for specific regions showing differences in perfusion, two sample *t*-tests were performed. Global normalization was performed by proportional scaling with the mean voxel value. Masking was applied using the threshold method (0.8 times the global value). The statistical height threshold was set at $P < 0.005$ uncorrected, and the extent threshold was set at $P < 0.01$ with correction for multiple non-independent comparisons.

Statistical analysis

Statistical analysis was performed using the SPSS 14.0J software program (SPSS Inc., Chicago, IL). Comparisons between the two groups were performed by independent sample *t*-tests. A value of $p < 0.05$ was accepted as significant.

Results

Age, years of education, duration of illness, neuropsychological test scores and ADL

No significant differences were found between high- and low-score groups with respect to age, years of education, or duration of disease by Student's *t*-test (Table 1). With the exception of KPT scores, no significant differences were found between high- and low-score groups with respect to ACE scores, MMSE scores, KPT memory scores or NPI subscale scores (Tables 1 and 2).

Comparison on ADL scales revealed that AD patients with a low KPT score got lower scores than those with a high KPT score, in the total scores of PSMS and the subscale scores of dressing, physical ambulation, shopping and responsibility for own medications among PSMS and IADL (Table 2).

rCBF

A group comparison of the SPM results between the high- and low-score groups were performed. Specific voxels with a significantly lower perfusion in the low-score group than in the high-score group are shown in Figure 1 and Table 3. A similar test for specific voxels with a significantly lower perfusion in the high-score group than in the low-score group found no cluster of voxels.

Figure 1 shows the z-score for each voxel in this cluster superimposed onto a three-way-glass brain view. It shows a significant cluster of voxels in the left subgenual cingulate gyrus (SGC), extending to right SGC. Table 3 shows the probability results of the SPM analysis and the location of peak z scores in terms of the MNI coordinates.

Discussion

Kana Pick-out Test score and rCBF

The KPT is a popular test of attention in Japan. This task requires parallel processing of

Table 1. Clinical characteristics and neuropsychological tests

GROUP	LOW SCORE	HIGH SCORE	T	P
Total (n)	20	20		
Sex (n) (male/female)	7/13	7/13		
Age (mean years ± S.D.)	74.2 ± 6.1	74.3 ± 6.5	0.075	0.940
Education (mean years ± S.D.)	11.1 ± 2.7	11.0 ± 2.7	−0.059	0.953
Duration of disease (mean years ± S.D.)	2.8 ± 2.5	2.6 ± 2.0	0.284	0.778
ACE score (mean ± S.D.)	62.5 ± 7.6	63.5 ± 8.6	0.409	0.685
MMSE score (mean ± S.D.)	22.1 ± 1.8	21.6 ± 2.3	−0.851	0.400
KPT score (mean ± S.D.)	4.8 ± 2.7	25.2 ± 6.1	13.657	0.000
KPT memory score (mean ± S.D.)	2.8 ± 3.0	4.0 ± 3.8	−1.144	0.260

Low score = Alzheimer's diseasae patients with low score on Kana Pick-out Test.
High score = Alzheimer's diseasae patients with high score on Kana Pick-out Test.
ACE = Addenbrook's cognitive examination; MMSE = Mini-mental State Examination.
KPT = Kana Pick-out Test; S.D. = Standard Deviation.

Table 2. Activities of daily living (ADL) and instrumental ADL

GROUP	LOW SCORE	HIGH SCORE	T	P
Neuropsychiatric Inventory (mean ± S.D.)				
Delusion	1.4 ± 3.4	2.1 ± 3.6	0.630	0.532
Hallucination	0.8 ± 2.7	0.3 ± 0.9	−0.787	0.436
Agitation/Aggression	1.2 ± 2.3	2.0 ± 3.2	0.910	0.368
Depression	1.3 ± 3.1	1.7 ± 3.0	0.362	0.719
Anxiety	1.3 ± 1.9	2.2 ± 3.3	1.065	0.294
Euphoria	0.4 ± 1.2	0.5 ± 1.2	0.128	0.899
Apathy	4.9 ± 4.4	2.9 ± 3.5	−1.618	0.114
Disinhibition	1.3 ± 3.2	1.9 ± 3.1	0.649	0.520
Irritability	0.9 ± 2.2	2.0 ± 3.1	1.291	0.204
Aberrant motor behavior	0.6 ± 2.0	0.0 ± 0.0	−1.371	0.178
PSMS (mean ± S.D.)	4.6 ± 1.3	5.7 ± 0.7	3.183	0.003
Toilet	0.9 ± 0.4	1.0 ± 0.0	1.831	0.075
Feeding	1.0 ± 0.0	1.0 ± 0.0	0.000	1.000
Dressing	0.8 ± 0.4	1.0 ± 0.0	2.179	0.036
Grooming	0.7 ± 0.5	0.9 ± 0.3	1.934	0.061
Physical ambulation	0.4 ± 0.5	0.8 ± 0.4	2.757	0.009
Bathing	0.9 ± 0.3	1.0 ± 0.2	0.588	0.560
IADL (mean ± S.D.)	4.7 ± 2.2	5.8 ± 1.7	1.857	0.071
Ablity to use telephone	0.9 ± 0.3	1.0 ± 0.0	1.453	0.154
Shopping	0.4 ± 0.5	0.7 ± 0.5	2.307	0.027
Food preparation	0.4 ± 0.5	0.4 ± 0.5	0.000	1.000
Housekeeping	0.9 ± 0.4	1.0 ± 0.0	1.477	0.153
Laundry	0.8 ± 0.4	1.0 ± 0.0	1.897	0.070
Mode of transportation	1.0 ± 0.0	1.0 ± 0.0	0.000	0.216
Responsibility for own medications	0.4 ± 0.5	0.6 ± 0.5	1.258	0.038
Ability to handle finances	0.7 ± 0.5	1.0 ± 0.2	2.147	0.071

Low score = Alzheimer's disease patients with low score on Kana Pick-out Test.
High score = Alzheimer's disease patients with high score on Kana Pick-out Test.
PSMS = Physical Self-Maintenance Scale; IADL = Instrumental Activities of Daily Living scale.
S.D. = Standard Deviation.

reading and picking out letters, and demands an appropriate allocation of attentional resources to the two activities. Therefore, the KPT is thought to be a suitable test of working memory and executive function (Tamura *et al.*, 2003), and to reflect prefrontal area function (Tachibana *et al.*, 2007).

