Smaller Regional Volumes of Brain Gray and White Matter Demonstrated in Breast Cancer Survivors Exposed to Adjuvant Chemotherapy

Masatoshi Inagaki, MD, PhD[1]
Eisho Yoshikawa, MD, PhD[2]
Yutaka Matsuoka, MD, PhD[3]
Yuriko Sugawara, MD, PhD[4]
Tomohito Nakano, MD[5]
Tatsuo Akechi, MD, PhD[6]
Noriaki Wada, MD[7]
Shigeru Imoto, MD, PhD[7]
Koji Murakami, MD, PhD[8]
Yosuke Uchitomi, MD, PhD[1]
and The Breast Cancer Survivors' Brain MRI Database Group

[1] Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan.

[2] Division of Psycho-Oncology, Shizuoka Cancer Center, Shizuoka, Japan.

[3] Division of Adult Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan.

[4] Department of Psychiatry and Behavioral Science, Tokai University School of Medicine, Kanagawa, Japan.

[5] Department of Psychiatry, Kitasato Institute Hospital, Tokyo, Japan.

[6] Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

[7] Division of Breast Surgery, National Cancer Center Hospital East, Chiba, Japan.

[8] PET Center, Dokkyo University School of Medicine, Tochigi, Japan.

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The members of the Breast Cancer Survivors' Brain MRI Database Group are Makoto Kobayakawa, MD, PhD (Department of Psychiatry, Hiroshima University Hospital, Hiroshima, Japan); Nobuya Akizuki, MD, PhD, and Maiko Fujimori, PhD (Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan); in addition to the authors listed above. All members of the group are authors of the current study and meet criteria for authorship.

Address for reprints: Yosuke Uchitomi, MD, PhD, Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577 Japan; Fax: (011) 81-4-7134-7026; E-mail: yuchitom@east.ncc.go.jp

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BACKGROUND. Previous studies have shown cognitive impairment in breast cancer survivors who were exposed to adjuvant chemotherapy. Neural damage by chemotherapy might have played some part in these findings. The current study explored the regional brain volume difference between breast cancer survivors exposed to adjuvant chemotherapy (C+) and those unexposed (C−).

METHODS. High-resolution 1.5-tesla brain magnetic resonance imaging (MRI) databases of breast cancer survivors and healthy controls were used. Brain images were preprocessed for optimal voxel-based morphometry. Comparisons of gray matter and white matter were performed between the C+ and the C− groups, by using MRI scans from within 1 year (the 1-year study, n = 51 and n = 55, respectively) or 3 years after their cancer surgery (the 3-year study, n = 73 and n = 59, respectively). As exploratory analyses, correlation analyses were performed between indices of the Wechsler Memory Scale-Revised and regional brain volume where the volumes were significantly smaller. As a reference, MRI scans of cancer survivors were compared with those of healthy controls (n = 55 for the 1-year study and n = 37 for the 3-year study).

RESULTS. The C+ patients had smaller gray matter and white matter including prefrontal, parahippocampal, and cingulate gyrus, and precuneus in the 1-year study. However, no difference was observed in the 3-year study. The volumes of the prefrontal, parahippocampal gyrus, and precuneus were significantly correlated with indices of attention/concentration and/or visual memory. Comparisons with healthy controls did not show any significant differences.

CONCLUSIONS. Adjuvant chemotherapy might have an influence on brain structure, which may account for previously observed cognitive impairments. *Cancer* **2007;109:146–56.** © *2006 American Cancer Society.*

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The survival rate of breast cancer patients is increasing with the development of systemic chemotherapy. In this situation, management of long-term side effects of potentially curative breast cancer treatment is of substantial importance to optimal quality of life of breast cancer survivors. Recently, impairments of cognitive function, which is a prerequisite for functioning in daily life, have been recognized as a possible long-term adverse effect, which has been termed "chemobrain".[1,2] Previous reviews have shown that most of these studies have consistently indicated impairments of various cognitive domains in breast cancer survivors exposed to adjuvant chemotherapy.[3–6] However, the neural mechanisms have not been fully studied.

Neural impairments caused by chemotherapeutic agents as shown in animals may play a part in these mechanisms. Although chemotherapeutic agents were thought initially to have little ability to penetrate the blood-brain barrier, recent studies have indicated higher concentrations than were expected in cerebrospinal fluid and brain tissue.[7–9] Chemotherapeutic agents are hypothesized to have neurotoxic potential through their ability to interfere with DNA and RNA synthesis and function, inhibition of microtubule formation, and/or immunosuppressive properties.[10,11] In animals, intracerebroventricularly injected methotrexate was reported to cause learning and memory impairments and damage to the hippocampal CA4 region.[12] Injection of doxorubicin into the caudate-putamen indicated neuronal death in the ventral tegmentum and thalamus.[13] Intraperitoneal injection of cyclophosphamide produced lesions within the cortex, thalamus, hippocampal dentate gyrus, and caudate nucleus in a dose-dependent fashion.[14] In the same report, cyclophosphamide and methotrexate showed a concentration-dependent neurotoxic effect on neuronal cell cultures. Another study has demonstrated that free radicals are a possible mechanism for the toxic effect of chemotherapeutic agents.[15]

Recently, neuroimaging techniques have developed dramatically, thus enabling investigation of brain structure in humans. In a preliminary investigation that used structural magnetic resonance imaging (MRI), Saykin et al. reported regional brain volumes in breast and lymphoma cancer survivors who lived more than 5 years after their initial treatment.[10] Results suggest that chemotherapy may be associated with reductions in regional brain volume. However, a further study is needed with a comparison group of cancer patients unexposed to chemotherapy to control for the impact of cancer diagnosis. Contrary to results of the Saykin et al. investigation, our study showed no significant difference in regional and whole-brain volumes between breast cancer survivors exposed to adjuvant chemotherapy and those unexposed 3 years after their breast cancer surgery.[16] Although a previous study indicated long-term cognitive impairment,[17] by taking previous reports that show recovery of cognitive impairments over time into consideration,[4,18–20] adverse changes in the brain structure may recover.

In the current study, we explore the regional brain volume difference between cancer survivors exposed to adjuvant chemotherapy and those unexposed in a 2-study setting (the 1-year study of <1 year after surgery and the 3-year study of >3 years after surgery). Our hypothesis was that smaller regional brain volumes would be associated with adjuvant chemotherapy. For secondary analysis, associations were examined between memory functions (as 1 of the cognitive functions) and the regional brain volume, where the volumes are significantly smaller in cancer survivors exposed to adjuvant chemotherapy.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center of Japan and was performed after obtaining written informed consent from patients. This study was conducted by using 2 databases of brain MRI scans from breast cancer survivors. One database (Long-Term-Survivors Database) comprised brain MRI scans of patients 3 years after their breast cancer surgery.[16] The other database (Follow-up Database) comprised brain MRI scans from 3–15 months after patients' breast cancer surgery and additional scans from 2 years after their first scan.

Subjects and Procedures

The 1-year study used baseline data from the Follow-up Database (Fig. 1). Subjects were recruited during follow-up visits to the Division of Breast Surgery, National Cancer Center Hospital East. We selected all patients who underwent their breast cancer surgery and who survived >3–15 months. The inclusion criteria were 1) female sex to minimize sex-based brain differences and 2) ages between 18 and 55 years. Exclusion criteria were 1) a history of cancer other than breast cancer or double cancer, 2) bilateral breast cancer, 3) clear evidence of residual or recurrent cancer, 4) current chemotherapy or radiation therapy, 5) a history of any neurological disorders, traumatic brain injury, or psychiatric disorders other than affective and anxiety disorders, 6) psychotropic

