

Unmet supportive needs of cancer patients in an acute care hospital in Japan—a census study

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Abstract

Purpose Little research has been done on supportive needs of cancer patients in acute hospitals in Japan. This study aims to comprehensively assess the unmet supportive needs of hospitalized cancer patients, as well as literacy and utilization of appropriate professional care.

Methods All cancer patients (aged 20 to 80 years) who were hospitalized in a university hospital in Tokyo during the designated 3-day period between September 1 and October 31, 2007 were recruited for participation in the

study. The M.D. Anderson Symptom Inventory, Brief Cancer-Related Worry Inventory, and Hospital Anxiety and Depression Scale were administered. Patients' knowledge and use of relevant services were evaluated. The results were compared with those of non-cancer patients in the same treatment settings.

Results A total of 125 cancer patients and 59 non-cancer patients were enrolled. Cancer patients and non-cancer patients equally suffered from physical symptoms (15–26% had severe appetite loss, 18–19% had severe dry mouth, and 16–22% had severe pain); however, psychological distress of cancer patients exceeded that of non-cancer patients (28.0% vs 8.5%; $p \leq 0.05$). Severe psychological distress was associated with severe worry about future prospects or interpersonal and social issues and presence of two or more severe symptoms. Two thirds of the patients with severe psychological distress knew about the psychiatric division, but only one third actually sought treatment.

Conclusions Needs related to psychological issues were more prevalent among cancer patients than among non-cancer patients, despite a similar level of physical distress. Special attention should be paid to cancer patients who worry over future prospects or interpersonal and social issues, and those who have two or more severe symptoms.

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Introduction

Cancer patients have diverse needs throughout the course of their illness. Identification and management of supportive needs is an essential component of comprehensive health care

for people with cancer, because unmet supportive needs have a detrimental effect on patients' well-being [32]. The most frequently reported unmet needs were those related to physical, psychological, informational, psychosocial, and daily living issues. Spiritual, communication, and sexuality issues have also been sporadically investigated [13].

Supportive needs of cancer patients differ between individuals and across time. Increased level of needs have been identified among patients who are young, female, unmarried, living in a rural location, or those who have a low income. Poor physical condition, advanced stage of illness at diagnosis, and current and/or past psychiatric problems are also associated with more complex needs [18]. Prevalence trends and predictors of unmet needs were highly variable in all domains and across the phases of illness [13]. During the newly diagnosed phase, patients were more likely to have unmet psychosocial (6–69%) and physical (44%) needs, compared with needs related to activities of daily living (5–10%), economic (11%), information (10–24%), or psychological (12–17%) [9, 21, 51, 60]. During the treatment phase, the prevalence of unmet needs for each domain had the largest variation compared with any other time over the course of the cancer. Unmet needs appear to be highest during the treatment and post-treatment phase [19, 20, 44]. High level of psychosocial needs is reported throughout the trajectory, especially during advanced/palliative phase [22, 37, 49, 58], with a gap between needs and service provision [5, 7].

Rigorous and systemic assessment of needs is the first critical step in supportive care that leads to the delivery and development of appropriate services [31]; however, very little research about cancer patients' needs has been done in Japan. Thus far, the research has been limited to ambulatory patients with specific types of cancer [29, 33], or the selected assessment tools were not validated for use with Japanese patients with cancer [29].

A study of unmet needs in an acute hospital setting is important in Japan, because 80% of the Japanese general population die in hospitals [23], and approximately 50% even prefer to spend the end-of-life period in a hospital rather than at home [45]. This is presumably because they may not cause burden to their family [15]. A nationwide survey demonstrated that 14–25% of the patients are reluctant to discuss end-of-life issues with physicians, which may be a barrier to introduction of quality palliative care [30]. Negative attitude towards palliative care among patients, their family members, and even physicians is one of the barriers against proper referral to palliative care and subsequent delay in terminating active anti-cancer treatment [27]. Misbelief and negative attitude about opioids hamper proper use of opioids [30, 38] and a substantial number of patients and families are currently dissatisfied with the available palliative care services [48].

The present study was conducted in a university hospital in central Tokyo. Survey in a university hospital has the following significance: in the Japanese medical system, patients are allowed to visit any hospital of their choice without paying extra money; the national health insurance covers 70–80% of the medical fee. Regardless of type of illness, health condition, or socioeconomic background, any patient can be seen at university hospitals. Approximately half of all Japanese physicians are initially trained at university hospitals; therefore, development of viable palliative care in university hospital settings is important for the overall progress of palliative care in Japan [28]. At the time of this study, even though a nationwide campaign to promote palliative care had been initiated, the hospital was not equipped with palliative care services. Unfortunately, this lack of services is not unusual in university hospitals in Japan.

First, we sought a validated needs-assessment scale; however, none of the psychometrically reliable scales, identified in a recent review [42], had been validated among Japanese subjects at the time of our survey. Therefore, we used a combination of several validated assessment scales as a substitute for a single needs-assessment scale. We aimed to comprehensively cover the domains that may contribute to the satisfaction and quality of life of the patients. Those domains are generally categorized into physical, psychological, psychosocial, informational, and spiritual issues and problems related to daily living, communication, and sexuality [13, 61]. We used the Japanese version of the M. D. Anderson Symptom Inventory (MDASI) [8, 35] to assess physical needs and daily living issues; the Brief Cancer Worry Inventory (BCWI) [16] to evaluate psychosocial, informational, communication, and sexuality issues; and the Japanese version of Hospital Anxiety and Depression Scale (HADS) [26] to assess undertreated psychological distress. We also attempted to identify factors associated with psychological distress, because psychological distress is highly influenced by unmet needs in other domains [63].

We compared cancer patients with non-cancer patients who were hospitalized in the same ward during the same study period. In the study-site hospital, as is usually the case with most hospitals in Japan, place of admission is determined by the site of primary illness and not by type of illness. For example, patients with chronic lung disease and patients with lung cancer are admitted to the same "pulmonary ward" and are cared for by the same nursing team and often seen by the same physician. Therefore, the non-cancer patients in the same ward served as a comparison group to identify areas that require further support among cancer patients.

In brief, this study aims to assess the unmet supportive needs of hospitalized cancer patients in a university hospital setting in Japan. All types of cancer sites and all stages of illness were included, and needs of cancer patients were

compared with non-cancer patients in the same treatment setting.

Patients and methods

Participants

This study was conducted in a 1,000-bed private general tertiary medical facility affiliated to a medical university located in the central Tokyo. The candidates for participation included all patients who were hospitalized during the study period and undergoing treatment or diagnostic testing for cancer in the medical, surgical, or radiological departments of the abovementioned hospital. Participants were recruited during the designated 3-day period between September 1 and October 31, 2007 (dates were determined by each department). Those who were aged 20 to 80 years and were able to complete a written questionnaire were eligible. Patients were excluded for surgical procedures within the week before the survey or if they were incapable of understanding and consenting to participation in the study (based on the judgment of the physician in charge). All patients who were not diagnosed with cancer and were hospitalized during the same period were approached for participation in the comparison group.