There have been only a few studies of the relationship between results of the KPT and rCBF (Nakatsuka *et al.*, 2003; Tachibana *et al.*, 2007). At a memory clinic, the mean rCBF among four outpatients whose MMSE score was normal but whose KPT scores were abnormal was reported to be decreased in the posterior cingulate gyrus

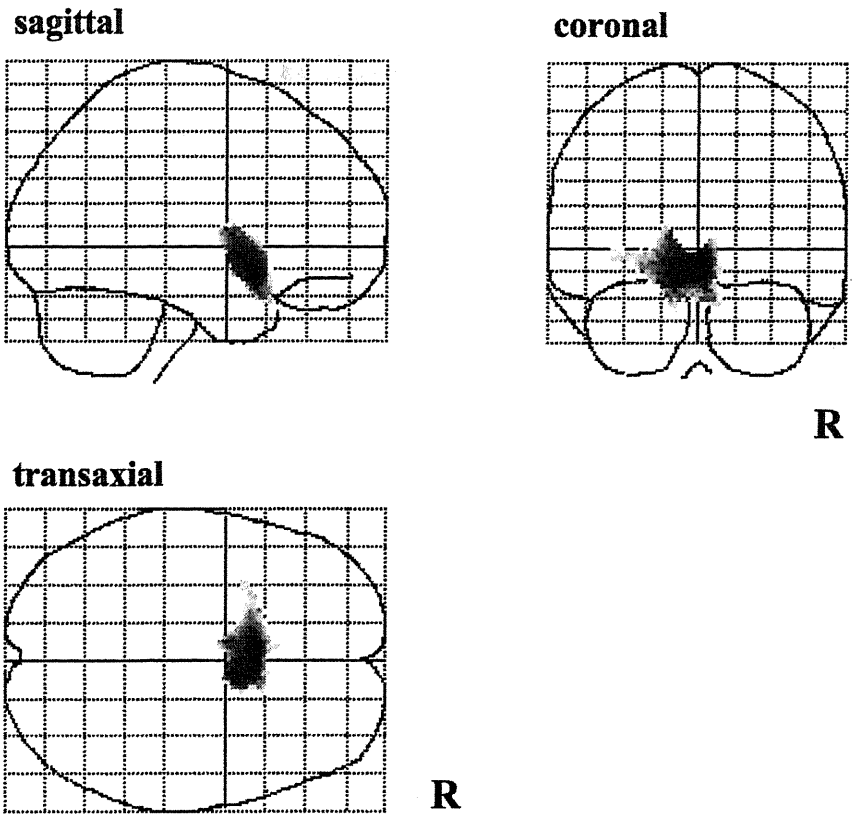

Figure 1. SPM (z) map of rCBF decrease in AD patients with low scores on the Kana Pick-out Test compared with AD patients with high scores. Three-way-glass view of the area of significant hypoperfusion.

Table 3. Significant regional uptake differences between AD patients with low and high scores on Kana Pick-out Test (KPT)

DIRECTION OF DIFFERENCE	NUMBER OF VOXELS	PEAK Z SCORES	COORDINATES (MNI) X	Y	Z
Decrease uptake in AD patients with low scores on KPT	1199	3.58	−8	16	−12
		3.49	4	14	−10
		3.15	−14	14	−6

AD = Alzheimer's disease; MNI = Montreal Neurological Institute.

and cinguloparietal transitional area, compared to the mean rCBF among four cases in which both the MMSE and the KPT scores were normal (Nakatsuka *et al.*, 2003). A functional MRI (fMRI) study of the four cases showed significant increases in blood oxygenation level-dependent signals in the prefrontal area, sensorimotor area, parietal association area, and visual cortex during performance of the computerized KPT (Tachibana *et al.*, 2007). Inconsistent with these two previous findings, we found rCBF in the bilateral SGC was decreased in AD patients with low scores on the KPT compared with AD patients with high scores.

The results of the three reports, including our own, were different from each other. What caused the differences? There are two major differences among the three studies. The first is a difference in the diseases. All subjects in the study by Tachibana *et al.* (2007) were cognitively normal subjects, whereas subjects in the other two studies were memory clinic outpatients. All eight cases in the study by Nakatsuka *et al.* (2003) were patients with subjective complaints of forgetfulness, but all eight cases showed normal MMSE scores. In our study, all 40 subjects were patients with AD, and the mean MMSE scores were 22.1 among patients with low

KPT scores and 21.6 among patients with high KPT scores.

The second was the difference in the methods of evaluating brain function. Tachibana *et al.* (2007) used fMRI, whereas the other two studies used brain SPECT. In the study by Nakatsuka *et al.*(2003), 99mTc-hexamethyl-propyleneamine oxine was injected intravenously, and the z-value, which shows the distance from the mean, was calculated by three-dimensional stereotactic surface projections (3D-SSP). Thus, the exact rCBF was not calculated, and deep brain structures such as the basal ganglia and thalamus were not evaluated. In this study, 99mTc-ECD was used, and rCBF was compared using SPM. The difference of patients and methods among three studies, we suppose, might influence the difference in results.

In addition, the number of participants in the three studies was different. In Nakatsuka's study, four subjects with low KPT scores were compared with another four subjects with normal KPT scores (Nakatsuka *et al.*, 2003). In Tachibana's study, four cases were examined with fMRI (Tachibana *et al.*, 2007). In this study, 20 subjects with low KPT scores were compared with 20 subjects with high KPT scores. The number of the participants in this study was larger than those of previous studies, which we believe is an advantage of this study.

Subgenual cingulate gyrus

The extensive interconnections between the posterior SGC and the nucleus tractus solitarius of the vagus led to this region initially being termed the "visceromotor cortex" (Drevets *et al.*, 2008), and the SGC is thought to be involved in autonomic conditioning functions (Vogt, 2005). At the same time, the SGC has been implicated in the modulation of emotional behavior on the basis of neuroimaging studies in humans (Drevets *et al.*, 2008). The SGC is activated during sad events (Vogt, 2005), and the mean gray matter volume of the SGC is abnormally reduced in subjects with mood disorders, irrespective of mood state (Drevets *et al.*, 2008). Moreover, a preliminary report in six patients suggested that deep brain stimulation of the SGC may provide a benefit in treatment-resistant depression (Lozano *et al.*, 2008).

The SGC is a very important area for mood disorder as stated above. Therefore, it is, of course, possible that a depressive mood affects the results of the KPT, and that a depressive mood among patients with AD causes both the low scores of KPT and hypoperfusion in the subcallosal area. However, in this study, depression scores in NPI did not differ between high- and low-score groups. Therefore, we believe that the relationship between low scores on the KPT and low perfusion in the SGC was not mediated by depressive mood.

The SGC has been implicated in the tracking of reward value (Rolls, 2000; 2004), and disinhibition in frontotemporal dementia showed unique associations with tissue loss in the SGC (Rosen *et al.*, 2005). The SGC possesses significant connections with the orbitofrontal cortex and amygdala (Doyon *et al.*, 1996), with the ventral striatum (Baker *et al.*, 1996), and with other limbic structures (Dupont *et al.*, 1994). Lesion of the SGC was reported to lead to impaired decision-making based on future consequences (Bechara *et al.*, 1994). The alterations of rCBF in the SGC could affect those neuronal networks related to executive functions, and correlate with scores of the KPT in mild AD. Our results suggest that functional activity of the subcallosal area is closely related to the score on the KPT. KPT might be a promising strategy to use for detection of the early stages of AD with low SGC function.

Significant metabolic decrease in specific medial prefrontal areas, namely the SGC and the anterior cingulate cortex, are reported to be initiated early in the course of AD (Fouquet *et al.*, 2009). In support of this contention, the same two medial prefrontal areas showed specific perfusion decrease from the entorhinal to the limbic neuropathologic Braak stages (Braak and Braak, 1991), corresponding to amnestic mild cognitive impairment and early AD, respectively (Bradley *et al.*, 2002).