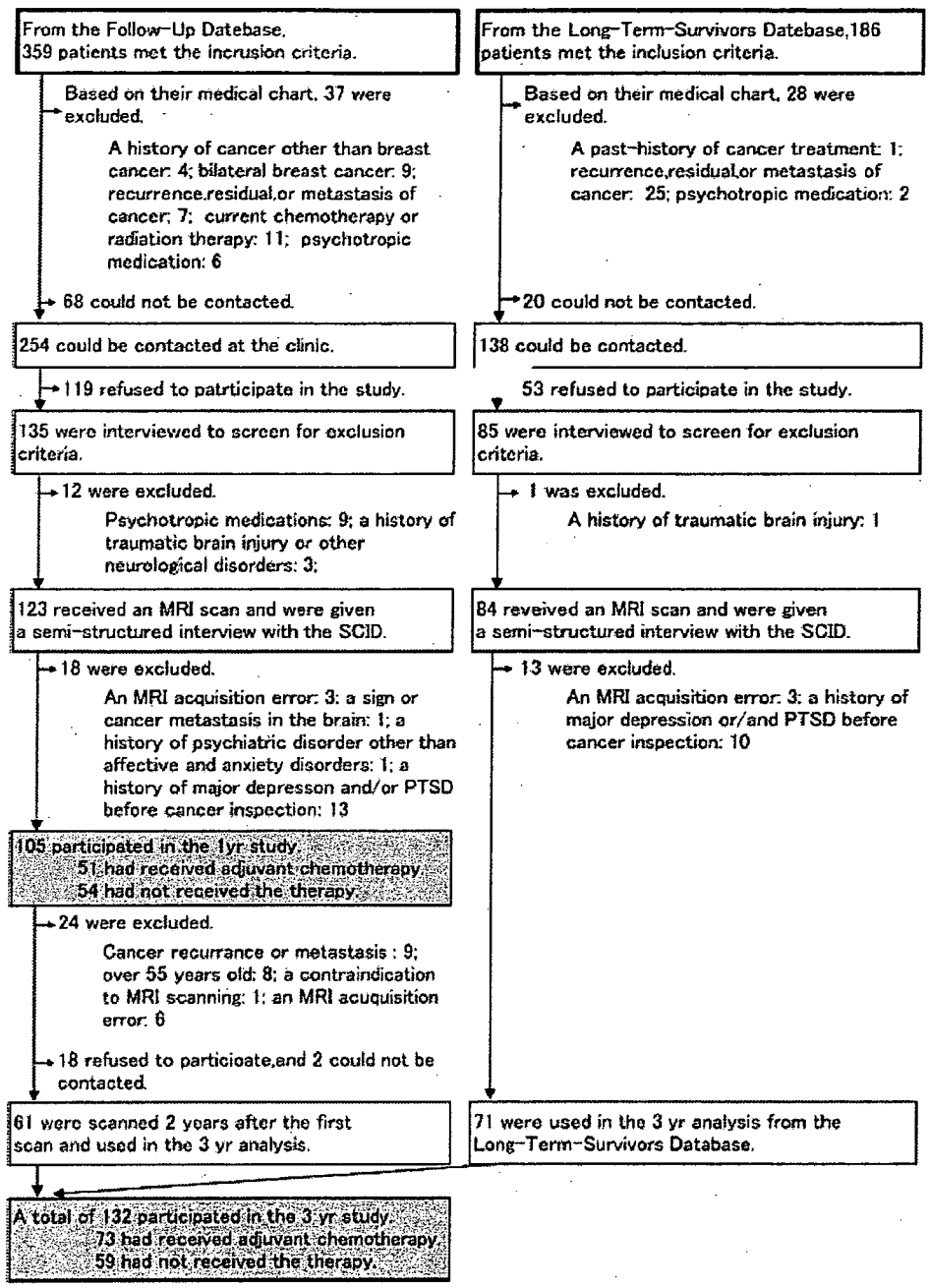

FIGURE 1. Subject sampling in the 1-year study and the 3-year study. SCID indicates the Structured Clinical Interview for DSM-IV Axis I Disorder, clinician version; MRI, magnetic resonance imaging; PTSD, post-traumatic stress disorder. In the 1-year study, the age and medical factors significantly differ between the 105 subjects and the 190 patients who did not participate because of our mistake to make contact with patients, patient refusal to participate, or MRI examination error were positive lymph node metastases found in their surgical tissue (31% versus 44%, $\chi^2 = 4.4$, $P = .04$), poor histological grade (27% versus 56%, $\chi^2 = 21.1$, $P < .01$), and receiving adjuvant chemotherapy (49% versus 62%, $\chi^2 = 5.1$, $P = .02$), respectively. In the 3-year study, age and medical factors that differed significantly between 132 subjects who participated in the study and 300 cancer survivors who did not participate were age (mean 44 years versus 46 years, $t = 3.7$, $P < .001$), presence of positive lymph node metastases (32% versus 43%, $\chi^2 = 4.9$, $P = .03$), poor histological grade (37% versus 49%, $\chi^2 = 4.9$, $P = .03$), and receiving hormonal therapy (35% versus 23%, $\chi^2 = 7.0$, $P = .01$), respectively.

TABLE 1
Demographic Information of Cancer Patients With and Without Adjuvant Chemotherapy, and Healthy Control Samples in the 1-Year and 3-Year Studies

	Sample 1 (1-Year study)			Sample 2 (3-Year study)		
	Patients		Healthy controls	Patients		Healthy controls
Characteristics	Adjuvant chemotherapy + (n = 51)	Adjuvant chemotherapy − (n = 54)	(n = 55)	Adjuvant chemotherapy + (n = 73)	Adjuvant chemotherapy − (n = 59)	(n = 37)
Age, mean ± SD, y	47.3 ± 5.2	46.3 ± 6.1	46.2 ± 6.7	48.2 ± 5.6	48.4 ± 4.8	48.0 ± 6.4
Handedness: right-handedness, no. (%)	51 (100)	51 (94.4)	51 (92.7)	73 (100)	55 (93.2)*	33 (89.2)
Height, mean ± SD, cm	155.0 ± 5.6	157.9 ± 5.8*	157.2 ± 5.0	156.4 ± 5.6	157.5 ± 6.0	156.6 ± 5.2
Weight, mean ± SD, kg	54.8 ± 6.6	56.9 ± 8.6	54.1 ± 7.9	55.1 ± 6.5	58.2 ± 8.7*	53.9 ± 8.0§
Education, mean ± SD, y	13.2 ± 1.7	13.2 ± 2.0	14.1 ± 1.9§	12.8 ± 1.7	13.2 ± 2.0	14.1 ± 1.7
Smoking, no. (%)	5 (9.8)	6 (11.1)	2 (3.6)	12 (16.4)	7 (11.9)	2 (5.4)
Accumulated alcohol consumption, mean ± SD, g × 10^3	27 ± 87	39 ± 59	29 ± 59	16 ± 42	47 ± 75†	38 ± 66
Postmenopausal, no. (%)	40 (78.4)	20 (37.0)†	16 (29.1)§	47 (64.4)	19 (32.2)†	15 (40.5)
Performance status: 0, no. (%)	30 (60.0)	43 (81.1)*	36 (97.3)§	67 (94.4)	57 (98.3)†	35 (97.2)
Clinical stage: 0–I, no. (%)	14 (27.5)	25 (46.3)*	NA	14 (19.2)	30 (50.8)†	NA
Lymphnode metastasis, positive, no. (%)	29 (56.9)	4 (7.4)†	NA	41 (56.2)	1 (1.7)†	NA
Histological type, no. (%)						
Carcinoma in situ	2 (3.9)	4 (7.4)	NA	1 (1.4)	4 (6.8)	NA
Invasive carcinoma	42 (82.4)	41 (75.9)	NA	61 (83.6)	49 (83.1)	NA
Special type	7 (13.7)	9 (16.7)	NA	11 (15.1)	6 (10.2)	NA
Histological grade: poor, no. (%)	21 (41.2)	7 (13.0)†	NA	36 (49.3)	13 (22.0)†	NA
Surgical type: partial mastectomy, no. (%)	25 (49.0)	32 (59.3)	NA	27 (37.0)	30 (50.8)	NA
Axillary lymphadectomy, no. (%)	42 (82.4)	28 (51.9)†	NA	68 (93.2)	43 (72.9)†	NA
Days after surgery, mean ± SD, d	345 ± 71	234 ± 103†	NA	1641 ± 360	1416 ± 316	NA
Protocol of adjuvant chemotherapy, no. (%)						
AC	3 (5.9)	NA	NA	15 (20.5)	NA	NA
CMF	40 (78.4)	NA	NA	37 (50.7)	NA	NA
EC	2 (3.9)	NA	NA	1 (1.4)	NA	NA
PTX	2 (3.9)	NA	NA	1 (1.4)	NA	NA
5-FU	0 (0)	NA	NA	9 (12.3)	NA	NA
5′-DFUR	0 (0)	NA	NA	1 (1.4)	NA	NA
HCFU	0 (0)	NA	NA	2 (2.7)	NA	NA
UFT	5 (9.8)	NA	NA	7 (9.6)	NA	NA
Days after adjuvant chemotherapy, mean ± SD, d	119 ± 47	NA	NA	1189 ± 359	NA	NA
Hormonal therapy	20 (39.2)	11 (20.4)*	NA	21 (28.8)	5 (8.5)†	NA
Radiation therapy, no. (%)	25 (49.0)	26 (48.1)	NA	23 (31.5)	19 (32.2)	NA
WMS-R index, mean ± SD						
Attention	99.4 ± 12.5	99.5 ± 11.5	99.6 ± 13.0	98.6 ± 10.4	103.0 ± 11.1*	NA
Verbal memory	96.9 ± 13.0	101.7 ± 14.5	99.2 ± 14.4	100.4 ± 15.6	103.3 ± 14.7	NA
Visual memory	101.9 ± 12.1	102.7 ± 11.4	101.4 ± 10.3	103.7 ± 10.4	104.1 ± 12.7	NA
Delayed recall	100.3 ± 10.4	102.5 ± 12.2	100.7 ± 12.6	103.9 ± 12.6	105.5 ± 11.5	NA
History of major depression, No. (%)	6 (11.8)	2 (3.7)	NA	20 (27.4)	8 (13.6)	0 (0)
History of PTSD, No. (%)	5 (9.8)	4 (7.4)	NA	5 (6.8)	2 (3.4)	0 (0)

NA indicates not applicable; PTSD, post-traumatic stress disorder; AC, regimen with doxorubicin and cyclophosphamide; CMF, regimen with cyclophosphamide, methotrexate and fluorouracil; EC, regimen with epirubicin and cyclophosphamide; PTX, paclitaxel; 5-FU, fluorouracil; 5′-DFUR, doxifluridine; HCFU, carmofur; UFT, tegafur/uracil; WMS-R, the Wechsler Memory Scale-Revised.

* Indicates significant difference ($P < .05$) between adjuvant chemotherapy group and no-adjuvant chemotherapy group.

† Indicates significant difference ($P < .01$) between adjuvant chemotherapy group and no-adjuvant chemotherapy group.