Procedure

Eligible patients who gave written consent were asked to fill out three self-report questionnaires: the MDASI, BCWI, and HADS. The measures used in this study do not literally assess unmet needs; alternatively, we attempted to supplement this by directly asking about awareness and utilization of relevant services. The relevant services included the pain clinic, psychiatric division, social services, rehabilitation medicine, and clinical nurse specialists. Research assistants provided support to participants who required help in filling out the questionnaires. These assistants were physicians or registered nurses who were not involved in the care of the participants. Participants' demographic and clinical data, including Eastern Cooperative Oncology Group performance status, were collected from the medical records.

This study was approved by the institutional review committee of Keio University School of Medicine and was registered in the national clinical trial registry, the UMIN-CTR (register number: UMIN000000811).

Measures

All the measures used in this study were previously standardized among Japanese cancer patients. The Japanese version of the MDASI is a 19-item self-report questionnaire

scored on an 11-point Likert scale (0–10). It is designed to assess the severity and impact of cancer-related physical and psychological symptoms within the past 24 h. The BCWI is a 15-item self-report questionnaire designed to assess cancer-related worries on a numeric scale (0–100). Severity of worry is calculated by totaling the scores for each item. The inventory consists of three factors: future prospects, physical problems, and social and interpersonal problems [16]. When assessing non-cancer patients, the item regarding “worry about cancer” was modified to “worry about your current illness”. The Japanese version of HADS is a 14-item self-report questionnaire designed to assess depression and anxiety. Each question is answered by choosing a score from 0 to 3. HADS total score of 20 or more or HADS depression subscale score of 11 or more indicates that the respondent is highly likely to have major depression. HADS total score of 11 or more, HADS depression subscale score of 5 or more, or HADS anxiety subscale score of 8 or more indicates that the respondent is highly likely to have an adjustment disorder or a major depressive disorder [26].

Statistical analysis

Cancer patients' data were compared with the non-cancer patients' data by using chi-square test for categorical variables, Mann–Whitney *U* test for non-parametric variables, and unpaired *t* test for continuous variables. Significance was set at $p < 0.05$. Mantel test was used to compare prevalence of moderate and severe symptoms on MDASI between cancer and non-cancer patients.

Stepwise logistic regression analysis (forward selection) was performed to explore for factors that predicted severe psychological distress. Major depression based on the results of the HADS was entered into the analysis as the dependent variable, and the following variables were entered as predictor variables: patients' demographic factors (age, gender, and performance status), presence of severe symptoms according to the MDASI, number of severe symptoms, and presence of severe worry in each BCWI domain. Predictor variables were dichotomized, according to age, into categories of 65 years or over and others, performance status into categories of three or over and others, MDASI symptoms (items 1 to 13) into categories of severe (score of 8 or over) and others, and mean score of BCWI domains into categories of 80 or over and others.

Results

Participants

Of the 287 patients who were approached, 215 (74.9%) met the inclusion criteria. The reasons for exclusion were

cognitive dysfunction (22 patients), severe physical condition (18 patients), decision of the physician in charge (four patients), and other unspecified reasons (38 patients). Of those, 184 patients (97 males and 87 females) gave written consent and were enrolled in the study (response rate, 85.6%). Differences in gender and age were not significant between those included and those excluded.

The demographic data of the participants are shown in Table 1. The participants consisted of 125 cancer patients with mean age of 58.9 years (SD=12.5) and 59 non-cancer patients with mean age of 61.2 years (SD=13.9). The majority of cancer and non-cancer patients were admitted for active treatment, and a few were admitted for evaluation and diagnosis. Few patients were admitted solely for palliative purpose; however, it should be noted that a large proportion of cancer patients have cancers that are considered unresectable or incurable; thus, even though the patients were admitted for active treatment, a substantial proportion of patients were implicitly at the stage of palliation. Opiates were prescribed for only 18 patients (12.1%).

Prevalence of physical and psychological symptoms

The mean number of severe symptoms was 1.9 (SD=2.6) in the cancer patient group and 1.7 (SD=2.5) in the non-cancer patient group, and the difference was not significant.

Figure 1 shows the results of the MDASI, listed in the order of prevalence. Symptoms related to psychological state outweighed physical symptoms. Cancer patients frequently (>20%) suffered from severe distress, lack of appetite, drowsiness, disturbed sleep, sad mood, and dry mouth, whereas the non-cancer patients frequently suffered from pain, disturbed sleep, numbness or tingling, and feelings of distress. There were no significant differences in the severity of any symptoms between cancer patients and non-cancer patients.

Severity of worries

Table 2 shows the severity of worries assessed by the BCWI. In all domains and for most items, worry was significantly more severe among cancer patients than among non-cancer patients. Worry was remarkable (mean score >50) among cancer patients with regards to treatment and prognosis, such as “the cancer itself”, “the cancer might get worse in the future”, “life and death”, “effect of current treatment”, “side effects of the treatment”, and “future of family members”. Cancer patients were significantly more worried about their “mental status” and “how to cope with the illness”.

The severity of worry was generally low with regards to physical symptoms and daily life issues, such as sexual problems, economic problems, relationships with family

members, and work or housework among cancer and non-cancer patients.

Age significantly correlated with the severity of all domains of worry, and the younger group had the most severe worries ($r=0.34$, $p<0.01$). Gender did not significantly correlate with the severity of worries. Performance status weakly correlated with the physical domain of worry, and worry became increasingly more severe as performance status declined ($r=0.15$, $p<0.05$).

Prevalence of psychological distress and predictive variables

As shown in Table 3, cancer patients had significantly higher total HADS scores and HADS anxiety subscale scores ($p<0.05$). Based on the cutoff scores recommended in a previous study [26], 93 (74.4%) of the 125 cancer patients suffered from psychological distress that corresponded to an adjustment disorder or major depression, and 35 (28.0%) suffered from severe psychological distress that corresponded to major depression. The prevalence of both was significantly higher in the cancer group. In the non-cancer group, 34 (57.6%) of 59 patients suffered from psychological distress that corresponded to an adjustment disorder or major depression, and only four (6.8%) suffered from severe psychological distress that corresponded to major depression.

Table 4 shows the results of a stepwise binary logistic regression analysis to identify factors associated with severe psychological distress. The analysis yielded a significant model (omnibus Chi-square=27.45, $df=3$, $p<0.001$), accounting for between 21.4% and 30.6% of the variance, with 76.3% of overall predictions being accurate. The future-prospects domain and social-and-interpersonal-problems domain of the BCWI and the presence of two or more severe symptoms according to the MDASI were significantly associated with severe psychological distress.