KPT and ADL

The KPT was developed to evaluate frontal executive function easily and quickly at the bedside (Kaneko, 1996; Inoue *et al.*, 2003). It has been reported that a range of deficits in executive functioning adversely affect the ability of AD patients to perform ADL (Njegovan *et al.*, 2001; Feldman *et al.*, 2001). In this study, AD patients with low scores on the KPT showed lower scores than those with high scores on the KPT in the total score of PSMS and the subscale scores of dressing, physical ambulation, shopping and responsibility for own medications among PSMS and IADL. Our results suggest that performance on the KPT is closely related to several ADL as well as rCBF in the SGC, independently of ACE and MMSE scores.

Limitation of this study

Our study has several limitations. The participants in this study consisted of patients with mild AD who were recruited at a university center. Thus,

our results apply only to a clinic-based mild AD outpatient population. Further study is needed to clarify the neural substrates of the KPT among aged subjects with normal cognitive function or patients with dementias other than AD. Secondly, we compared rCBF between two groups with AD patients and found a difference in the SGC between two groups. It does not mean that the SGC is the only important area for performing the KPT. However, regardless of the above limitations, this is the first report to assess the neural substrates of performance on the KPT among patients with mild AD.

Conflict of interest

None.

Description of authors' roles

Y. Kishimoto was involved in data analysis and wrote the paper. S. Terada designed the study, analyzed the data and wrote the paper with Y. Kishimoto. S. Sato assisted in preparing the statistical design and supervised the statistical analysis. O. Yokota, H. Honda and N. Takeda collected the data. All authors discussed the results and conclusions. Y. Uchitomi supervised the study design, participated in data analysis and assisted with writing the paper.

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Perseverative errors on the Wisconsin Card Sorting Test and brain perfusion imaging in mild Alzheimer's disease

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ABSTRACT

Background: The Wisconsin Card Sorting Test (WCST) has long been used to investigate deficits in executive function in humans. The majority of studies investigating deficient WCST performance focused on the number of categories achieved (CA) and the number of perseverative errors of the Nelson type (PEN). However, there is insufficient evidence that these two measures reflect the same neural deficits.

Methods: Twenty AD patients with high PEN scores, and 20 age- and sex-matched AD patients with low PEN scores were selected. All 40 subjects underwent brain SPECT, and the SPECT images were analyzed by Statistical Parametric Mapping.

Results: No significant differences were found between high and low PEN score groups with respect to years of education, Addenbrooke's Cognitive Examination scores, and Mini-Mental State Examination scores. However, higher z scores for hypoperfusion in the bilateral rectal and orbital gyri were observed in the high PEN score group compared with the low PEN score group.

Conclusions: Our results suggest that functional activity of the bilateral rectal and orbital gyri is closely related to PEN scores on a modified WCST (mWCST). The PEN score on a mWCST might be a promising index of dysfunction of the orbitofrontal area among patients with mild AD.

Key words: Alzheimer's disease (AD), cerebral blood flow (CBF), perseveration, perseverative errors of Nelson type (PEN), Wisconsin card sorting test (WCST)

Introduction

Alzheimer's disease (AD) is the leading cause of late-onset dementia worldwide. Although the first neuropsychological deficit in AD is episodic memory loss (Perry and Hodges, 1999; Perry *et al.*, 2000), the presence of frontal or executive deficits in patients with even mild AD is now widely recognized (Perry *et al.*, 2000). Current evidence suggests that after an initial amnestic stage in AD, attention and executive functions are the first non-memory domains to be affected, before deficits in language and visuospatial functions occur (Perry and Hodges, 1999; Perry *et al.*, 2000). Moreover, perseveration errors are frequently found even in mild AD (Pekkala *et al.*, 2008). However, brain perfusion imaging evidence suggests the relative preservation of the frontal lobes in AD (Johnson *et al.*, 1987). It is, therefore, somewhat surprising that AD produces marked impairment in the attentional and executive functions, which have been linked with frontal lobe function, before deficits in language and visuospatial function occur (Perry and Hodges, 1999).

The Wisconsin Card Sorting Test (WCST) has long been used to investigate deficits in executive function in humans (Milner, 1963; Nelson, 1976). The subject is asked to match test cards to reference cards according to the color, shape, or number of stimuli on the cards. After a fixed number of correct matches, the sorting rule is changed without notice, and the subject must shift to a new mode of classification. Thus, the WCST measures cognitive flexibility, that is, the ability to alter a behavioral response mode in the face of changing contingencies (set-shifting) (Monchi *et al.*, 2001). Perry *et al.* found that 15% of minimally impaired patients with AD (Mini-Mental State Examination (MMSE)

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score 24–30) and 50% of mildly demented patients with AD (MMSE score 18–23) were impaired on the modified WCST (mWCST) (Perry *et al.*, 2000). The WCST is a complex problem-solving task that probably requires multiple cognitive processes rather than a single unitary function (Nagahama *et al.*, 2003). The majority of studies that investigated deficient mWCST performance in AD focused on the number of categories achieved (CA) and the number of perseverative errors of the Nelson (PEN) type (Perry *et al.*, 2000; Nagahama *et al.*, 2003). However, there is insufficient evidence that these two measures reflect the same neural deficit and that both measures equally indicate executive dysfunction (Takeda *et al.*, 2010). On the contrary, it has been reported that the CA and PEN scores of dementia patients are each related to regional cerebral blood flow (rCBF) in different brain regions (Takeda *et al.*, 2010).

As far as we could find, there have been only two studies of the relationship between WCST scores and rCBF in patients with dementia (Nagahama *et al.*, 2005; Takeda *et al.*, 2010). The first report by Nagahama *et al.* showed that the "stuck in set" type perseveration error (similar to the perseverative errors defined by Nelson) was associated with reduced rCBF in the rostrodorsal prefrontal cortex (PFC) in 72 elderly subjects including 51 patients with AD (Nagahama *et al.*, 2005). They used stereotaxic volume of interest analysis, and examined only four small areas in the frontal lobes (rostrodorsal PFC, posterior PFC, ventrolateral PFC and anterior cigulate area). Moreover, they did not include the effects of MMSE scores and CA scores of patients.

The second study (Takeda *et al.*, 2010) reported that PEN scores correlate with rCBF in the right thalamus of 77 subjects including 31 patients with AD. They analyzed the data using the rCBF quantification software program 3DSRT (Takeuchi *et al.*, 2002). The usefulness, validity, and objectivity of 3DSRT have been reported previously (Takeuchi *et al.*, 2002). However, these two studies include normal subjects and patients with dementias other than AD. There have been no studies on the relationship between PEN scores and rCBF in AD patients.

This study aimed to compare the rCBF of AD patients with high and low PEN scores on the mWCST, and to investigate the neural substrate important for the PEN scores on the mWCST of AD patients. Because functional neuroimaging studies of the WCST have confirmed the involvement of the PFC (Berman *et al.*, 1995; Monchi *et al.*, 2001; Konishi *et al.*, 2002), we predicted a relationship between PEN scores and prefrontal hypoperfusion among AD patients.

Methods

Modified Wisconsin Card Sorting Test

Owing to the long time required for administration of the original WCST and the refusal of some patients to complete the test due to frustration or fatigue, a number of modifications to the WCST have been developed (Nagahama *et al.*, 2003). We used this modification of Nelson's version using 48 (2×24) response cards that share one and only one attribute with the stimulus cards (Nelson, 1976). Patients were not informed of the correct sorting principle, nor were they told when the principle would shift during the test, but they were informed of the three possible categories before testing. The patients were required to determine which one was correct based solely on the feedback indicating whether each response was right or wrong. When the patient maintained a correct progression through six trials, the rule was changed without warning. The testing in this study continued until 48 cards were sorted (Nagahama *et al.*, 2005).