§ Indicates significant difference ($P < .01$) between cancer patients group and healthy control group.

medication taken within 1 month before participation in the study, 7) a history of substance abuse or dependence, 8) a family history of early dementia, 9) any physical symptoms that interfered with daily life, 10) possible dementia defined as a score of <24 on the Mini-Mental State Examination,[21,22] 11) a history of major depression and/or post-traumatic stress disorder (PTSD) before inspection for cancer diagnosis to exclude regional brain volume changes brought about by these disorders,[23] and 12) any contraindication to undergoing an MRI scan.

For the 3-year study, subjects were collected from the Follow-Up Database and the Long-Term-Survivor Database. From the Follow-Up Database, 105 subjects who participated in the 1-year study were asked to participate in the follow-up more than 2 years after their 1-year study.[16] Figure 1 indicates a summary of the recruitment of participants to the 1-year study and to the 3-year study.

We recruited healthy subjects, who lived in the same geographic areas as the patients, by using advertisements in the local newspaper. The inclusion and exclusion criteria were the same as those for cancer patients except for the requirement of a history of breast cancer surgery. Fifty-five healthy controls participated in the 1-year study. After 2 years, 37 of 55 healthy controls participated again in the 3-year study.

Neuropsychological Measurements

The Wechsler Memory Scale-Revised Japanese version was performed. The Wechsler Memory Scale-Revised (WMS-R),[24] a memory function scale validated in Japanese,[25,26] consists of indices of Attention/Concentration, Immediate Visual Memory, Immediate Verbal Memory, and Delayed Recall to estimate memory function. This scale is among the most generalized and widely used in the world.

Image Data Processing for Optimized Voxel-based Morphometry

MRI scans were conducted on a 1.5-tesla MRI unit (Signa Scanner, GE Medical Systems, Milwaukee, Wis), with 3-dimensional, spoiled gradient-recalled acquisition of 1.5-mm contiguous sections under the following conditions: field of view = 230 mm, matrix = 256 × 256 pixels, repetition time = 25 milliseconds, echo time = 5 milliseconds, and flip angle = 45°.[16]

The theory and algorithm of voxel-based morphometry (VBM) for Statistical Parametric Mapping 2 (SPM2) software (Wellcome Department of Cognitive Neurology, London, UK) have been well documented.[27] VBM was carried out by using an optimized method.[28] First, optimized study-specific template sets for the 1-year study and for the 3-year study comprising a T1 image and a priori gray matter, white matter, and cerebrospinal fluid images were created on the basis of brain images of participants in the 1-year study and the 3-year study, respectively. All scans were spatially normalized to customized templates, and then they were smoothed with an 8-mm, full-width half-maximum (FWHM) smoothing kernel, followed by averaging to create customized templates. Next, for the study group MRI scans, a brain extraction procedure that incorporated a segmentation step was used to remove nonbrain tissue from the MRI images.[28,29] Extracted gray matter and white matter images were normalized to the gray matter and white matter templates.[27,30] The normalization parameters were then reapplied to the original structural images to maximize optimal segmentation of fully normalized images, and these normalized images were segmented into gray matter/white matter and cerebrospinal fluid/noncerebrospinal fluid partitions.[31] Segmented images were modulated by the Jacobian determinants from spatial normalization to correct for volume changes that were introduced during nonlinear spatial transformations.[28] Finally, images were smoothed with a 12-mm FWHM kernel.[27,32]

Statistical Analysis

Student t test, Mann-Whitney U test, or χ^2 tests were used for comparison of background and medical factors. α levels were set at $P < .05$ (2-tailed).

By using SPM2, group differences in each of the gray matter and white matter scans were compared between the cancer patients exposed to their adjuvant chemotherapy and those unexposed, by using ANCOVA models, respectively, with age, alcohol consumption, intracranial volume, and background characteristics significantly different between these 2 groups (in the 1-year study, number of days after surgery and current hormonal therapy; in the 3-year study, handedness and current hormonal therapy) as nuisance variables. The intracranial volumes (sum of the gray matter, white matter, and cerebrospinal fluid volumes) were calculated from non-normalized segmented images during optimized-VBM preprocessing. Height and weight were not included as nuisance variables because intracranial volumes were modeled. Medical factors that seemed to be causes or results of adjuvant chemotherapy were not included as nuisance variables to avoid overmatching between the 2 groups. The groups were compared

using statistical *t*-test contrasts within SPM2. The distribution of morphological differences across each of the total gray matter or white matter was assessed initially on a voxel-by-voxel basis; clusters of over 400 voxels were used to suppress small clusters possibly arising by chance, and a threshold of $P < .001$ was used, uncorrected for multiple comparisons. Inference was centered on differences that achieved a significance of $P < .05$, after family-wise error correction for multiple comparisons.[33] In all analyses, we reported the Montreal Neurological Institute (MNI) coordinates of voxels of statistical significance.[34]

To see the effect of cancer on the brain structure as a reference, MRI scans of cancer survivors were compared with those of healthy controls, by using ANCOVA models with age, alcohol consumption, intracranial volume, and background characteristics significantly different between these 2 groups (in the 1-year study, year of education and menopausal state; in the 3-year study, no additional covariate) as nuisance variables.

For subanalyses, we examined the correlations between indices of the WMS-R and regional brain volume of the voxel where cancer survivors exposed to adjuvant chemotherapy had a significantly smaller brain region. Regional brain volumes of the voxels were calculated by using the region of interest (ROI) function in the SPM2 software as a substitution for the regional brain volume index.

RESULTS

Table 1 shows the background and medical factors of each group in both the 1-year study and the 3-year study. Eight percent of the survivors in the 1-year study and 8% of those in the 3-year study received tegafur and uracil (UFT) for <80 days. Ten percent of survivors in the 1-year study and 7% in the 3-year study received 5 of 6 cycles of their cyclophosphamide, methotrexate, and 5-fluorouracil regimen, and others completed their regimen in the 1-year study and in the 3-year study, respectively. In other cases, quantities of each of the administered chemotherapeutic agents complied with the protocols of each regimen.

The peak voxel coordinates of the smaller regions in cancer survivors exposed to adjuvant chemotherapy compared with those unexposed using corrected $P < .05$ are presented in Table 2. Figures 2 and 3 indicate superimposed images of the statistical *t* map (regional brain volume in cancer survivors exposed to adjuvant chemotherapy less than regional brain volume in those unexposed) on the template T1 image in the 1-year study. There was no significantly bigger region in cancer survivors exposed to adjuvant chemotherapy in the 1-year study. As an ad hoc analysis, we performed comparisons of gray matter and white matter between cancer survivors exposed to a cyclophosphamide, methotrexate, and 5-fluorouracil regimen (n = 40) and those unexposed to any adjuvant chemotherapy (n = 54). The distributions of regional brain volume difference were similar to those observed in the primary comparisons in the 1-year study (data not shown). There were no significantly smaller regions in gray matter and white matter when we used a corrected $P < .05$ in cancer survivors exposed to adjuvant chemotherapy in the 3-year study, as shown in Table 2.

In referential analyses, there were no significantly smaller or bigger regions in gray matter and white matter between cancer survivors and healthy controls in the 1-year study and in the 3-year study.

Table 3 indicates that significant correlations between memory functions and regional brain volumes

TABLE 2
Regions of Smaller Gray Matter and Nearest Gray Matter to Smaller White Matter in Breast Cancer Survivors With Adjuvant Chemotherapy Compared With Those Without Adjuvant Chemotherapy

	Coordinates of peak difference						
	x	y	z	Side	*t* score*	Corrected *P*	Region†
1-year study (3 to 15 months after breast cancer surgery)							
Gray matter	30	66	8	Right	4.77	.031	Middle frontal gyrus
	10	71	4	Right	4.73	.035	Superior frontal gyrus
	13	65	−12	Right	4.66	.045	Superior frontal gyrus
	21	−40	−11	Right	4.63	.048	Parahippocampal gyrus
White matter	−11	−60	64	Left	5.38	.005	Precuneus
	35	43	30	Right	5.12	.013	Middle frontal gyrus
	−13	−33	−5	Left	4.97	.023	Parahippocampal gyrus
	10	49	−1	Right	4.95	.025	Cingulate gyrus
	−10	49	44	Left	4.93	.026	Middle frontal gyrus
3-year study (27 to 39 months after breast cancer surgery)							
Gray matter							None
White matter							None

* All scores significant ($P < .05$) after family-wise error correction for multiple comparisons over each area of gray or white matter.
† Gray matter or nearest gray matter regions were indicated.