Literacy rate and rate of utilization of relevant services

Table 5 shows the percentage of patients who knew about (literacy rate) and who used (utilization rate) the relevant services. About two thirds of the patients knew about the psychiatric division, but less than 50% knew about social services, the pain clinic, and clinical nurse specialists. The literacy and utilization rates of cancer patients and non-cancer patients were not significantly different, except that the psychiatric division was more likely to be used by cancer patients.

Among the patients suspected of having major depression ($n=39$), 24 patients (61.5%) were aware of the psychiatric division, but only 11 patients (29.7%) actually used it; thus, 13 (33.3%) of the 39 patients who were

Table 1 Demographics of the participants

	Total (%)	Cancer (n=125)	Non-cancer (n=59)	p ^a	
Male	97 (52.7)	68 (54.4)	29 (49.2)	0.53	
Female	87 (47.3)	57 (45.6)	30 (50.8)		
Age (year)	59.6 (SD = 13.1)	58.9 (SD = 12.5)	61.2 (SD = 13.9)	0.27	
Surgical ward	128 (69.57)	83 (66.4)	45 (76.3)	0.17	
Medical ward	56 (30.43)	42 (33.6)	14 (23.7)		
ECOG performance status				0.30	
0	21 (11.5)	13 (10.5)	8 (13.6)		
1	85 (56.5)	64 (51.6)	21 (35.6)		
2	47 (25.7)	29 (23.4)	18 (30.5)		
3	24 (13.1)	14 (11.3)	10 (17.0)		
4	6 (3.2)	4 (3.2)	2 (3.4)		
Cancer progression					
Curable/resectable		33 (26.4)			
Advanced		82 (65.6)			
Not identified		10 (8.0)			
Treatment phase					
Diagnostic (pretreatment)	8 (4.3)	6 (4.8)	2 (3.4)		
Active treatment	141 (76.6)	97 (77.6)	44 (74.6)		
Palliative	23 (12.5)	14 (11.2)	9 (15.3)		
Not identified	12 (6.5)	8 (6.4)	4 (6.8)		
Purpose of admission					
Examination/diagnosis	9 (4.9)	5 (4.0)	4 (6.8)		
Chemotherapy	64 (34.8)	64 (51.2)	0 (0.0)		
Other disease-targeted pharmacotherapy	23 (12.5)	0 (0.0)	23 (39.0)		
Radiotherapy	19 (10.3)	19 (15.2)	0 (0.0)		
Operation	53 (28.8)	33 (26.4)	20 (33.9)		
Local operation	1 (0.5)	0 (0.0)	1 (1.7)		
Rehabilitation	14 (7.6)	6 (4.8)	8 (13.6)		
Symptom control	34 (18.5)	22 (17.6)	12 (20.3)		
End-of-life care	3 (1.6)	3 (2.4)	0 (0.0)		
Others	8 (4.3)	6 (4.8)	2 (3.4)		
Use of opioids					0.13
Yes	18 (9.8)	15 (12.0)	3 (5.1)		
No	166 (90.2)	110 (88.0)	56 (94.9)		
Primary site of illness					
Gastrointestinal (surgical)	30 (16.3)	23 (18.4)	7 (11.9)		
Musculoskeletal	27 (14.7)	9 (7.2)	18 (30.5)		
Gastrointestinal (medical)	24 (13.0)	17 (13.6)	7 (11.9)		
Gynecological	20 (10.9)	20 (16.0)	0 (0.0)		
Hematological	18 (9.8)	18 (14.4)	0 (0.0)		
Head and neck	16 (8.7)	14 (11.2)	2 (3.4)		
Dermatological	10 (5.4)	3 (2.4)	7 (11.9)		
Urological	10 (5.4)	7 (5.6)	3 (5.1)		
Respiratory (medical)	7 (3.8)	3 (2.4)	4 (6.8)		
Neurosurgical	7 (3.8)	4 (3.2)	3 (5.1)		
Cardiovascular	4 (2.2)	0 (0.0)	4 (6.8)		
Respiratory (surgical)	4 (2.2)	3 (2.4)	1 (1.7)		
Radiological ^b	4 (2.2)	4 (3.2)	0 (0.0)		
Rehabilitation medicine ^c	3 (1.6)	0 (0.0)	3 (5.1)		