For the mWCST, the number of CA and PEN were evaluated. In mWCST, the mean of the PEN score was reported to be 4.8 ± 5.6 among the normal elderly (mean age, 70.8) (Nagahama *et al.*, 2003). In this study, patients with a PEN score ≥ 16 (mean + 2SD among normal elderly) were placed in the high PEN score group, while patients with a PEN score ≤ 10 (mean + 1SD among normal elderly) were placed in the low PEN group.

Subjects

Twenty AD patients with dementia severity of 0.5 (suspicious) or 1 (mild) based on the Clinical Dementia Rating (CDR) (Hughes *et al.*, 1982) and whose PEN score on the mWCST was over 15, were selected from 227 consecutive Japanese patients who were fully examined at the Memory Clinic of Okayama University Hospital between April 2004 and March 2008. In addition, 20 AD patients at the Memory Clinic with low PEN scores on the mWCST, matched for age, sex ratio, education, Addenbrooke's Cognitive Examination (ACE) scores (Mathuranath *et al.*, 2000; Yoshida *et al.*, 2011), and CA scores on mWCST, were also selected.

They all (i) underwent general physical and neurological examinations and extensive laboratory testing, including thyroid function tests, serum vitamin B12, and syphilis serology; (ii) took the MMSE (Folstein *et al.*, 1975), ACE (Mathuranath *et al.*, 2000), and frontal assessment battery (FAB) (Dubois *et al.*, 2000; Kugo *et al.*, 2007) within one week of scanning; (iii) underwent brain SPECT as well as head MRI; and (iv) were diagnosed with probable AD according to the criteria formulated

by the NINCDS-ADRDA (McKhann *et al.*, 1984); (v) had a dementia severity of 0.5 or 1 on the CDR (Hughes *et al.*, 1982); and (vi) they or their nearest relatives gave written informed consent.

The exclusion criteria were: (i) complications from other neurological diseases or illnesses, (ii) history of mental illness or substance abuse prior to the onset of dementia, (iii) any evidence of focal brain lesions on head MRI, (iv) treatment with cholinesterase inhibitors, antipsychotics, antidepressants or anxiolytic drugs, and (v) left handedness or ambidexterity.

Information was also gathered from caregivers familiar with the patient's daily behavior. To serve as an informant, the caregiver was required to be living with the patient. The profile of each subject (age, sex, years of education, and years of disease duration) was recorded. The Physical Self-Maintenance Scale (PSMS) and the Lawton Instrumental Activities of Daily Living (IADL) scale (Hokoishi *et al.*, 2001) were scored based on the information from caregivers.

Other instruments

ACE was developed to provide a brief test sensitive to early stage dementia, and is capable of differentiating between dementia subtypes including AD, frontotemporal dementia, progressive supranuclear palsy, and other parkinsonian syndromes (Mathuranath *et al.*, 2000). ACE includes MMSE but extends it to encompass important areas not covered by MMSE, such as frontal-executive function and visuospatial skills. ACE has a sensitivity comparable to the Dementia Rating Scale (Mathuranath *et al.*, 2000), a well-established dementia screening tool that is widely used in research, but not in clinical practice because of its length and difficulty of administration. For this study, we used the Japanese version of the ACE described by Yoshida *et al.* (2011). The reliability of the Japanese version of ACE is excellent, and its validity is, to some extent, established (Yoshida *et al.*, 2011).

The FAB consists of six items, and the score on each item ranges from 0 to 3. A lower score indicates a greater degree of executive dysfunction. The six subtests of FAB explore (1) similarities (conceptualization), (2) lexical fluency (mental flexibility), (3) Luria motor sequences (programming), (4) conflicting instructions (sensitivity to interference), (5) a go/no-go test (inhibitory control), and (6) prehension behavior (environmental autonomy). For this study, we used the Japanese version of FAB described by Kugo *et al.* (Dubois *et al.*, 2000; Kugo *et al.*, 2007). The reliability of the Japanese version of FAB is good to excellent, and its validity is, to some extent, established (Kugo *et al.*, 2007).

The Physical Self-Maintenance Scale (PSMS) and Instrumental Activities of Daily Living Scale (IADL) are validated scales for the assessment of activities of daily living (ADL) (Hokoishi *et al.*, 2001). The PSMS is a six-item scale that rates self-care ability in toileting, feeding, dressing, personal hygiene and grooming, locomotion (physical ambulation), and bathing. The IADL scale assesses patients' ability to perform eight complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundry, mode of transportation, responsibility for medications, and ability to manage finances.

Ethics

The study protocol was approved by the Committee of Okayama University Hospital on Human Research. After providing participants with a complete description of the study, written informed consent was obtained.

Brain perfusion SPECT imaging

All subjects were examined by brain perfusion single-photon emission computed tomography (SPECT). Patients were examined in a comfortable supine position with their eyes closed in quiet surroundings. First, the passage from the heart to the brain was monitored after intravenous administration of 99mTc-ethylcysteinate dimer (ECD, 600 MBq, Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan). Ten minutes after the angiography, SPECT images were obtained using a triple-head, rotating gamma camera interfaced to a minicomputer (GCA9300A/ DI; Toshiba, Tokyo, Japan) equipped with a fanbeam, low-energy, high-resolution collimator. Sixty projection images over a 360° angle in a 128 × 128 matrix were acquired. All images were reconstructed using ramp-filtered back-projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.12 cycles/cm). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

Data analysis

Spatial reprocessing and statistical analysis of images was performed on a voxel by voxel basis using Statistical Parametric Mapping 2 (SPM2, Wellcome Department of Imaging Neuroscience, UK) running on MATLAB (The Mathworks, Inc., Natick, MA, USA). All SPECT images of each subject were normalized to the standard brain of the Montreal Neurological Institute (MNI), and spatial normalization was performed with 12-parameter

Table 1. Demographic characteristics and neuropsychological tests

	LOW PEN SCORES	HIGH PEN SCORES	p value
Number	20	20	
Age	70.0 ± 8.5	70.8 ± 11.4	0.778
Gender	10 M/10 F	10 M/10 F	–
Duration of disease	3.2 ± 2.1	3.0 ± 2.6	0.790
Education	10.7 ± 2.3	11.3 ± 2.9	0.478
Modified Wisconsin Card Sorting Test			
CA	0.9 ± 0.9	0.9 ± 0.9	0.856
PEN	7.3 ± 2.2	20.2 ± 6.3	0.000
ACE	68.3 ± 13.7	68.3 ± 13.3	0.991
Visuospatial	5.5 ± 2.6	5.0 ± 2.1	0.460
Language	26.0 ± 2.0	26.2 ± 2.0	0.701
Orientation	8.1 ± 2.6	8.3 ± 2.2	0.796
Memory	2.3 ± 2.7	2.5 ± 2.7	0.817
MMSE	23.2 ± 3.5	23.0 ± 4.4	0.814
FAB	12.0 ± 2.8	10.9 ± 3.0	0.232
Similarities	1.5 ± 1.1	1.2 ± 1.2	0.496
Lexical fluency	1.6 ± 0.9	1.7 ± 0.9	0.863
Luria*	1.7 ± 1.0	1.8 ± 1.0	0.754
Conflicting instructions	2.5 ± 1.0	2.2 ± 1.2	0.395
Go/no-go test	1.8 ± 1.1	1.1 ± 1.0	0.035
Prehension behavior	3.0 ± 0.0	3.0 ± 0.0	1.000
PSMS	5.3 ± 1.2	4.8 ± 1.5	0.208
IADL	4.9 ± 1.7	4.9 ± 1.7	1.000