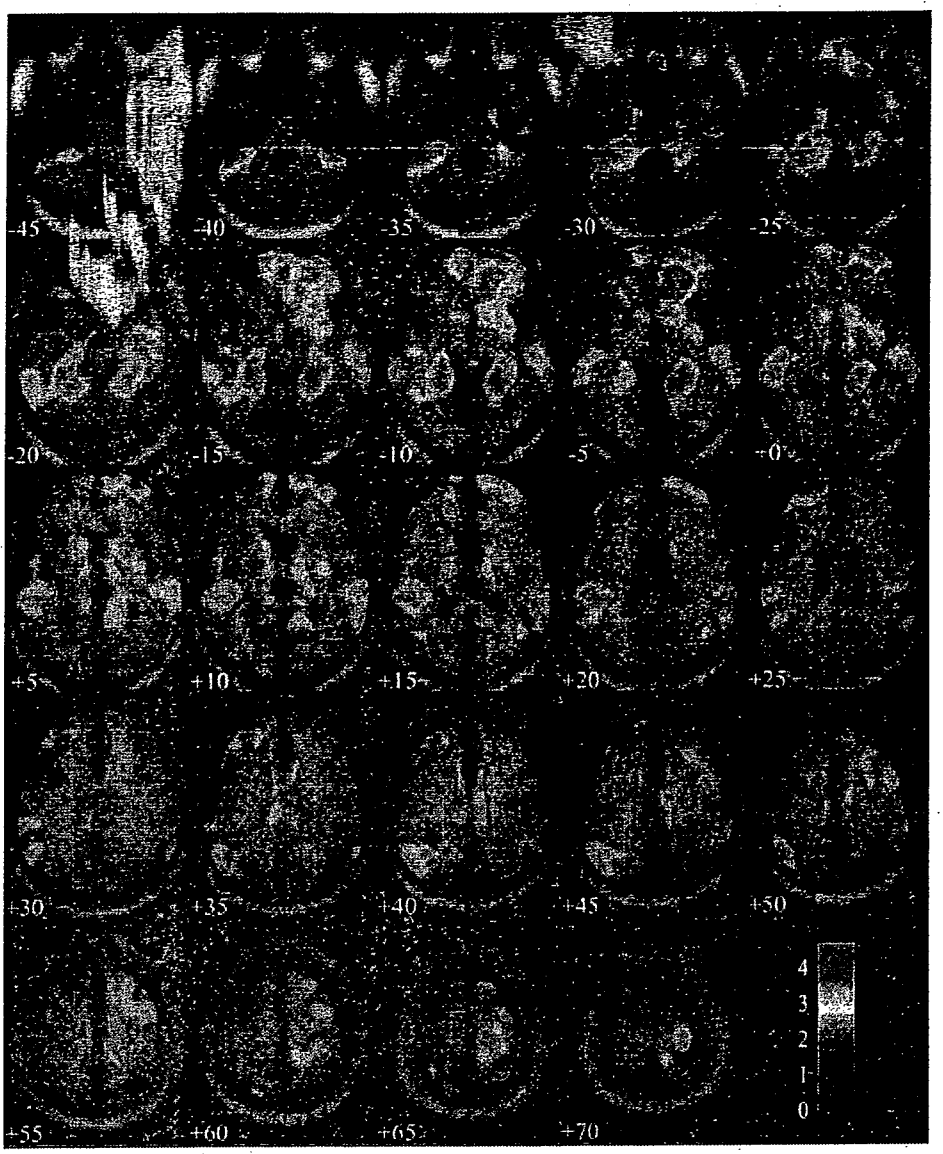

FIGURE 2. The superimposition of the *t*-value map of smaller gray matter in cancer survivors exposed to their adjuvant chemotherapy compared with those unexposed onto coronal slices of the customized T1 template image in the 1-year study. The color bar indicates the *t* value.

at the coordinates are significantly smaller in cancer survivors exposed to adjuvant chemotherapy in the 1-year study.

DISCUSSION

The current study showed smaller right prefrontal and parahippocampal gyrus in cancer survivors who were exposed to adjuvant chemotherapy before the mean of 4 months, compared with those unexposed. These volume differences were not found in cancer survivors at a mean of 4.2 years after completion of their adjuvant chemotherapy. In subanalyses, the volumes of the right superior frontal gyearus, 1 of the smaller regions in cancer survivors exposed to adjuvant chemotherapy, were associated with memory functions. These results indicate a potential effect of adjuvant chemotherapy on brain structure, and the change of the brain structure may be associated with memory function.

A previous report using VBM in 10 breast cancer and 2 lymphoma survivors (>5 years) exposed to chemotherapy showed smaller regional gray matter and cortical and subcortical white matter brain

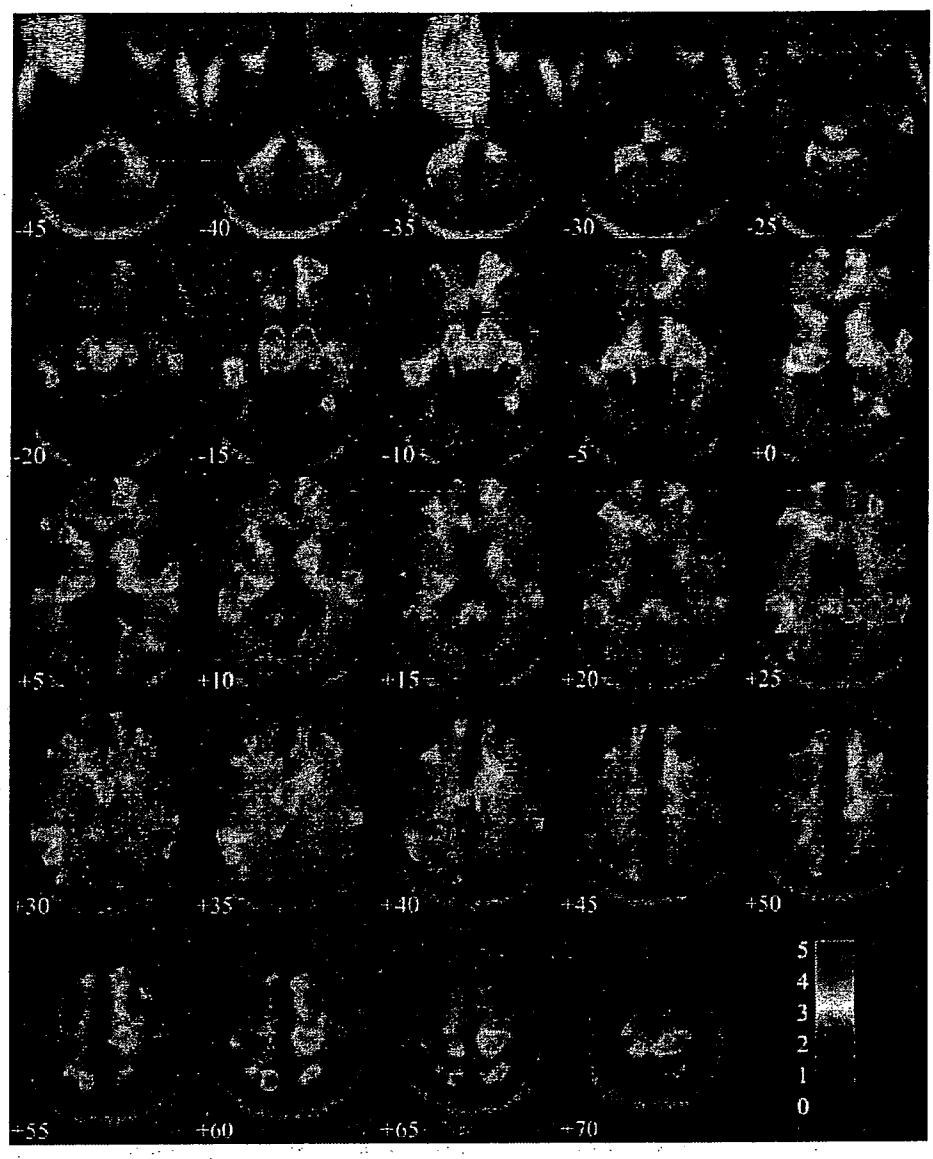

FIGURE 3. The superimposition of the *t*-value map of smaller white matter in cancer survivors exposed to their adjuvant chemotherapy compared with those unexposed onto coronal slices of the customized T1 template image in the 1-year study. The color bar indicates the *t* value.

regions compared with healthy controls.[10] Chemotherapeutic agents included in the previous report were similar to those in the current study. Contrary to results of the previous report, the results of the current study did not show any significant difference in regional brain volume as shown in the 3-year study. These findings were consistent with our previous study where we used a manual tracing method, which is a different method from the VBM, to measure regional brain volume.[16] That study indicated that there were no significantly smaller hippocampal and amygdalar volumes among breast cancer survivors who had survived >3 years since their surgery. This difference in results may be caused by differences in the methods, such as number and characteristics of subjects, comparisons with cancer survivors unexposed to chemotherapy, and/or use of corrections for multiple comparisons, as in the current study.

The current study indicated regional brain volume differences in the superior and middle frontal gyri, parahippocampal gyrus, cingulate gyrus, and

TABLE 3
Correlations Between Memory Functions and the Regional Brain Volume in the 1-Year Study

	x-y-z coordinate (Region)								
	Gray matter regions				White matter regions				
	30 66 8 (mFG)	10 71 4 (sFG)	13 65 −12 (sFG)	21 −40 11 (pHG)	11 60 64 (Pc)	35 43 30 (mFG)	13 33 −5 (pHG)	10 49−1 (CG)	−10 49 44 (mFG)
WMS-R index									
Attention/concentration	0.15	0.25*	0.08	0.12	0.21*	−0.03	0.06	0.09	0.12
Visual memory	0.10	0.24*	0.12	0.20*	0.13	−0.02	0.11	0.04	0.08
Verbal memory	−0.01	0.11	0.09	0.06	0.16	0.05	0.03	0.02	0.01
Delayed recall	−0.03	0.09	−0.01	−0.01	0.13	−0.02	−0.02	−0.08	−0.08

WMS-R indicates the Wechsler Memory Scale-Revised; mFG, middle frontal gyrus; sFG, superior frontal gyrus; pHG, parahippocampal gyrus; Pc, precuneus; CG, cingulate gyrus. Data indicate *r* value of the Pearson correlation test.