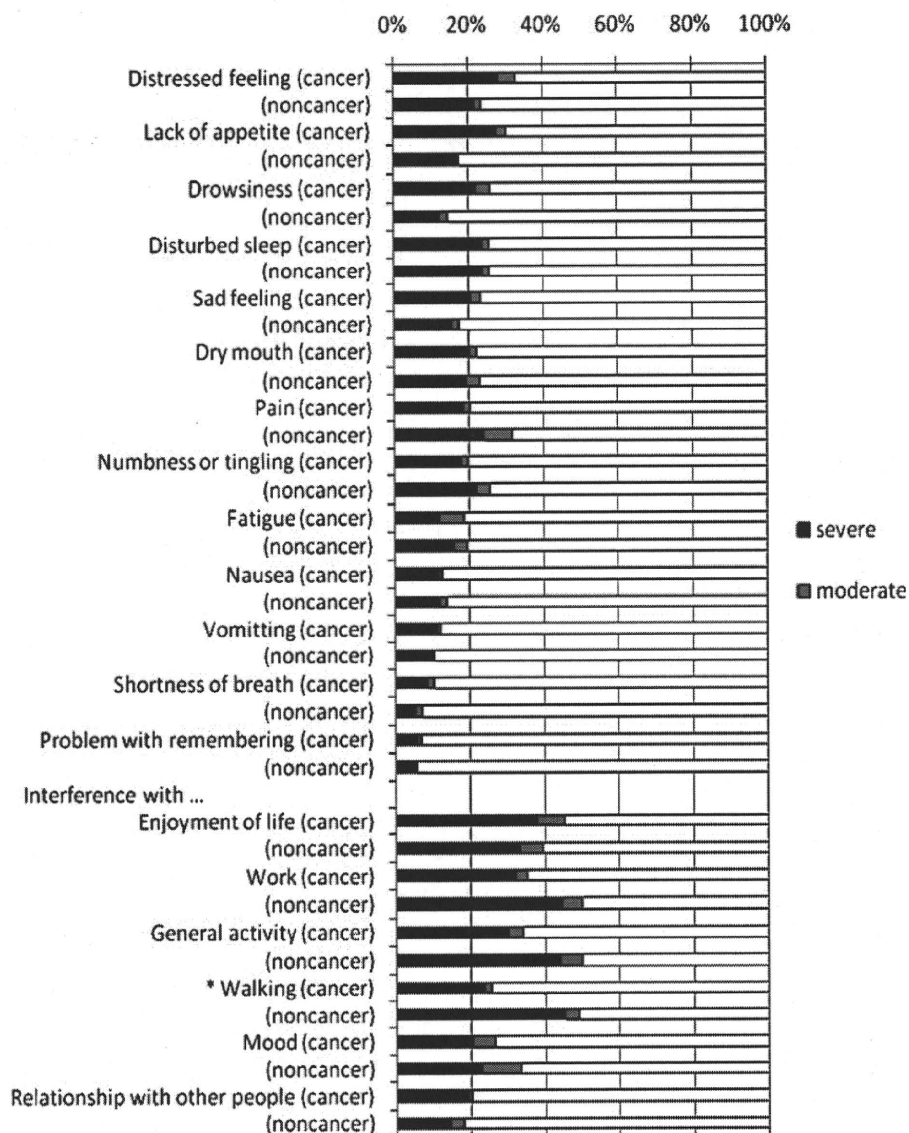
ECOG Eastern Cooperative Oncology Group

^a Chi-square test for gender, for whether medical or surgical division, for performance status and for use of opioids. Student's *t* test for age

^b Admitted for radiologic treatments, site unspecified

^c Admitted for multi-system rehabilitation therapy, site unspecified

Fig. 1 Distribution of severity for M.D. Anderson Symptom Inventory



suspected of having major depression did not consult the psychiatric division even though they knew it was available. Fifteen (38.5%) of the 39 patients did not know about the availability of psychiatric service.

Among the patients suspected of having an adjustment disorder ($n=127$), 87 patients (68.5%) knew of the availability of the psychiatric division, but only 17 patients (13.7%) actually used it; therefore, 70 (55.1%) of the 127 patients suspected of having an adjustment disorder did not consult the psychiatric division even though they knew about the availability of the service, and 40 (38.5%) of 127 patients did not know about the availability of psychiatric help. Only 15 (38.5%) of the patients with moderate-to-severe pain ($n=39$) knew about the services offered by the pain clinic, and only six patients (15.4%) actually used the clinic.

Discussion

The aim of our study was to comprehensively assess the unmet supportive needs of cancer patients who were hospitalized in an acute care hospital. Our results demonstrated that a substantial number of patients experience a wide range of symptoms and had worries that were undertreated. Detection and appropriate management of these symptoms and worries appear to be a pervasive problem.

Although there were no significant differences in the severity of each physical symptom between cancer patients and non-cancer patients, cancer patients are more likely to be psychologically distressed. These findings are consistent with other studies from Australia [46] and Finland [43], reporting that cancer patients have more needs in psychological domains than in physical domains. Our study

Table 2 Severity of worries

Item content and domains of worries	Cancer patients		Non-cancer patients		<i>p</i> ^a
	Mean	SD	Mean	SD	
Item content					
Current illness itself	71.0	26.2	54.2	34.3	<0.01
Illness might get worse in the future	66.9	29.6	43.5	35.3	<0.001
Life and death of self	56.5	33.1	31.0	34.3	<0.001
Ability to cope with the illness	55.5	29.8	38.0	31.5	<0.001
Effect of current treatment	53.4	30.1	38.7	30.9	<0.01
Side effects of the treatment	52.2	31.1	32.6	30.8	<0.0001
Future of family members	51.2	33.7	29.3	33.0	<0.0001
Mental status	49.1	27.6	33.7	29.9	<0.001
Physical symptom	46.5	29.5	40.7	30.5	0.22
Ability to do job or house work	41.3	33.7	39.3	35.0	0.71
Economic problems	39.8	32.4	32.7	33.3	0.17
Change of appearance	38.3	31.4	22.9	28.3	<0.001
Relationships with medical staff	25.6	26.9	15.0	23.9	<0.05
Relationships with family members	24.1	25.5	18.5	28.6	0.18
Sexual issues	16.3	24.6	13.3	24.4	0.46
Domains					
Future prospects	59.0	29.4	40.0	32.7	<0.0001
Physical problems	38.0	29.2	27.7	28.5	<0.01
Social and interpersonal problems	36.0	30.4	27.6	30.7	<0.05
Total	46.2	29.7	33.0	30.9	<0.0001

^a Student's *t* test

showed a higher rate of depression and anxiety than found in the Finnish study.

The distribution and frequency of each symptom were similar to the results of previous studies [4, 43]. Among the symptoms covered by the MDASI, feelings of distress, lack of appetite, disturbed sleep, drowsiness, and sad feelings were the most prevalent symptoms. Dry mouth was another frequent symptom among both cancer patients and non-cancer patients, suggesting another important area that requires care and attention. Tong et al. [54] reported that dry mouth was the most common oral symptom among medical oncology patients. Furthermore, they found that the symptom was associated with lower performance status and poorer quality of life.

Severe pain was present in 18.4% of our cancer group. Although the World Health Organization guidelines declare that 90% of cancer pain can be eliminated by proper analgesic use [62], our results showed a failure of the medical system in meeting this standard. It appeared that patients' pain is not adequately relieved even in a university hospital in the capital city. This unfortunate finding is evidenced by a low rate of opium usage and low rate of referrals to a pain specialist. The results of our study were

marginally better than those reported in the UK [14], Finland [43], and The Netherlands [56], but our findings replicate a series of previous reports showing the inadequacy of pain treatment in Japan [36, 52, 55].

Possible reasons of low opioid usage include (1) patients' cultural view of pain behaviors [17], (2) patients' beliefs and negative attitudes toward opioids, (3) under-detection of pain due to lack of routine screening, (4) insufficient knowledge and skills in prescribing opioids among physicians [38, 53], and (5) exclusion of severely ill patients from our sample. A nationwide survey showed that approximately 40% of the general population believes that cancer pain is not relievable, and approximately 30% believe that opioids cause addiction and shorten life [30, 38]. Further investigation into pain management is needed.

The results of the BCWI suggested that cancer patients had more severe worries and concerns about a larger range of issues compared with non-cancer patients. The severity of worry increases as their performance status declines. Their worry is more severe with regards to the course of illness and treatment, and issues related to mental status and coping with the illness. They worry less about social and interpersonal issues, including sexual and financial issues.