All data are means ± SD. p value, unpaired and two-tailed t tests.
PEN = perseverative errors of the Nelson type; CA = categories achieved.
ACE = Addenbrooke's cognitive examination.
MMSE = Mini-Mental State Examination.
FAB = frontal assessment battery; Luria* = Luria motor sequences.
PSMS = Physical Self-Maintenance Scale.
IADL = Lawton Instrumental Activities of Daily Living.

affine and non-linear transformations (Friston *et al.*, 1995). The voxel sizes of the reslice option were 2 mm × 2 mm × 2 mm. The non-linear parameter was set at 25 mm cut-off basis functions and 16 iterations. All the normalized SPECT images were then smoothed with an isotropic gaussian kernel filter (12-mm full-width at half-maximum). To examine the images for specific regions showing differences in perfusion, two sample *t*-tests were performed. Global normalization was performed by proportional scaling with the mean voxel value. Masking was applied using the threshold method (0.8 times the global value). The analysis used a threshold of $p < 0.01$ at the voxel level and results were considered significant at $p < 0.05$ (corrected) at the cluster level.

Statistical analysis

Statistical analysis was performed using the SPSS 14.0J software program (SPSS Inc., Chicago, IL). The two groups were compared using independent sample *t*-tests. A value of $p < 0.05$ was accepted as significant.

Results

Clinical characteristics and neuropsychological tests

No significant differences were found between high and low PEN score groups with respect to age ($p = 0.778$), disease duration ($p = 0.790$), or years of education ($p = 0.478$) (Table 1).

With the exception of PEN scores on mWCST ($p < 0.001$), no significant differences were found between high and low PEN score groups in CA scores on the mWCST ($p = 0.856$), ACE ($p = 0.991$), MMSE ($p = 0.814$), FAB ($p = 0.230$), PSMS ($p = 0.208$), or IADL ($p = 1.000$) (Table 1). There were no significant differences between high and low PEN groups in the four subscale scores on ACE. Comparison of FAB subscales revealed that AD patients with high PEN scores got lower scores than those with low PEN scores in the subscale score of the go/no-go test (Table 1).

Regional cerebral blood flow (rCBF)

The areas of hypoperfusion in the high PEN score group that were not present in the low PEN score

Table 2. Significant regional uptake differences between AD patients with low and high PEN scores on mWCST

DIRECTION OF DIFFERENCE	NUMBER OF VOXELS	PEAK Z SCORES	COORDINATES (MNI) X	Y	Z
Decreased uptake in AD patients with high PEN scores on mWCST	528	2.89	−4	52	−10
		2.58	8	46	16
		2.57	2	42	18

AD = Alzheimer's disease; MNI = Montreal Neurological Institute; mWCST = modified Wisconsin Card Sorting Test.

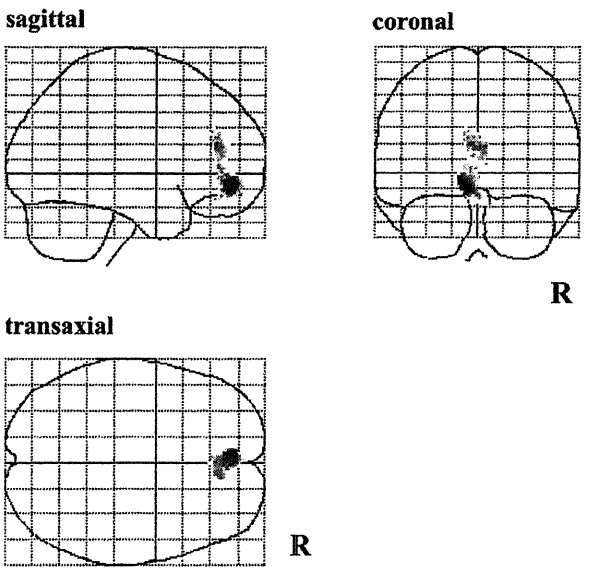

Figure 1. SPM (z) map of rCBF decrease in AD patients with high PEN scores on the modified WCST compared with AD patients with low PEN scores. Three-way-glass view of the area of significant hypoperfusion.

group according to the SPM analysis are shown in Figure 1 and Table 2. A similar test for areas of hypoperfusion in the low PEN score group that were not present in the high PEN score group found no cluster of voxels. Figure 1 shows the z score for each voxel in this cluster superimposed onto a 3-way glass brain view. Figure 1 shows a significant cluster of voxels in the left rectal gyrus extending to the right rectal gyrus and bilateral orbital gyrus (in the ventromedial PFC). Table 2 shows the probability results of the SPM analysis and the location of peak z scores in terms of MNI coordinates.

Discussion

Ventromedial PFC and WCST

We predicted hypoperfusion in the PFC among AD patients with high PEN scores, and we revealed in this study that rCBF in the bilateral rectal and orbital gyrus among AD patients with high PEN scores was lower than that among AD patients with low PEN scores. Therefore, the results are in accordance with our hypotheses. It was reported that all patients with lesions involving regions of the ventromedial PFC (vmPFC) were impaired on WCST, and that most patients without ventral prefrontal damage performed normally on WCST (Schnyer *et al.*, 2009). Our results also suggest the importance of the vmPFC in WCST.

The vmPFC is reported to play a key role in implementing probabilistic rules (Bhanji *et al.*, 2010), and patients with vmPFC damage show deficits in learning reward-punishment rules (Hartstra *et al.*, 2010). Moreover, vmPFC is involved in guiding decision-making when strategies change (de Wit *et al.*, 2009). Therefore, difficulty in changing a strategy when the rules are altered might cause the increase in PEN scores on WCST as a matter of course.

WCST and rCBF in AD and other neurodegenerative diseases

In this study, the PEN score of WCST was significantly associated with rCBF in the bilateral rectal and orbital gyrus. However, the results of other studies are not always consistent with our findings (Nagahama *et al.*, 2005; Takeda *et al.*, 2010). What causes the difference?

Nagahama *et al.* showed that the "stuck in set" type perseveration error was associated with reduced rCBF in the rostrodorsal PFC (Nagahama *et al.*, 2005). They did not examine rCBF in the ventromedial PFC and calculated the correlation of perseveration errors to rCBF without adjusting the CA scores. Therefore, if MMSE scores or CA scores correlate with rCBF in the rostrodorsal PFC, the correlation of perseveration error to rCBF in the rostrodorsal PFC is not specific to perseveration error. The CA score was reported to correlate with rostrodorsal PFC (Takeda *et al.*, 2010). Therefore, the correlation of perseveration error to rCBF in

the rostrodorsal PFC might be affected by the correlation of CA score to rCBF in the rostrodorsal PFC.