* Indicates significant association ($P < .05$).

precuneus. The significantly smaller volume of the superior frontal gyrus in the current study was correlated with the attention/concentration and visual memory indices of the WMS-R. The prefrontal cortex, including superior and middle frontal gyri, has been reported to have roles in various functions including memory, planning, execution, monitoring of cognitive processing and behavior, and inhibition and change in circumstantial behavior.[35] Not all, but many, of the studies in cancer survivors exposed to adjuvant chemotherapy have reported impairments in various cognitive domains including attention/concentration and visual memory functions.[3–6] The structural differences of the superior and middle prefrontal gyrus may partly account for some of the previously reported cognitive impairments and complaints referred to as "chemobrain". A previous positron emission tomography study of breast cancer survivors in whom the researchers had found significant neurocognitive changes associated with adjuvant chemotherapy, including impairment of verbal learning, demonstrated hypometabolism in the superior frontal gyearus. In addition to the prefrontal cortex, the parahippocampal gyrus is associated with cognitive functions, such as memory function.[36] Recently, the precuneus was also thought to have important roles in self-centered mental imagery strategies and episodic memory retrieval,[37] and these concepts lead us to suppose the potential engagement of structural changes in these brain regions in cognitive impairments caused by adjuvant chemotherapy.

The distribution of the regional brain volume differences observed in the 1-year study did not reappear in the 3-year study. Results from the 1-year and 3-year studies can lead us to speculate that the brain volume change related to adjuvant chemotherapy may well recover over the course of time. Although a previous report showed cognitive impairments in cancer survivors even after a long period following completion of adjuvant chemotherapy,[17] several longitudinal studies[18–20] and a review article[4] have demonstrated recovery from cognitive impairment in breast cancer survivors exposed to adjuvant chemotherapy. Regional brain structural changes and cognitive impairments observed in cancer survivors exposed to adjuvant chemotherapy may recover in time.

In reference comparisons between cancer survivors and healthy controls both in the 1-year study and in the 3-year study, there were no significant differences in regional brain volume. These results support the idea that cancer had little influence on the main analyses of the current study. We did not include healthy controls in the primary comparisons. We did not make a model, such as a 2-factorial ANCOVA in which 1 factor is cancer survivors versus healthy controls and the other factor is whether chemotherapy was received or not, because of the lack of any healthy controls exposed to adjuvant chemotherapy.

The current study has several limitations. 1) Background and medical factors were entered into statistical models as nuisance variables, and medical factors usually used to judge the application of adjuvant chemotherapy and factors reported as a result of adjuvant chemotherapy were not entered to avoid overadjustment. Given potential biases, results need to be interpreted with caution. 2) Effects of each regimen or each chemotherapeutic agent on regional brain volumes were unclear. 3) Pathophysiological mechanisms of volume differences were unclear. The

other reason we did not explore effects of each chemotherapeutic agent in the study setting was that interactions between each chemotherapeutic agent may exist and may make our inference difficult. 4) The VBM has several limitations. A method with higher sensitivity, such as a manual tracing method like those reported previously,[16] should be used. 5) The current study did not have any specific functional targets related to each of the detected regions. Functions related to brain regions significantly different in volume from those in the current study need to be examined by using specific neuropsychological tasks and neuroimaging of brain function.

In conclusion, the current study showed significantly smaller regional brain volumes in areas related to cognitive functions in cancer survivors who received adjuvant chemotherapy. The smaller regional brain volumes were not observed at more than 3 years after completion of adjuvant chemotherapy. Results lead to the idea that adjuvant chemotherapy could have a temporary effect on brain structure. These findings can provide new insights for future research to improve the quality of life of cancer patients who receive adjuvant chemotherapy.

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Mental health literacy in Japanese cancer patients: Ability to recognize depression and preferences of treatments—comparison with Japanese lay public

Toru Okuyama[1,2]*, Yoshibumi Nakane[3], Chiharu Endo[1,2], Takashi Seto[4], Masashi Kato[2], Nobuhiko Seki[4], Tatsuo Akechi[1], Toshiaki A. Furukawa[1], Kenji Eguchi[5] and Takashi Hosaka[2]

[1] Department of Psychiatry and Cognitive-behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Japan
[2] Course of Specialized Clinical Care, Psychiatry, Tokai University School of Medicine, Japan
[3] Department of Social Science, Nagasaki International University, Japan
[4] Course of Internal Medicine, Medical Oncology, Tokai University School of Medicine, Japan
[5] Oncology Center, Tokai University School of Medicine, Japan

*Correspondence to: Department of Psychiatry and Cognitive-behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601 Japan. E-mail: okuyama@med.nagoya-cu.ac.jp

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Abstract

***Background*: Insufficient knowledge about mental illness and its treatment has been shown to constitute a major barrier to its adequate care for mental illness in the lay public (LP). We therefore examined Japanese cancer patients' (CP) ability to recognize depression and their preferences of its treatments.**

***Participants and Method*: One hundred lung CP and 300 LP were selected at random to participate in the study. Structured interviews using a vignette of a person with both cancer and depression were conducted with CP, and those using a vignette of a person with depression were carried out with LP, respectively.**

***Results*: Only 11% of CP recognized the presence of depression in the vignette, while 25% of LP did ($p<0.001$). There were few significant differences in the preference for standard psychiatric treatments between CP and LP: standard treatments such as antidepressants (CP: 39%, LP: 36%) were less often rated as helpful, whereas non-standard treatments such as physical activity (CP: 85%, LP: 66%) were most often rated as helpful.**

***Conclusions*: The results indicated that cancer patients' knowledge about mental illness and its treatment were insufficient. Psychological education may reduce patient-related barriers to seek and to utilize optimal mental health care in cancer patients.**

Keywords: depression; cancer; stigma; psychiatry; oncology

Introduction

Serious physical illness such as cancer often causes psychological distress, and its psychological impact on patients has been one of the important aspects of clinical oncology. The prevalence of depression among cancer patients has been reported 15–25 %, although there is variability in prevalence depending on the subject characteristics such as cancer phase and method used to assess depression [1]. Since depression is not only emotionally distressing but also reduces the sufferers' quality of life, causes family burden and increases usage of health care, provision of appropriate treatment is indispensable [2].

However, psychological distress including depression is often under-recognized and under-treated in cancer patients [1,3–5]. This problem has been reported repeatedly in primary care. The National Depressive and Manic-Depressive Association (NDMDA) Consensus Statement on the Under-Treatment of Depression categorized barriers to under-treatment of depression into patient factors (underestimation by themselves, limited access to treatment, preference for and adherence to treatments), provider factors (insufficient education about depression diagnosis and treatment in medical schools and postgraduate education program, limited training in the interpersonal skills to manage emotional distress, lack of time, and so on), and health care barriers (lack of adequate insurance, poor collaboration among different types of providers, and so on) [6].

In the cancer setting, provider factors regarding under-estimation and under-treatment of depression have been recognized [3,5,7]. In our understanding, however, few studies have reported patient factors in cancer patients. Cancer patients may have more difficulty in recognizing depression for several reasons. They may think that depression

is a natural emotion, or that somatic symptoms associated with depression may be attributed to the underlying cancer itself. With regard to psychological care, cancer patients may find it more familiar than the lay public does, since the concept of palliative care has been spreading gradually both in cancer patients and in medical staffs in Japan, and cancer patients must be more familiar with hospital services. On the other hand, cancer patients may be reluctant to see psychiatrists. Shimizu *et al.* reported that only 28% of depressed inpatients with cancer, screened by nurses, accepted psychiatric referral [8].

Mental health literacy has been defined as the ability to gain access to, understand, and use information in ways which promote and maintain good mental health [9]. This concept includes the ability to recognize the presence of mental illness and to utilize various types of professional help or treatments. Low mental health literacy is one of the core issues of patient-related barriers to treatment. Some studies have reported only 30–40% of the lay public can recognize depression accurately [9,10]. Other studies reported many of the lay public believe that standard depression treatment is not so effective [11].

Mental health literacy may be influenced by different cultures. A previous study, conducted by Jorm and Nakane, investigated the difference in mental health literacy between members of the Australian and Japanese lay public using the same methodology as applied in this study (described below) [12]. They found that Japanese people were less likely to recognize depression in a vignette (23% in Japanese, 65% in Australian), and less likely to discuss mental disorders with others outside the family, and are less optimistic about full recovery. On the other hand, attitudes toward standard psychiatric treatments were not so different. About two-third of each groups rated psychiatrist as helpful, but less than half of them rated taking antidepressants or psychotherapy as helpful, and less than 20% of them rated admission to the psychiatric ward as helpful.

In summary, there are likely to be various barriers which prevent adequate psychological care in cancer patients. Although patient related barriers are important to understand their help-seeking behavior, few studies have focused on this issue. The purpose of this study is to assess the Japanese cancer patients' (CP) ability to recognize depression and their preferences of its treatments, and to compare them with those of the lay public (LP).

Participants

Cancer patients (CP)

Patients with lung cancer were randomly sampled at the outpatient clinic of the Respiratory Medicine Division of the Tokai University Hospital, Japan. The eligibility criteria for patients were (a) age of 18 or older, (b) have been informed of the cancer diagnosis, (c) to be well enough to complete the questionnaires and participate in a brief interview, and (d) not to be suffering from severe mental or cognitive disorders.