Table 3 Mean scores of Hospital Anxiety and Depression Scale and prevalence of major depression and adjustment

	Cancer (n=125)		Non-cancer (n=59)		<i>p</i>
HADS score					
Total	13.9 ^a	7.4 ^b	11.4 ^a	6.8 ^b	0.03
Depression subscale	7.2 ^a	3.9 ^b	6.2 ^a	3.7 ^b	0.08
Anxiety subscale	6.7 ^a	4.2 ^b	5.2 ^a	3.6 ^b	0.02
Prevalence					
Major depression (MDD)	35 ^c	28.0%	5 ^c	8.5%	0.001
Adjustment disorder or MDD	93 ^c	74.4%	34 ^c	57.6%	0.022

Student's *t* test for HADS scores and chi-square test for prevalence

Major depression: HADS total score ≥ 20 or HADS depression subscale ≥ 11

Adjustment disorder: HADS total score ≥ 11 or HADS depression subscale ≥ 5 or HADS anxiety subscale ≥ 8

HADS Hospital Anxiety and Depression Scale, *SD* standard deviation

^a Mean

^b SD

^c *n*

There are several possible reasons for these findings. First, the patients in our study were undergoing active treatment, and such patients may be more concerned about their illness and the ongoing treatment than about daily life issues that lie ahead after discharge. In fact, the results of previous needs studies [46, 50] suggest that cancer patients who are evaluated in medical facilities are more likely to emphasize needs and concerns related to cancer and treatment, whereas cancer patients evaluated in the community are more likely to report that daily life issues have a greater impact on their quality of life [57]. The medical staff should be aware that all issues must be addressed at some point in the course of treatment, even though the patients' interest in future concerns is less acute during the hospital stay. Second, ethnicity and culture may have influenced the low level of worry about sexual issues, because Japanese people are generally less likely to report

sex-related problems, although it is uncertain whether this is purely due to cultural differences or due to their hesitancy to report them [24]. Further study is needed to explore whether these foci of worry change according to the stage of cancer treatment and treatment setting. The medical staff should be sensitive to changes in patients' needs in order to offer relevant information.

The results of the HADS imply high prevalence of major depression and adjustment disorders among our sample. Psychological distress, especially major depression, has a strong negative impact on quality of life, treatment compliance, length of hospital stay, health-care costs, morbidity, and possibly mortality among cancer patients [41]; therefore, early intervention is crucial. Despite the high prevalence of psychological distress, the utilization rate of the psychiatric division was low. About one third of the patients with psychological distress did not even know

Table 4 Factors associated with severe psychological distress in cancer patients

	Beta	SE	Wald	<i>df</i>	<i>p</i>	Odds ratio	95% CI	
							Lower	Upper
Domains of worries (BCWI)								
Future prospects	1.26	0.49	6.56	1	0.01	3.53	1.34	9.28
Social and interpersonal problems	2.10	0.90	5.46	1	0.02	8.16	1.40	47.52
Clinical symptoms (MDASI)								
Number of severe symptoms ≥ 2	1.03	0.49	4.47	1	0.03	2.81	1.08	7.34

Binary stepwise logistic regression analysis (forward selection)

SE standard error, *df* degree of freedom, *CI* confidence interval, *MDASI* M.D. Anderson Symptom Inventory, *BCWI* Brief Cancer Worry Inventory

Table 5 Literacy rate and utility rate of relevant services

	Cancer patients (<i>n</i> =125)					Non-cancer patients (<i>n</i> =59)				
	Number of patients	Literacy rate ^a		Utilization rate ^b		Number of patients	Literacy rate ^a		Utilization rate ^b	
Psychiatry division										
Total	125	81	64.8%	17	13.6%	59	43	72.9%	2	3.4%
Patients with major depression	35	20	57.1%	9	25.7%	5	4	80.0%	2	40.0%
Patients with adjustment disorder	58	42	72.4%	5	8.6%	29	27	93.1%	0	0.0%
Others	32	19	59.4%	3	9.4%	25	10	40.0%	0	0.0%
Pain clinic										
Patients with moderate to severe pain	38	6	15.8%	3	7.9%	22	10	45.5%	4	18.2%
Others	87	30	34.5%	5	5.7%	37	10	27.0%	1	2.7%
Rehabilitation unit	125	98	78.4%	41	32.8%	59	50	84.7%	30	50.8%
Social services	125	56	44.8%	12	9.6%	59	31	52.5%	5	8.5%
Clinical nurse specialists	125	32	25.6%	12	9.6%	59	20	33.9%	5	8.5%

^a Number (percent) of patients who knew about the service

^b Number (percent) of patients who used the service

that they could use the psychiatric division. These patients might have received better treatment if their psychological problems had been detected and if they had been properly referred to the psychiatric division. Patients and staff share responsibility for the failure to access psychiatric services, because psychological distress is overlooked by both patients and the staff [34, 39, 40]. In addition, misunderstandings and negative attitudes towards psychological distress and psychiatric treatment hinders access to care [7, 11]. Proper psychoeducation and referral programs may reduce the patient-related barriers to seeking and utilizing optimal mental health care services among cancer patients [6, 47]. Raising physicians' awareness of psychological problems may enhance commitment between patients and physicians [12].

The results of the logistic regression analysis indicated that cancer patients who worry over future prospects and over interpersonal and social issues are at higher risk for severe psychological distress. The risk for patients with two or more severe symptoms was almost three times higher than the risk of those with one or no severe symptoms; thus, the medical staff should pay careful attention to such patients.

Our study had several limitations. First, our sample only included a small number of hospitalized patients in a single facility. Second, patients in very severe condition or with cognitive impairment were excluded. Such patients are likely to have more severe symptoms and more problems, thus the needs may be underestimated in our study. Third, the cross-sectional design using self-report questionnaires limits the power of assessment. The prevalence of major

depression and adjustment disorder was higher than in previous studies of Japanese cancer patients [3, 25, 26], and this may be due to usage of self-report questionnaires. Fourth, heterogeneous clinical nature of the sample made the results more difficult to interpret, as was suggested by the review of literature [13]. Fifth, physical and prognostic conditions were not matched between the cancer group and the comparison group. In previous studies, there was a comparable prognosis for cancer and non-cancer patients. For example, Addington-Hall et al. conducted retrospective interviews with relatives, friends, or other caregivers of patients who died of stroke [2] and a retrospective survey among relatives, friends, or other caregivers for non-cancer patients with similar symptom burden within a year of death [1]. Another study compared chronic respiratory diseases and lung cancer in the final 12 months of life [10]. Although these studies have limited accuracy because of retrospective design, there is evidence to suggest that non-cancer patients in the palliation phase have equally severe physical and psychosocial needs and possibly a greater problem with unmet information needs than cancer patients. It seems likely that the terminal non-cancer population also needs promotion of specialized palliative care. Sixth, the census method, although helpful for service planning, belies the unique needs of individual patients. Lastly, this study lacks direct measurement of quality of life and satisfaction of the participants, thus making the result difficult to interpret. Although this study covers various domains that may affect patients' quality of life and satisfaction, interrelations among those needs can be potentially damaging as a whole, because meeting a certain

area of need may impair other domain of need, and may result in impaired satisfaction or quality of life. In this sense, needs of cancer patients should be assessed upon a strong conceptual theory on multiple domains of needs, quality of life, and satisfaction; however, assessment tool that stands upon robust theory is scarce so far [59].