Our previous report showed that PEN scores correlate with rCBF in the right thalamus (Takeda *et al.*, 2010). Twenty-nine of 40 AD patients in this study were also included in the previous study. In that study, the data were analyzed, using the rCBF quantification software program 3DSRT (Takeuchi *et al.*, 2002). The 3DSRT divides each hemisphere into 12 arbitrary segments and each segment includes a relatively broad area. For example, the callosomarginal segment includes the superior frontal, medial frontal, and paracentral lobules, anterior cingulate, and subcallosal, orbital, and rectal gyri (Takeuchi *et al.*, 2002). Therefore, if PEN scores correlate strongly with only a small region in the frontal lobe, the correlation of PEN scores to a broad segment such as the callosomarginal segment in the 3DSRT could obscure statistically significant results in smaller regions. In this study, rCBF in whole voxels of brains of high and low PEN score groups were compared. This approach facilitates identification and analysis of smaller, discrete regions of interest. Moreover, both Nagahama *et al.* (2005) and Takeda *et al.* (2002) studied a mixture of subjects including different etiologies, MCI, and elderly subjects, whereas this study included only patients with AD. The difference in subjects might influence the results.

Ventromedial PFC and AD

We found a decrease in rCBF in the ventromedial PFC among AD patients with high PEN scores. Significant metabolic decreases in ventromedial prefrontal areas are reported to begin early in the course of AD (Fouquet *et al.*, 2009). In support of this contention, the same two medial prefrontal areas showed specific perfusion decreases from the entorhinal to the limbic neuropathologic Braak stages (Braak and Braak, 1991), corresponding to amnestic mild cognitive impairment and early AD, respectively (Bradley *et al.*, 2002). Our results suggest that some AD patients suffer from frontal neuropsychological deficits and frontal hypoperfusion in the early stage, and that those patients might be included in a so-called frontal variant of AD (Johnson *et al.*, 1999; Woodward *et al.*, 2010).

WCST and the go/no-go task

In this study, AD patients with high PEN scores got lower scores on the go/no-go task on FAB than those with low PEN scores. The go/no-go task, in which the participant must inhibit a response that was previously given to the same stimulus, can assess the difficulty in controlling impulsiveness (Drewe, 1975). Therefore, the go/no-go task is commonly used to investigate processes of selective attention or response inhibition (Ambach *et al.*, 2008). Response inhibition is difficult for patients with damage to the ventral part of the frontal lobes (Rolls *et al.*, 1994). Thus, the PEN score on mWCST may be a promising index to detect dysfunction of the orbitofrontal area among mildly affected AD patients, and equally these results suggest that the go/no-go task from the FAB may possess particular utility as a bedside test of orbitofrontal dysfunction in AD.

Limitations of this study

The results in this study should be interpreted with some caution: (1) the relatively small sample size, comprising only 20 AD patients with high CA scores and 20 AD patients with low CA scores, may limit the sensitivity to actual group differences and associations between neuropsychological functions and neural activation; (2) the low spatial resolution of SPECT scans may limit detection of alterations in small regions, thus increasing the risk of false negatives and interference from surrounding regions as well (Takeuchi *et al.*, 2002); (3) PEN and CA scores on mWCST were evaluated, but other subscales of WCST were not investigated and therefore we cannot discuss the relationship of other subscales with the PEN scores; and (4) stereotypical behaviors among AD patients were not scored. Future studies including such data will be important in relating or translating SPECT findings into clinically relevant understanding of behavior.

Conclusions

We compared rCBF between patient groups with high and low PEN scores on mWCST, and found that the high PEN score group showed lower rCBF in the bilateral rectal and orbital gyrus. Hypoperfusion of the orbitofrontal area might therefore be related to perseveration in AD patients. Further studies on the other scores on mWCST will shed light on the neural substrate of mWCST.

Conflict of interest

None.

Description of authors' roles

S. Terada designed the study, analyzed the data and wrote the paper. S. Sato assisted in preparing the statistical design and supervised the statistical analysis. H. Honda collected the data and was

involved in data analysis. O. Yokota, E. Oshima, Y. Kishimoto and N. Takeda collected data. All authors discussed the results and conclusions. Y. Uchitomi supervised the study design, participated in data analysis and assisted with writing the paper.

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Review Article: Palliative Care

Importance of Rehabilitation in Cancer Treatment and Palliative Medicine

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Although rehabilitation for cancer patients is being practiced in clinical settings, it has not been very well recognized in cancer care. However, interest has been turning to cancer rehabilitation in recent years in association with advances in palliative care and the increasing numbers of patients who survive for long periods, while enduring symptoms caused by cancer or adverse effects associated with treatment. The fact that cancer patient rehabilitation fees were newly established in the 2010 revision of the Japanese medical service fees has propelled interest in this topic. Rehabilitation can be applied throughout the entire phase from the time of diagnosis to the terminal stage, and it is an approach that can involve psychosocial aspects as well as physical aspects. Although its effectiveness has not been adequately demonstrated, especially in the area of palliative medicine, rehabilitation for cancer patients is expected to be an important means of supporting the hopes of patients and their families, and attempting to maintain and improve patients' quality of life.

Key words: ADL – QOL – rehabilitation

INTRODUCTION

Advances in treatment techniques have been associated with increases in cancer patient survival rates, and the numbers of long-term cancer survivors have been rising. Nevertheless, many cancer patients experience impairments in everyday living as a result of adverse effects or sequelae associated with treatment or as they reach the terminal stage of their disease. Rehabilitation may play a role as one approach to maintaining and improving the quality of life (QOL) of such cancer patients.

Approaches to cancer patient rehabilitation that take both psychosocial aspects and physical aspects into consideration are important, based on 'adequately understanding the strong connections between the patients' physical, psychological and social aspects (1)'. Thus, the involvement of representatives of a variety of occupations, including psychologists, clinical psychologists and nurses, and not just such rehabilitation specialists such as physical therapists, occupational therapists or speech therapists is important for the rehabilitation of cancer patients; thus, a multidisciplinary team care is required. However, not many reports on the rehabilitation of cancer patients have appeared since the comprehensive research reports on the need for rehabilitation were first published by Lehmann et al. (2) and by Harvey et al. (3) in 1982. One reason for this lack of research is that as rehabilitation was originally performed mainly for the purpose of improving and raising the level of activities of daily living (ADL), there has been little demand from either healthcare providers or patients for proactive intervention in cancer care with regard to rehabilitation, which has had a strong image of being intended to improve ADL and return patients to their former lives. In recent years, however, interest has turned to the association between cancer rehabilitation and the increasing numbers of patients who survive for long periods, while enduring symptoms caused by cancer or the adverse effects associated with treatment or the association with advances in palliative care.

Dietz (4) has classified cancer rehabilitation according to cancer patients' physical and individual needs into four

categories: preventive, restorative, supportive and palliative (Table 1). Based on these categories, the effectiveness of rehabilitation has been reported for each stage of cancer treatment, from physical rehabilitation during the acute stage of treatment (5–8) to the rehabilitation of physical aspects and psychological aspects during the terminal stage (9–12), but it remains difficult to claim that cancer rehabilitation is generally acknowledged adequately. In view of these situations, Dietz (13) has pointed out that it will be necessary to focus on a concept of care that asks, 'What is the best support that can be provided to enable cancer patients to readapt to society', and DeLisa (14) has stated that 'now that cancer patients' survival rate has increased, attention should be turned to maintaining cancer patients' QOL and prolonging it'. In other words, a shift to an approach that aims to maintain the QOL of patients at a high level and not just improve their function and prognosis has become necessary.