Lay public (LP)

A part of the existing data from the Australia–Japan Survey of Mental Health Literacy was used for this study [12]. In summary a household survey was carried out of Japanese adults aged 20–69 years by research companies under the conduct of the second author (Y.N.). Home-visit sampling and interviews were conducted in 25 districts covering both metropolitan and rural areas. Also stratified sampling method by age and sex was used. A total of 1000 people participated in the study using the depression vignette described below. Study method has been described in detail elsewhere [12]. Data from all participants aged 40 or over were used in this study, to approximate the average age of LP group to the CP group.

This study was approved by the Institutional Review Board and the Ethics Committee of the Tokai University, Japan. Full written informed consent was obtained from each patient after full explanation of the study.

Methods

A structured interview using depression vignette, developed by Jorm *et al.* was conducted [9]. The original version in English was translated into Japanese using forward–backward translation, and same structured interview was conducted in both groups.

The original vignette was used in the LP group. We modified this vignette for use in the CP group to approximate the vignette to a typical cancer patient. As a result, the vignette for use in the CP group has cancer, and is 65 years old, which is the average age of onset of lung cancer in Japan. Otherwise, the two vignettes have the same depressive symptoms, which satisfy the diagnostic criteria for major depression. In both group, participants were randomly assigned to receive either the male or female version of the vignette. Pilot survey using this modified vignette was conducted of 10 lung cancer patients. The interviews with cancer patients were conducted by the third author (C.E.) in a separate room which ensured privacy in our hospital.

Vignette for LP (male version): Mr. A is 30 years old. He has been feeling unusually sad and miserable for the last few weeks. Even though he is tired all the time, he has trouble sleeping

Table I. Subject demographics

	Cancer patients $N=100$	%	Lay public $N=300$	%	p-value
Age	66 ± 10		N/A		
40–49	7	7	100	33	<0.001
50–59	14	14	100	33	
60–69	43	43	100	33	
70–	36	36	0	0	
Female	20	20	150	50	<0.001
Having spouse	78	78	262	87	0.02
> 10 years education	70	70	262	89	<0.001
Advanced cancer (IIIb, IV, or recurrence)	77	77	—	—	
Having metastasis	50	50	—	—	
ECOG* performance status 2 or worse	6	6	—	—	

*ECOG: Eastern Cooperative Oncology Group.
N/A: not available.

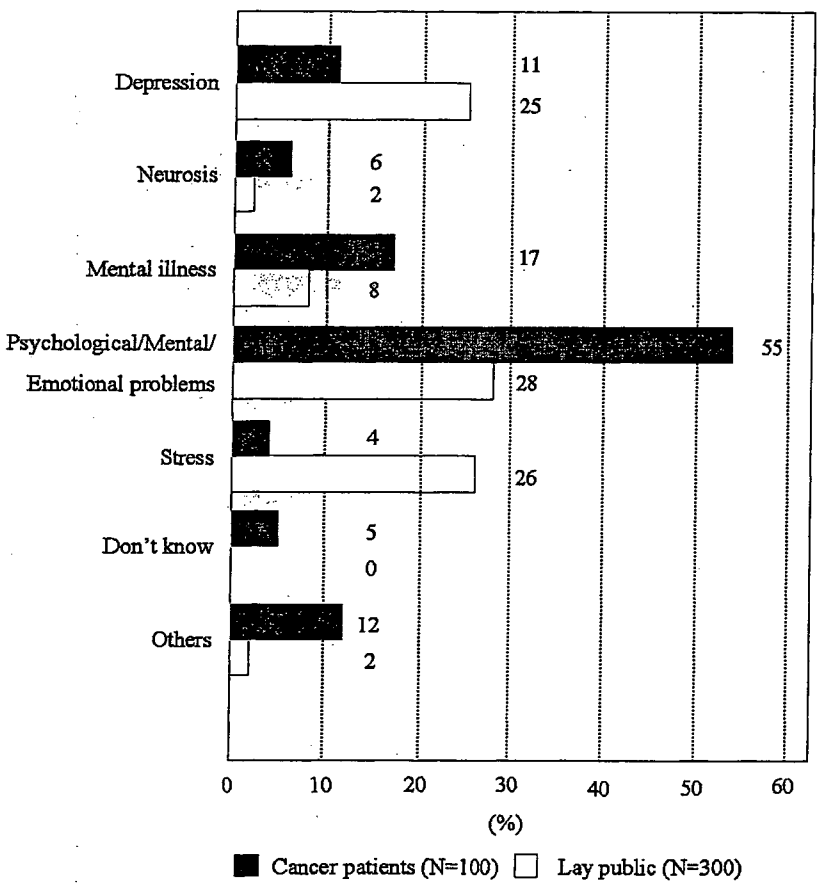

Figure 1. Participants' recognition of the problem in the vignette. Eleven percent of CP recognized the presence of depression in the vignette, while 25% of LP did ($p<0.001$, Chi-square test)

pharmacist, and naturopath/herbalist as helpful (Figure 2).

Rating of pharmacological treatments

There were no significant differences in the rating of psychotropics such as antidepressants, hypnotics, antipsychotics, and tranquilizers between the groups. CP significantly more often rated vitamins/minerals, pain relievers, and antibiotics as helpful (Figure 3).

Rating of non-pharmacological treatments

CP significantly more often rated lifestyle intervention such as exercise and getting out more as helpful than LP did. Again, there were no significant differences in the rating of standard psychiatric treatment such as admission to the

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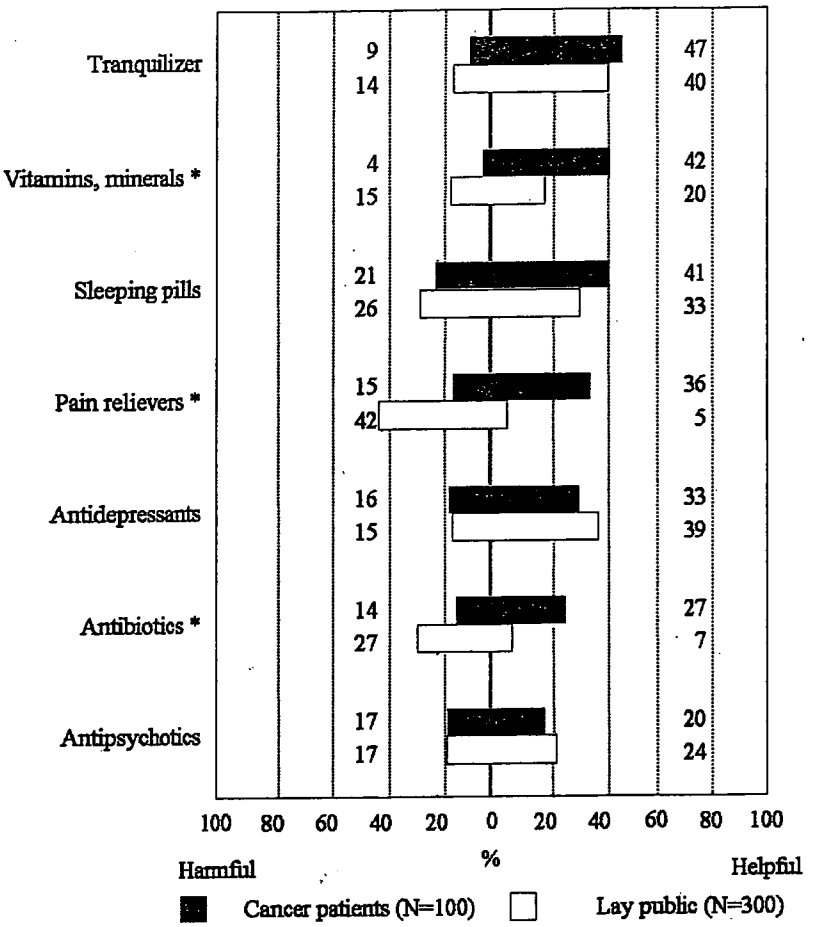

Figure 3. Proportion of participants who rated various pharmacological treatments harmful or helpful (* significant difference between CP and LP ($p<0.007$)). There were no significant differences in the rating of psychotropics such as antidepressants, hypnotics, antipsychotics, and tranquilizers between the groups

recovery went up to 97% in both group. In both instance, there were no significant difference in the belief of the vignette's outcome between CP and LP.

Discussion

A recent intensive review reports that many studies consistently found that lay public tend to under-recognize mental illness, and to think psychological intervention favorable than pharmacotherapy. That also points out that few attitude researches have not been carried out among other populations, including patients with somatic illness [13]. This is the first study which has investigated mental health literacy in patients with cancer, compared with the lay public. Our results revealed that: (1) CP had more difficulty in recognizing depression in the vignette than did the lay public; (2) there were few significant differences in preference of standard depression treatments between CP and LP: non-standard treatments were frequently more often rated as helpful compared with standard treatments.

Recognition of depression in CP is poor, as we had expected. Since about half of cancer patients mentioned 'emotional problems', cancer patients tend to consider depression as a "reactive" emotional state. Or cancer patients might have difficulty in recognizing depression because they, as well as medical professionals [14], attribute physical symptoms such as appetite loss and fatigue in the vignette to cancer itself. The original Australia–Japan Survey of Mental Health Literacy study reported 65% of the Australian lay public could recognize 'depression' [12]. In view of this result, there must be much room to improve the recognition of depression by providing psychosocial education in Japan.