These limitations are outweighed by the following. To our knowledge, no needs research involving all patients in all stages of illness in acute care hospitals has been conducted in Japan. Weakness of our study design is set-off by the use of standardized assessment instruments [46, 50].

In conclusion, cancer patients in an acute care hospital suffer from a variety of physical, psychological, and social needs that are undertreated. Psychological issues are more prevalent among cancer patients than among non-cancer patients, despite the same level of physical distress. Considering high prevalence of various unmet needs and low rate of literacy and utilization of relevant services, routine screening for both psychological and physical symptoms is essential. Medical staff should pay special attention to cancer patients who worry over future prospects or interpersonal and social issues, and those with two or more severe symptoms. Further research is needed in this population, incorporating search for patients' satisfaction and quality of life, as well as relationship among various domains of needs.

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Acquired personality traits of autism following damage to the medial prefrontal cortex

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Recent neuroimaging studies on “theory of mind” have demonstrated that the medial prefrontal cortex (PFC) is involved when subjects are engaged in various kinds of mentalising tasks. Although a large number of neuroimaging studies have been published, a relatively small amount of neuropsychological evidence supports involvement of the medial PFC in theory of mind reasoning. We recruited two neurological cases with damage to the medial PFC and initially performed the standard neuropsychological assessments for intelligence, memory, and executive functions. To examine theory of mind performance in these two cases, four kinds of standard and advanced tests for theory of mind were used, including first- and second-order false belief tests, the strange stories test, and the faux pas recognition test. Both patients were also requested to complete the questionnaire for the autism-spectrum quotient. Neither case showed impairment on standard theory of mind tests and only mild impairments were seen on advanced theory of mind tests. This pattern of results is basically consistent with previous studies. The most interesting finding was that both cases showed personality changes after surgical operations, leading to characteristics of autism showing a lack of social interaction in everyday life. We discuss herein the possible roles of the medial PFC and emphasize the importance of using multiple approaches to understand the mechanisms of theory of mind and medial prefrontal functions.

Keywords: Theory of mind; Mentalising; Autism-spectrum quotient; Medial prefrontal cortex; Anterior cingulate cortex.

INTRODUCTION

Recent studies in social neuroscience have focused on the neural bases of cognitive processes for understanding other minds. A number of neuroimaging studies of “theory of mind” have demonstrated that the medial prefrontal cortex (PFC) or anterior cingulate (paracingulate) cor-

tex is involved in various kinds of tasks requiring mentalising functions (Brunet, Sarfati, Hardy-Baylé, & Decety, 2000; Castelli, Happé, Frith, & Frith, 2000; Gallagher & Frith, 2003; Gallagher et al., 2000; Vogeley et al., 2001). This area has been recognized as one of the “social brain” areas, together with areas such as the superior temporal sulcus, amygdala, insula, posterior

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cingulate (retrosplenial cortex), and fusiform gyrus (Brüne, Ribbert, & Schiefenhövel, 2003; Wheatley et al., 2007). Although previous studies have shown that these areas play different roles in self-related processing, the medial PFC has been identified as one of the cortical midline structures subserving self-related processings such as monitoring, self-awareness, agency, and autobiographical memory (for review, see Northoff & Bermpohl, 2004). Among all these areas, the medial PFC has been considered essential for understanding mental states of self and others in social situations.

Another neuroscientific approach to theory of mind involves neuropsychological investigations to examine the performance of brain-damaged cases. The initial study by Happé, Brownell, and Winner (1999) reported that following right hemisphere damage, cases showed impaired understanding of materials requiring attribution of mental states. Several other studies examining the effects of brain lesions on theory of mind performance have reported that focal frontal lesions impair the ability to infer mental states of others (Bach, Happé, Fleming, & Powell, 2000; Happé, Malhi, & Checkley, 2001; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Stuss, Gallup, & Alexander, 2001). More careful examinations to understand the roles of different areas within the frontal lobe have indicated that right ventromedial prefrontal lesions impair detection of deception (Stuss et al., 2001) and empathy processing (Shamay-Tsoory et al., 2003), whereas lesions in the internal capsule impair advanced theory of mind performance for understanding the thoughts and feelings of fictional characters (Happé et al., 2001). Conversely, other studies have suggested that the ability to understand mental states was found to be intact in cases with orbitofrontal lesions (Bach et al., 2000).

Another comprehensive neuropsychological study of over 30 cases with unilateral (right or left) frontal lobe lesions found that both groups exhibited impaired performance on first- and second-order false belief tests (Rowe, Bullock, Polkey, & Morris, 2001). Stone, Baron-Cohen, & Knight (1998) tested performance on first- and second-order false belief tests and the faux pas recognition test in cases with orbitofrontal damage, and found that bilateral orbitofrontal lesions resulted in difficulty only in the ability to recognize a faux pas. Although these studies focused on the effects of damage to the frontal lobe, it remains unclear whether selective damage

to the medial PFC yields any impaired performance on various kinds of theory of mind tests.

Some previous studies have actually examined the performance of cases with selective damage to the medial PFC. Baird et al. (2006) tested two cases and reported intact intellectual, memory, and language abilities, and visuo-perceptual functions, but weak or impaired performance on selective executive function tests. No theory of mind performance was tested in that study. Another neuropsychological study addressed the question of theory of mind impairment by testing a case with a selective lesion in the medial PFC (Bird, Castelli, Malik, Frith, & Husain, 2004). They carefully examined performance of the patient on various kinds of theory of mind tests, but found no significant impairment on tests, and thus stated that extensive medial frontal regions are not necessary for theory of mind performance. The findings from both studies have some important implications for our understanding of the effects of damage to the medial PFC. Most interesting was the finding that following the damage to this area, cases did not show any severe impairment on test performance, including theory of mind performance. However, the data are currently too limited to reach solid conclusions on the effects of medial prefrontal damage.

Another unresolved question is concerned with personality changes in cases. In the classic case of Phineas Gage, damage to the orbitofrontal cortex resulted in severe behavioral disturbances in everyday life (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Harlow, 1848). A number of previous studies have reported that cases with damage to the orbitofrontal cortex show severe sociopathic personality change (Eslinger & Damasio, 1985; Saver & Damasio, 1991). However, the question of whether cases with lesions involving the medial PFC, located in the vicinity of the orbitofrontal cortex, show any personality change remains unanswered. A recent meta-analysis of 39 functional imaging studies for autism-spectrum disorders indicated that the medial PFC was less activated during social task performance (e.g., theory of mind tests) in autism-spectrum disorders compared to neurotypical controls (Di Martino et al., 2009). Cases with damage to the medial PFC may show personality changes, leading to characteristics of autism.