On the other hand, the recognition or practice of rehabilitation in the cancer area is not adequate. In this article, I will first outline the rehabilitation that is performed during each phase and the points to bear in mind while performing such rehabilitation. Next, I will report on rehabilitation needs, then on the current state of affairs with regard to cancer rehabilitation in Japan, including the results of our own research. Finally, I will describe the current problems and perspectives regarding rehabilitation for cancer patients.

REHABILITATION DURING EACH PHASE

The areas in which rehabilitation can be applied during the various phases of disease have been summarized in a table (Table 2) (15). Below, I have summarized the kinds of rehabilitation that are performed during each phase as well as some points to bear in mind.

Rehabilitation Before and After Surgical Treatment

First, promoting early postoperative ambulation and improving physical functions so that patients can return as closely as possible to their lives before surgery is a goal common to rehabilitation for all diseases. During this phase, many patients have just started treatment, and rehabilitation should be conducted with sufficient consideration of the fact that many patients have a tendency to become psychologically depressed during this phase as a result of their 'cancer' diagnosis or changes in their body image as a result of surgery. When performing rehabilitation, it is important to first determine how a patient's disease has been explained to him or her and how the patient perceives his or her disease. In addition, determining what issues patients and their families are concerned about at present and with regard to their future makes it possible to provide them with information to allay their concerns.

Now that the length of hospital stays in Japan has been shortened, the time available to conduct inpatient rehabilitation has also been limited. Thus, some problems may arise, while the patients are going about their daily lives after their discharge from hospital that were not recognized, while the patients were hospitalized. Patients often spend the next several years being concerned about recurrence, and another role of rehabilitation is to provide patients with a place to go for consultation when they have concerns after being discharged.

Rehabilitation During Chemotherapy

Physical strength tends to diminish during chemotherapy as a result of the adverse effects, such as nausea/vomiting, myelosuppression or peripheral neuropathies. Rehabilitation aims to encourage ambulation consistent with the patient's condition even during chemotherapy and to prevent disuse

Table 1. Classification of cancer rehabilitation

(1) Preventive rehabilitation
Starts soon after cancer has been diagnosed. Performed before or immediately after surgery, radiotherapy or chemotherapy. No impairments of function present yet. Preventing impairments is the purpose of the rehabilitation measures
(2) Restorative rehabilitation
Aims for the maximal recovery of function in patients with remaining function and ability Attempts to achieve maximal functional recovery in patients have impairments of function and decreased abilities
(3) Supportive rehabilitation
Increases self-care ability and mobility using methods that are effective (e.g. guidance with regard to self-help devices, self-care and more skillful ways of doing things) for patients whose cancer has been growing and whose impairments of function and declining abilities have been progressing. Also includes preventing disuse, such as contractures, muscle atrophy, loss of muscle strength and decubitus
(4) Palliative rehabilitation
Enables patients in the terminal stage to lead a high QOL physically, psychologically and socially, while respecting their wishes. Designed to relieve symptoms, such as pain, dyspnea and edema and to prevent contractures and decubitus using heat, low-frequency therapy, positioning, breathing assistance, relaxation or the use of assistive devices

Quoted from ref. no. 4.

Table 2. Possible contributions of rehabilitation in the various phases of the disease

Phase of disease	Possible contributions of rehabilitation
I. Treatment	1. Evaluating the effects of treatments on function
	2. Preserving and restoring function through exercise, edema management and increased activity
	3. Controlling pain using heat, cold and transcutaneous electrical nerve stimulation
II. Posttreatment	1. Developing and supporting a program to help restore daily routines and promote a healthy life-style
	2. Educating the patient about what to self-monitor
	3. Supervising a maintenance program of exercise, edema management, and mobility management and m
III. Recurrence	1. Educating the patient about the impact of recurrence and its effect on function
	2. Educating the patient about what to monitor in the context of the new clinical status
	3. Supervising the patient in an appropriate program to restore function or prevent its decline
IV. End of life	1. Educating patient/family regarding mobility training, good body mechanics and assistive devices
	2. Pain management (non-pharmacologic treatment) and symptom control
	3. Maintaining independence and quality of life

Quoted from ref. no. 15.

syndrome and maintain physical and muscle strength by performing mild exercise therapy and sedentary occupational therapy. Failure to resume ambulation during treatment and the development of severe disuse syndrome often occur, especially among infants and the elderly. It is important for the rehabilitation staff to visit the patient regularly and to make movement a habit, even if only a little at a time, by incorporating activities that the patients enjoy.

Moreover, many patients today receive outpatient chemotherapy as well as inpatient chemotherapy, and treatment is expected to shift even further toward an outpatient setting. Patients undergoing outpatient chemotherapy continue their daily lives at home while receiving treatment. Continuing to work and keep house, while experiencing the adverse effects of treatment often imposes a major burden on patients. The rehabilitation staff should determine which activities a patient considers to be important in his or her life so that the patient can recognize their own symptoms and acquire his or her desired ADL, with the rehabilitation staff proposing activities that will help the patient to do what he or she wants to do. Giving the patients the sense that they are able to control their own activities in this way is an important link to preserving their self-confidence.

Rehabilitation During the Recurrence and Advanced Stages

Patients with recurrent and advanced cancer experience a variety of symptoms associated with cancer progression. Because patients also sometimes develop disuse syndrome and their general condition rapidly deteriorates when they are deprived of opportunities to move as a result of general malaise and feeling tired, it is desirable to maintain a minimum of self-care in their everyday lives, i.e. feeding, elimination and bathing, whenever possible.

As the disease progresses, patients are compelled to cope with physical symptoms that develop one after another. Faced with these circumstances, caution is required when dealing with patients during this phase, when they are also often confronted with situations that may make the cure of their disease difficult. Because many patients are trying to concentrate on treatment during the phase, with the aim of a cure, the improvement of physical functions is often ranked first among patient's hopes with regard to rehabilitation. However, when they approach the transition period, it becomes necessary to consider what it is that they really want to do in anticipation of the future deterioration of their physical condition. It takes time for this transition to occur, and the feelings of patients and their families may change markedly. It is important to recognize that fluctuating feelings are natural, and it may be necessary to listen closely to the patients and their families from time to time and await their choices. In terms of the goals of rehabilitation, the rehabilitation staff should interact with the patients and their families in a manner that will enable them to accept reality and to identify their goals. The rehabilitation approach should also take into consideration the environment surrounding the patient, including the patients' own remaining functional activities as well as the human support that is available, the utilization of healthcare devices, and the utilization of social resources, so that patients are able to achieve whatever they hope to do.

Rehabilitation During the Terminal Stage

Patients' and their families' needs are most important during the terminal stage. When patients express strong wishes, such as 'I want to go to the bathroom' and 'I want to walk', up until the very end, it is sometimes possible to satisfy their wishes by teaching family members how to assist them,

making adjustments to the environment around the bed and around the bathroom, and by making walking aids available, even when there is no prospect for improvement in the patients' functions. Communication with patients and their families also becomes important during this phase, and when communication becomes difficult for patients, providing support designed to achieve understanding among patients, their families and the staff by introducing communication aids or assisting with conversation is another important role of rehabilitation.