When asked about various possible helpful approaches, we could find few statistical differences in the preference for the psychiatric standard treatments between CP and LP; standard treatments such as antidepressants were less often rated as helpful, whereas non-standard treatments such as physical activity were most often rated as helpful. The interesting finding in CP is that endorsement of standard psychiatric treatments was not correlated with recognition of psychiatric treatments. It would be influenced certain beliefs which act as a barrier to the utilization of these psychiatric treatments. We investigated such beliefs in this study and will report their details elsewhere.

When asked about medications, CP favored pain relievers and antibiotics significantly more often than LP did. Patients might think the vignettes condition may be caused by underlying pain or physical problem. They additionally favored vitamins and minerals to alleviate psychological distress. The difference may be explained by the familiarity of CP to complementally and alternative medicine (CAM): a nation wide study reported the prevalence of CAM users among Japanese cancer patients as 44.6%, and the proportion is greater than patients with benign tumors (22.5%) [19].

When asked about non-pharmacological treatments, both gave the highest rate of endorsement to lifestyle interventions such as physical activity, getting out more, although CP preferred them more than did LP. Cancer patients may be more conscious about a "healthy" lifestyle.

This study had several limitations. First, any reliability data on the interview had not been examined in the study. But this interview was highly structured and included no open questions. Second, the demographical characteristics of the two groups were significantly different, although there is no consistent knowledge about the association between mental health literacy and epidemiological characteristics. Third only outpatients with lung cancer were included in the CP group. Attention should be paid when applying the results of this study to patients with different characteristics.

Despite these limitations, our results indicate that mental health literacy in Japanese lung cancer patients is insufficient, and may be one of the major barriers to accessing adequate psychological care. It must be helpful to reduce such barriers by providing information regarding psychological problems frequently seen in cancer patients and providing support strategies to decrease such distress. In addition, medical professionals should understand their patients' needs for, and preferences towards psychological care, and should provide interventions which really meet the needs. Further research is also needed to investigate provider-related and health system-related barriers to the psychological care in cancer patients. An integrated approach to reduce these 3 aspects of the afore-mentioned barriers to accessing appropriate psychological care would surely be fruitful in achieving improvement of the psychological aspect of cancer medicine, and would therefore contribute to a patients' better quality of life for cancer patients.

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All of the authors declare that we have no financial and proprietary interest in the subject matter or materials.

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The differential impact of executive attention dysfunction on episodic memory in obsessive-compulsive disorder patients with checking symptoms vs. those with washing symptoms

Ichiro M. Omori [a,b], Yoshie Murata [a], Tomoaki Yamanishi [a], Shutaro Nakaaki [a,*], Tatsuo Akechi [a], Masahiko Mikuni [b], Toshiaki A. Furukawa [a]

[a] *Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan*
[b] *Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, Showa-machi, Maebashi, Gunma 371-8511, Japan*

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Abstract

Neuropsychological studies of obsessive-compulsive disorder (OCD) have pointed to memory and attention deficits among its sufferers, but these reports have largely ignored the possibility that cognitive disturbances may vary across OCD clinical subtypes, or that their interactions may differ between subtypes. The purpose of the present study was to determine whether 'checkers' and 'washers' demonstrate differences in their memory and executive attention function. Fifty-three outpatients with primary DSM-IV diagnosis of OCD with typical checking ($n = 27$) or washing ($n = 26$) rituals participated in the study. Patients were administered the Wechsler Memory Scale-Revised and a comprehensive neuropsychological battery to assess executive attention function. Various neuropsychological tests were then subjected to factor analysis. Neuropsychological test results and obtained factor scores were compared between 'washers' and 'checkers'. Effects of these factor scores on memory by OCD subtypes were examined. No significant difference in terms of demographic and clinical variables was found between the two groups. Checkers displayed performance deficits on Stroop test, Trail Making Test, GO/NO GO test (commission errors) and category fluency. Three factors, inhibition, cognitive flexibility, and multi-tasking, were obtained. Statistically significant differences were observed between the two groups on the inhibition and the cognitive flexibility scores, but not on the general memory or the multi-tasking score. There was a statistically significant interaction between groups and the inhibition score. Only among 'checkers', a significant correlation was noted between the inhibition factor and the general memory, while no such correlation was observed among 'washers'. Among 'checkers', poor general memory was related to inhibition deficits.

Keywords: OCD; Clinical subtype; Neuropsychology; Executive attention function; General memory; Inhibition

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by obsessions and compulsions that are severe enough to interfere with daily functioning and cause significant distress (American Psychiatric Association, 1994). Obsessions are defined as persistent thoughts, impulses or ideas that are experienced as inappropriate and that generate anxiety or distress. Compulsions are defined as repetitive behaviors or mental acts that are typically performed in an attempt to relieve the distress brought on by the obsessions. The two most common types of compulsions are checking compulsions, in which individuals repeatedly check to see if they have correctly completed an activity, and washing compulsions, in which individuals repeatedly wash themselves.

There is substantial evidence that OCD has been associated with brain dysfunction and cognitive abnormalities (Chamberlain et al., 2005). Neural systems involved in OCD have been identified with the use of functional

* Corresponding author. Tel.: +81 52 853 8271; fax: +81 52 852 0837.
E-mail address: hzi05510@nifty.com (S. Nakaaki).

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neuroimaging methods, such as positron emission tomography (PET) (Baxter et al., 1987; Swedo et al., 1989), single photon emission computed tomography (SPECT) (Machlin et al., 1991; Busatto et al., 2000) and functional magnetic resonance imaging (f-MRI) (Pujol et al., 1999; Ursu et al., 2003). These studies have provided consistent evidence of increased and/or decreased activity in local regions such as the anterior cingulate cortex, the orbitofrontal cortex (OFC) and the caudate nucleus.

Further evidence of frontal-striatal dysfunction comes from studies noting an association between OCD or OCD-like behavior and neurologic disorders, such as Parkinson disease (Daniele et al., 1997), Gilles de la Tourette syndrome (Como et al., 2005), Huntington disease (Cummings and Cunningham, 1992) and frontal lobe injury (Donovan and Barry, 1994; Berthier et al., 1996).

These findings, taken together, have led investigators to hypothesize that OCD subjects have specific neuropsychological deficits related to changes in brain function and these deficits exacerbate and/or maintain symptoms. Many studies have examined memory and executive attention function in OCD. However results of these studies were frequently inconsistent. Several studies have found that OCD patients have selective neuropsychological deficits in executive attention function, verbal and non verbal memory, and visuospatial and visuoconstructial skills (Kuelz et al., 2004; Muller and Roberts, 2005). A number of studies have also investigated interrelations between different neuropsychological variables in OCD and these found that impaired use of organization strategies may also contribute to memory dysfunction (Savage et al., 1999, 2000). On the other hand, some studies found no evidence of neuropsychological deficits in OCD (Abbruzzese et al., 1995; Simpson et al., 2006).

OCD is a heterogeneous condition that is likely composed of multiple clinical subtypes that are unique in terms of their etiological pathways and their psychological correlates (McKay et al., 2004). Nonetheless previous work on neuropsychological deficits has largely ignored the possibility that cognitive disturbances may vary across subtypes, and the possibility that their interactions may differ between subtypes.

We therefore set out to compare the neuropsychological performance in the domains of memory, executive attention function among checkers and washers, and to evaluate the mediating effects of executive attention function on memory in OCD.

2. Methods

2.1. Subjects

Study patients were consecutive Japanese patients with OCD who attended the outpatient clinic at the Nagoya City University Hospital between October 2001 and June 2005. Diagnosis was made on the basis of a structured interview by trained psychiatrists using the structured Clinical Interview for DSM-IV Patient Version (SCID-P). Participants had to be between 18 and 55 years of age. Exclusion criteria were current or past neurological or other significant medical illness, current or past substance dependence, current or past psychiatric disorder including schizophrenia, mood disorder or anxiety disorder other than OCD, mental retardation and pregnancy. Because depressive mood and anxiety could interfere with neuropsychological performance, Beck Depression Inventory-II (Beck et al., 1996) and State-Trait Anxiety Inventory (Spielberger et al., 1970) were administered.

Severity of OCD was assessed with the clinician-rated 10-item Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a,b).

In order to compare the medication dosage of different drugs prescribed for the patients, the equivalence of each drug was calculated in accordance with the advice of previous study (Bollini et al., 1999), as follows by standardizing the recommended therapeutic doses with respect to the recommended dose of clomipramine (150 mg/day). For instance, fluvoxamine, whose therapeutic daily dosage is 150 mg, was considered equivalent to clomipramine. The therapeutic daily dosage for paroxetine was 30 mg and so the prescribed dosage was multiplied by five.

The study was approved by the Ethics Committee of Nagoya City University Medical School and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before enrollment into this study.

2.2. Definition of clinical subtypes of OCD

To compare neuropsychological deficits between 'pure checkers' and 'pure washers', we defined clinical subtypes of OCD as follows. First, we ascertained OCD symptoms using the Y-BOCS symptom check list (Goodman et al., 1989a,b), a comprehensive list with examples of the most common obsessions and compulsions organized into 13 categories (seven obsessions; aggressive, contamination, sexual, hoarding, religious, symmetry, somatic. Six compulsions; cleaning, checking, repeating, counting, ordering, hoarding). Five symptom dimensions of these 13 categories were identified in a previous study (Mataix-Cols et al., 1999), namely contamination/cleaning, aggressive/checking, symmetry/ordering, hoarding, and sexual/religious. In this study, we quantified responses on each of the 13 major categories in accordance with the advice of previous study (Mataix-Cols et al., 1999) as follows: 0 (absent) = patient did not have any of the symptoms under that category; 1 (mild) = patient had at least one of the symptoms under that category, but it was not considered as major problem; 2 (major problem) = at least one of the symptoms in that category was considered as major problem. Subsequently we determined the patient's score on each dimension by the highest score for any of the symptom categories comprising that dimension.