Although previous neuropsychological studies of cases with damage to the medial PFC have shed light on the functions of this area, the

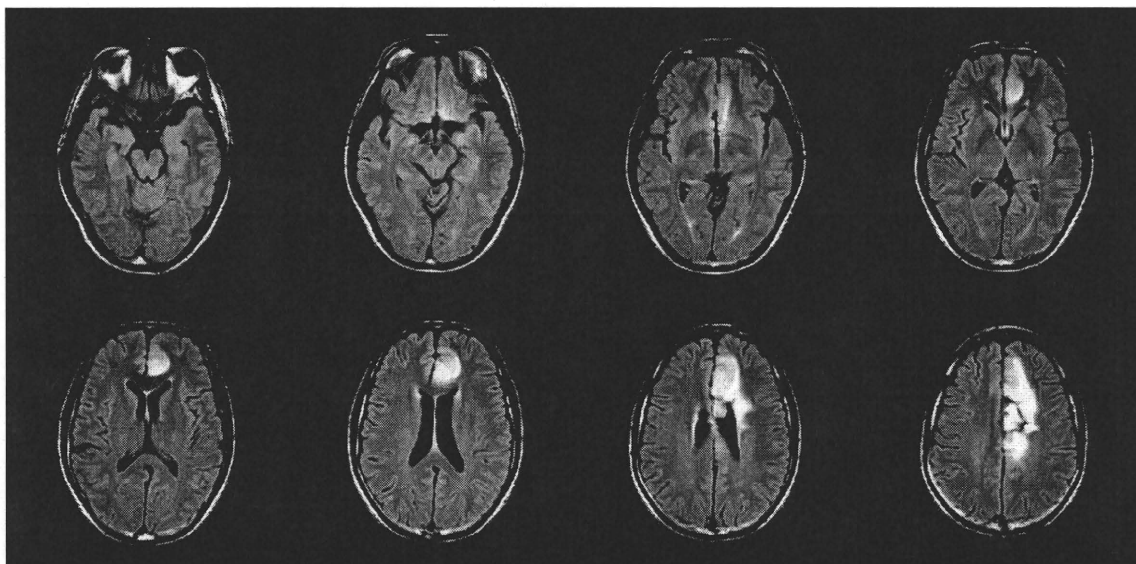


Figure 1. Transverse MRI with FLAIR acquisition of TO's brain. Left sides of images correspond to right side of the brain.

number of studies remains limited and actual effects on social functions following damage to this area remain poorly understood (Gallagher & Frith, 2003). We present herein two cases with damage to the medial PFC and report on their performance on various kinds of theory of mind tests, whether personality changes were evident, and behavioral disturbances in daily activities.

METHODS

Profiles of cases with medial prefrontal damage

We tested two individuals, TO and HC, with damage to the medial PFC. The first case, TO, was a 31-year-old man. A full-time employee of a big electronics company in Japan, he had undergone neurosurgery for brain tumor. Magnetic resonance imaging (MRI) with FLAIR (fluid attenuated inversion recovery) acquisition revealed that damage extended through the left-dominant medial prefrontal and anterior cingulate cortices, reaching the left supplementary motor area (Figure 1). The right hand and leg were moderately paralyzed for a few months after surgery, but those symptoms later resolved.

The most striking aspect on TO was a reported change in personality. According to his self-report, he noticed that his sense of reality was attenuated after surgery, leading him to feel detached from the world despite being sure of

his location, and this feeling often occurred in a manner similar to a panic attack. These symptoms partly resembled the characteristics of depersonalization. He also mentioned that surgery had made him feel depressed, anxious and withdrawn from everything.

The second case, HC, was a 56-year-old man. An employer of a small private company in Japan, he had undergone surgery following rupture of a right pericallosal artery aneurysm. MRI with T1-weighted spin-echo acquisition revealed that the area of damage included the right-dominant medial prefrontal and anterior cingulate cortices, extending slightly into the right supplementary motor area (Figure 2).

According to self-reports, he noticed that his memory had deteriorated after surgery, with a feeling that most daily episodes could not be clearly remembered. He reported difficulty doing two things simultaneously, and became aware that everything needed a strong effort to be done. He also mentioned that his personality had changed after surgery, leading him to notice that feelings of sadness and anger had been dimmed and that he had become much more depressive, anxious and withdrawn compared to his previous personality.

Neuropsychological assessment

Three months after surgery, six of the more frequently used neuropsychological assessments

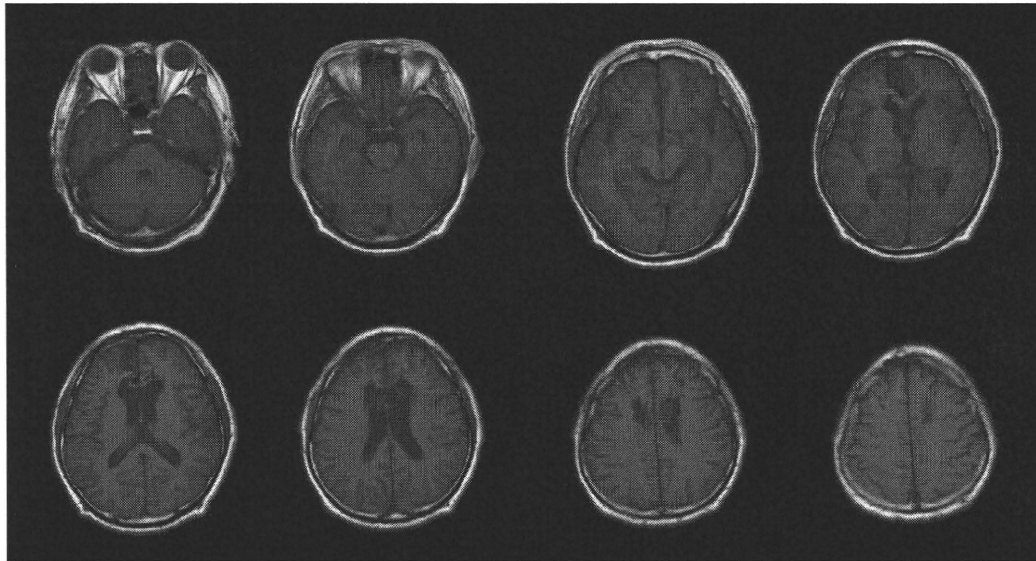


Figure 2. Transverse MRI with T1-weighted spin-echo acquisition of HC's brain. Left sides of images correspond to right side of the brain.

were conducted to examine higher-order cognitive functions in these cases. We selected: (1) Wechsler Adult Intelligence Scale-Revised (WAIS-R) for general intelligence, (2) Wechsler Memory Scale-Revised (WMS-R) for memory and attention, (3) Rey Auditory-Verbal Learning Test (RAVLT) for verbal recall ability, (4) Rey-Osterrieth Complex Figure Test (ROCFT) for visuoconstructive skills and visual memory, (5) Wisconsin Card Sorting Test (WCST) for abstract reasoning and ability to appropriately shift cognitive strategies, and (6) Stroop Test for selective attention and inhibition. The results of neuropsychological assessments in both cases are shown in Table 1.