Moreover, even when a patient's general condition deteriorates, it is possible to perform rehabilitation until the very end by going to the patient's bedside and touching the patient's body through palliative interventions, such as range of motion (ROM) exercises for the patients' limbs, massage for swollen lower limbs or breathing assistance.

As stated earlier, rehabilitation can be applied throughout the entire phase of disease from the time of diagnosis until the terminal stage, and involvement with psychosocial aspects not just physical aspects can be included as one possible approach.

REHABILITATION NEEDS

Several studies have already been conducted regarding the needs of cancer patients in relation to rehabilitation. A survey of the rehabilitation needs during the initial stage of treatment in the USA revealed that 87% of the patients had rehabilitation needs, and recovery from deconditioning; improvement of impaired mobility, restricted ROM and impaired ADL, and a need for distraction were cited as rehabilitation needed (16). In the Netherlands, it was reported that 26% of the participants desired specialized support to strengthen physical functions, to deal with their physical and social situation, and to find new goals in their lives (17). In addition, broader needs were cited in relation to the lives of those living at home, including with respect to financial matters, the performance of housework and means of transportation (18). However, the results of interventions to meet such needs have never been elucidated.

Moreover, in a questionnaire survey of the families of patients who had died in a palliative care unit in Japan, pain, impaired mobility and ADL impairments were mentioned as problems during the hospital stay, and it was shown that even during the terminal stage 85% of the patients wanted to be able to walk or to move about in a wheelchair, and interventions with regard to these aspects were said to be effective and satisfactory (12). However, what patients themselves feel is effective and satisfactory has never been elucidated in proxy evaluations by bereaved families, and there have been no reports of investigations of the families' degree of satisfaction or changes in their emotions.

We therefore provided rehabilitation to 23 inpatients of a cancer hospital for 2 weeks and conducted a survey of the patients and their families to determine what changed before and after the rehabilitation (19). The performance status (PS) of the patients was 3 in 12 cases (52.2%) and 4 in 8 cases (34.8%); thus, 87% of the patients had a PS of 3–4. The rehabilitation that was performed consisted mainly of standing training, gait training and upper limb function training. The results of the rehabilitation interventions included changes in several physical aspects and considerable changes in the emotional states of both the patients and their families (evaluated using a face scale). Thus, psychological suffering was alleviated by the rehabilitation efforts. When the patients and their families were surveyed separately with regard to how they felt about the effectiveness of the rehabilitation, the patients mentioned 'a feeling of relief as a result of receiving guidance' and 'psychological support', while the families mentioned content related to the impact of the rehabilitation on the psychological aspects of the patients, such as 'effective in terms of mental aspects', 'fun' and 'restoration of self-confidence'. Based on the earlier-mentioned findings, rehabilitation for cancer patients may be effective not only in terms of physical aspects, but also in terms of psychological aspects.

CURRENT STATUS OF CANCER REHABILITATION IN JAPAN

In March 2006, we conducted a survey on the current status of cancer rehabilitation by mailing questionnaires to 1693 nationwide healthcare institutions certified as general hospitals, long-term care hospitals or multi-unit hospitals according to evaluations performed by the Japan Council for Quality Health Care in December 2005. The survey asked whether the institutions had performed rehabilitation for cancer patients in 2005, and the institutions that had performed cancer rehabilitation were surveyed as to the nature of the rehabilitation that was performed, the stage of the cancer patients' disease, the type of cancer, the number of patients who received rehabilitation, the occupations of the personnel who provided the rehabilitation and whether the institution had a specialized cancer rehabilitation facility or equipment. In addition, the institutions where cancer rehabilitation was not being performed were asked about whether there was a need for cancer rehabilitation, the settings in which they felt that there was a need, the reason why rehabilitation was not being performed, and whether there were any plans to perform rehabilitation in the future (20).

Valid replies were received from 1045 (62.0%) of the healthcare institutions nationwide, and 864 (82.7%) of them were institutions that had performed rehabilitation for cancer patients in 2005. However, we could clarify the exact number of cancer patients who received rehabilitation. In terms of the nature of the rehabilitation, large percentages replied that they had performed rehabilitation for physical functions: gait training in 92.1%, muscle strength training in 88.9% and joint ROM training in 85.6%. A large percentage of the institutions (73.6%) also provided training with regard

to ADL. Small percentages of the institutions performed specialized rehabilitation for lymphedema care, postoperative head and neck cancer care, colostomy care after colorectal cancer surgery, urostomy care after surgery for urinary tract cancer or rehabilitation that focused on mental and psychological aspects. Of the 181 institutions that had not performed rehabilitation for cancer patients, 171 (94.5%) replied that they felt a need for rehabilitation for cancer patients. The most common settings in which a need was felt were when 'patients would say that they wanted to stand up and walk again' and 'patients would say that they wish they could go to the bathroom without needing help from anyone'.

The above results indicated a large need for rehabilitation for cancer patients, but it was not concluded to what extent the current status met the needs of cancer rehabilitation. This survey also showed that the system for performing cancer rehabilitation is inadequate and that it is needed to assess strategies designed to develop and disseminate rehabilitation programs for cancer patients.

CURRENT PROBLEMS AND PERSPECTIVES

As stated already, although the need for the rehabilitation of cancer patients has been recognized, the degree of recognition in the field of oncology remains somewhat low. The fact that there have been few reports demonstrating its effectiveness can be cited as one of the reasons for this state of affairs. Recently, a systematic review regarding the health effects of exercise during cancer rehabilitation has been established (21). Ten studies were reviewed, and improvements in physical functioning, strength, physical activity levels, QOL, fatigue, immune function, hemoglobin concentrations, potential markers of recurrence and body composition were reported. However, all the studies were limited by incomplete reporting and methodological limitations.

We also systematically reviewed the effectiveness of cancer rehabilitation in palliative care using the keywords 'cancer' AND 'palliative care' AND 'rehabilitation' to search a medical literature database (PubMed) on 17 August 2009. We restricted the study design to intervention studies (retrospective studies and case reports were excluded, and music therapy was also excluded) and to studies that focused on physical functions and daily living functions. After conducting discussions twice a year (a total of four times), we performed a systematic review of the following survey items: lead author, name of the country, journal name, year of publication, number of subjects, cancer site, proportion of females, age, composition of the rehabilitation team, intervention (method, frequency and time per day), main outcomes and main results. As a result, only eight documents were retrieved, and three of them were randomized controlled trials (in submission). Thus, although rehabilitation is being practiced in the palliative care area, the evaluation of its outcome will be a future task.

We have not devoted much attention to the particulars of rehabilitation in this review because considerable variation exists in the interventions that are actually being performed for individual patients and because the interventions have been established as rehabilitation techniques and are not specifically performed only for cancer patients. Instead, the task from now on will be to determine how rehabilitation personnel may acquire knowledge about cancer and incorporate established techniques into cancer care.

CONCLUSION

Interest in cancer rehabilitation in Japan has increased since cancer patient rehabilitation fees were newly established in the 2010 revision of medical care service fees. However, it is still hard to say that the need for rehabilitation services has been adequately acknowledged in cancer care and that future research is needed because high-quality literature evidence is still lacking.

Rehabilitation is expected to become an important support that sustains the hopes of patients and their families, as it is said that 'Being able to maintain and improve ADL as much as possible, while skillfully using remaining physical strength is a great joy and is linked to the desire to live'.

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Conflict of interest statement

None declared.

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