We considered patients to be checkers if they obtained a score of 2 on the aggressive/checking dimension, and to be washers if they obtained a score of 2 on the contamination/cleaning dimension. To compare 'pure checkers' and 'pure washers', we excluded patients from this study with the following types of symptoms: (1) coexistence of both aggressive/checking and contamination/cleaning as major problem or symptom and (2) existence of hoarding, and/or sexual/religious obsessions, and/or symmetry/ordering as the major problem.

In order to confirm our clinical subtyping, we also employed the Maudsley Obsessional-Compulsive Inventory (MOCI) (Hodgson and Rachman, 1977), widely used and considered to be a sound self-report instrument for assessing the existence and extent of different symptoms of OCD (checking, washing, slowness, doubt).

2.3. Neuropsychological tests

All the subjects were administered commonly used neuropsychological tests, that have shown discrepant results or no differences between OCD subjects and controls in prior studies (Kuelz et al., 2004; Muller and Roberts, 2005), to assess the episodic memory and executive attention function.

All the tests have been standardized in Japanese. The entire battery took between 3 and 4 h altogether and was administered in one day with an appropriate break if the subject asked for it, and tests were given in the same order to all subjects. The trained examiner who administered the battery was blinded to the clinical assessment (including symptom severity and clinical subtypes).

A description of the tests follows.

2.3.1. Episodic memory

2.3.1.1. Wechsler Memory Scale-Revised (WMS-R). WMS-R was originally developed by Wechsler (Wechsler, 1987) and is accepted as a comprehensive measure of memory. The test measures immediate and delayed verbal and visual memory and also attention/concentration. The weighted sum scores of general memory of the WMS-R were used for analysis.

2.3.2. Executive attention function

2.3.2.1. Stroop test. The Stroop test (Golden, 1978) is used to assess capacity for action monitoring function. In this test, subjects were asked to report the color of the ink in which a color name is printed (the characters are printed in a color different than the color name). The time taken to complete the reporting and the number of incorrect color names are recorded and used for analysis. We used the Chinese character version (Kato, 2001).

2.3.2.2. Trail Making Test (TMT A and B). During Part A of the Trail Making Test (Reitan, 1958), subjects were instructed to quickly connect 25 numbered circles (1–25) randomly distributed over a paper without lifting the pencil from the paper. During Part B, subjects were required to connect 25 circles which contain numbers (1–13) or Japanese characters (the first 12 in the Japanese alphabet) and must sequentially alternate between numbers and characters. Time to completion was measured for each part. In order to remove the speed element from the test evaluation, we used a subtracted time (TMT B – TMT A) as the dependent measure.

2.3.2.3. GO/NO GO test. This test examines the ability to attend and respond to relevant targets while inhibiting responses to distracters (Bannon et al., 2002). We used the computer program (Superlab Pro 2.0). All the stimuli were presented on the center of a computer screen in a quiet room, and all the responses were recorded by the computer. Subjects were presented with circles of two different colors (red, green) on the computer screen. This test was conducted under two different conditions. In the first condition, 100 stimuli were presented. During this block, subjects were instructed to press the mouse key (GO stimuli) when the red color circle appeared and to withhold a response (NO GO stimuli) when the green color circle appeared on the screen. In the second condition, during the next 100 stimuli, subjects were instructed to press the mouse key when the green color circle appeared and to withhold a response when the red color circle appeared on the screen. The green color or red color stimuli were presented at random during each condition. The results were expressed as the percentage of omission errors for the GO stimuli, and percentage of commission errors for the NO GO stimuli.

2.3.2.4. Letter fluency. The subject was asked to say as many words as possible that begin with a specific letter (A, Fu), excluding proper nouns, numbers, and the same word with a different suffix, within 1 min (Baldo and Shimamura, 1998). Total number of words produced was the dependent measure.

2.3.2.5. Category fluency. The subject was asked to say as many words as possible that belong to a specific category (animals, vegetables) within 1 min (Baldo and Shimamura, 1998). Total number of words produced was the dependent measure.

2.3.2.6. WAIS-R digit symbol sub-tests. The Wechsler Adult Intelligent Scales-Revised (WAIS-R) (Wechsler, 1981) is actually a test battery since each test within the scale assesses specific aspects of cognition and can be used independently from other tests in the battery. We used digit symbol sub-tests to measure attention performance.

2.3.2.7. Wisconsin card sorting test (WCST). This widely used test was devised to assess the frontal lobe function (Heaton et al., 1993). Four stimulus cards with symbols differing in color, shape and number are placed in front of the subject who is given a pack of 128 response cards. The

subject is instructed to place each response card under one of the four stimulus card and is told that the examiner will say if the coupling criterion is right or wrong. The indices considered for the test evaluation are as follows: (1) perseverative errors; a perseverative error is one in which the subject continuous to sort the card in the same way after examiner says the card is wrong or change criteria. (2) Categories achieved; numbers of categories achieved by the subject.

2.3.2.8. Dual task (pencil-and-paper version). The mu index calculated from this test is used to assess multi-tasking (Baddeley et al., 1997). In this test, the highest level of Foreword Digit Span is determined first by strings of digits. Then, in one single-task condition, the subjects are presented with lists of digits at their own span for 2 min. Performance was therefore measured by the percentage of sequences correctly repeated. In another single-task condition, a trail of boxes is presented and the subjects are required to cross out each of the boxes within 2 min. In the dual-task condition, the subjects are to perform both of the aforementioned tasks simultaneously within 2 min. The subject's capability is expressed as mu score, which is calculated as follows: $mu = \{1 - (pm + pt)/2\} * 100$, where pm corresponds to the difference between the proportion of the lists recalled under single and the dual-task condition, and pt is calculated using formula $pt = (ts - td)/ts$; in this latter formula, ts represents the number of boxes crossed out under the single-task condition, and td the number of boxes crossed out under the dual-task condition. Score under 100 indicate impairment.

2.4. Statistical analysis

We used SPSS 11.5 (SPSS Inc., 2002) for statistical analyses. Group differences in demographics and clinical characteristics were analyzed using independent samples *t* tests. Group differences in categorical variables were examined with χ^2 tests. Neuropsychological tests to assess the episodic memory and executive attention function were compared between groups using independent samples *t* tests. Statistical tests were two-tailed, and *P* values <.05 were considered significant. Corrections for multiple comparisons were not made to avoid missing potential effects.

A comprehensive neuropsychological test battery comprises a large number of tests whose interrelationships are not self-evident. Moreover, comparing the two groups according to each individual test risks inflation of type I error due to multiple comparison. To identify underlying variables that explain the pattern of correlations within executive attention deficits, and to identify a small number of factors that explain most of the variance observed in a much larger number of manifest variables, various neuropsychological tests for executive attention function were subjected to factor analysis (maximum-likelihood method). We used Kaiser's criterion (Eigenvalues greater than 1) and Cattel's Scree test to determine the number of factors to extract. The initial factor solutions were then subjected to Promax rotation in order to facilitate their interpretation.

Factor scores were computed for the retained factors and were compared between 'washers' and 'checkers'. Effects of these factor scores on general memory by OCD subtypes were examined by analysis of covariance. The correlation between factor scores and general memory was determined using Pearson's correlation coefficient. All tests used two-tailed comparisons with significance level set at $P < .05$.

3. Results

3.1. Patients

There were no significant differences in age, gender, handedness, years of education, duration of illness, medication dosage (mg/day clomipramne equivalent), severity of depression and anxiety and severity of OCD symptoms between the checkers and the washers (Table 1). No washers had checking rituals, but some had symmetry/ordering, hoarding, sexual/religious symptoms not as major problems. No checkers had washing rituals, but some had symmetry-ordering, hoarding, sexual/religious symptoms not as major problems. There were significant differences in the washing, checking and doubting subscales of the MOCI between the washers and the checkers, but no significant differences in slowness subscale.

3.2. Neuropsychological tests

There were significant differences between the washers and the checkers on some of the neuropsychological tests studied (Table 2). Checkers displayed performance deficits on Stroop test, Trail Making Test, GO/NO GO test (commission errors) and category fluency.

All 11 test results of neuropsychological tests for executive attention function were entered into a factor analysis, and a three-factor solution was extracted. GO/NO GO test (omission errors) could not be clearly assigned to any of the factors with factor loadings of 0.18 on factor I, 0.15 on factor II and – 0.19 on factor III. To keep the resulting factor model as parsimonious as possible, and due to its lower factor loadings compared with the other tests, we decided not to include GO/NO GO test (omission errors).

A final factor analysis was conducted on the remaining 10 test results, producing three factors accounting for 70.0% of the total variance (Table 3). The factor I accounted for 37.4% of the variance and included Stroop test (false number), TMT (subtracted time), Stroop test (time), GO/NO GO test (commission errors). Stroop test and GO/NO GO test were regarded to be measures of response inhibition (Bannon et al., 2002), therefore we named the first factor "inhibition". The factor II accounted for 17.4% of the variance and included letter fluency, category fluency and digit symbol. Fluency tests were regarded to be measures of cognitive flexibility. Troyer et al. (1997) suggested that two important components of fluency