TO's score on the intelligence test showed dissociation between verbal and performance intelligence quotient (IQ), with an inferior score on performance IQ. In the IQ test, he showed difficulty in performing subtests of block design, object assembly and digit symbols.

In terms of memory performance, TO showed lower scores on some measures for identifying delayed recall performance (e.g., delayed recall on WMS-R, RAVLT, and ROCFT) as compared to his relatively higher scores on other measures. The results of mild amnesia were consistent with his self-report regarding daily activities. For instance, he reported often becoming confused in remembering whether he has taken his medication.

TABLE 1
Neuropsychological assessments of TO and HC

<i>Test</i>	<i>TO</i>	<i>HC</i>
<i>Intelligence</i>		
Wechsler Adult Intelligence Scale-Revised (WAIS-R)		
Full scale IQ	88	91
Verbal IQ	101	92
Performance IQ	76	92
<i>Memory</i>		
Wechsler Memory Scale-Revised (WMS-R)		
Verbal memory	94	90
Visual memory	87	99
General memory	90	92
Attention and concentration	88	94
Delayed recall	65	100
Rey Auditory-Verbal Learning Test (RAVLT)		
Immediate recall, trials		
1-5	6-9-9-10-11/15	3-7-10-9-11/15
Delayed recall	5/15	7/15
Delayed recognition	11/15	14/15
Rey-Osterrieth Complex Figure Test (ROCFT)		
Immediate recall	35/36	36/36
Delayed recall	4/36	22/36
<i>Executive function</i>		
WCST (Wisconsin Card Sorting Test)		
Categories achieved	4	5
Total perseverative errors	1	0
Stroop Test		
24 non-interference colour naming (errors)	14s (0)	22s (0)
24 interference colour naming (errors)	26s (1)	29s (1)

TO's performances on tests for executive function were all within normal range. Performance on the standardized aphasic test did not show any difficulties in language activities.

The second case, HC, showed an intellectual performance within normal range. In terms of memory performance, he exhibited normal scores on WMS-R, although scores on RAVLT and ROCFT were somewhat lower. In fact, in terms of daily activities, he showed difficulty with temporal-order judgments for everyday episodes within a time range of a few days.

HC's performance on tests for executive function was also within normal range. Performance on the standardized aphasic test did not show any difficulties in language activities.

Experimental investigations

We tested the two cases using four types of story comprehension task to clarify theory of mind performance. These included: (1) first-order false belief test (Baron-Cohen, Leslie, & Frith, 1985; Frith & Frith, 1999), (2) second-order false belief test (Baron-Cohen, 1989), (3) strange stories test (Happé, 1994), (4) faux pas recognition test (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999). The first-order false belief test is one of the most famous tests for theory of mind reasoning. This test assesses the ability to recognize that others can have false beliefs about the world that can differ from reality, and that people's behaviors can be predicted by the representation of others' mental states. The more complex second-order false belief test requires participants to understand a second person's concerns about the world, based on social interactions of minds in which people are concerned about each other's mental states.

The last two tests were used to examine the more advanced theory of mind reasoning ability in the cases. The strange stories test assesses the ability to infer mental states in a story context for social understanding. We selected seven stories for each case: pretence; lie; white lie; figure of speech; double bluff; irony; and persuasion. A previous study reported that subjects with autism-spectrum disorders show impaired provision of context-appropriate mental state explanations for strange stories, compared to normal control subjects (Happé, 1994).

As well as the strange stories test, we used the faux pas recognition test to assess the ability to

recognize inappropriate statements in a story context (Baron-Cohen et al., 1999). We selected the original 10 faux pas stories and 10 control stories with no faux pas for TO and 7 faux pas stories and 7 control stories for HC, due to reported fatigue during testing. Subjects were presented with each story and asked whether a faux pas was contained. If a faux pas was detected, they were then asked for an explanation of it. We also requested that each subject answer two additional questions to test story comprehension in each story, to see whether a comprehensive understanding of each story was achieved. Baron-Cohen et al. (1999) reported that subjects with autism-spectrum disorders show impaired detection of faux pas on the faux pas recognition test compared to normal control subjects, despite intact story comprehension.

In addition, TO and HC were required to complete all 50 items in the Autism-Spectrum Quotient (AQ) questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). This questionnaire was developed as a self-administered method of screening for adults with normal intelligence and traits associated with autism-spectrum disorders. Score ranges from 0 to 50 in the questionnaire. Adults with Asperger syndrome or high-functioning autism show a mean score of 35.8, significantly higher than controls with a mean score of 16.4 (Baron-Cohen et al., 2001). Another recent study has shown that the threshold score for suspected Asperger syndrome or high-functioning autism is 26.0 (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). The present study used the Japanese version of the questionnaire, for which significantly high reliability has been shown in test-retest and inter-rater measures (Wakabayashi, Tojo, Baron-Cohen, & Wheelwright, 2004). In this version, adults with Asperger syndrome or high-functioning autism show a mean score of 37.9, significantly higher than controls with a mean score of 18.5 (Wakabayashi et al., 2004).

RESULTS

Theory of mind tests

Both cases passed the first- and second-order false belief tests, providing expected answers suggesting a proper understanding of each story. In terms of advanced theory of mind tests, both

cases showed good performance on the strange stories test. Overall percentage of providing appropriate explanations for given stories was 85.7% (just one error out of seven) in TO and 100% in HC on the strange stories test. On the faux pas recognition test, the percentage of detecting faux pas and having appropriate explanations was 60.0% in TO and 100% in HC for the provided faux pas stories. In contrast, the percentage of detecting “no” faux pas was 70.0% in TO and 57.1% in HC for the provided control stories. Both cases thus reported faux pas even in control stories without any faux pas. In addition, both cases showed higher scores on the two questions for story comprehension (92.5% for TO and 89.3% for HC).

Autism-spectrum quotient

AQ scores were 31 for TO and 29 for HC, above the threshold score for Asperger syndrome or high-functioning autism of 26 as defined by Woodbury-Smith et al. (2005). Interestingly, both cases spontaneously reported just after completing the questionnaire that they were sure that some of the personality traits focused on in the questionnaire identified the actual personality changes they felt. We then asked them to complete the AQ again for what they supposed their original personality was before surgery. AQ scores for purported pre-surgical state of the two cases were 13 for TO and 23 for HC, much lower than the initial scores and below the threshold score for Asperger syndrome or high-functioning autism. Both cases thus appear to have developed some autistic personality traits following surgical operations. All items representing autistic personality traits developed after surgical operations in both cases are listed in Table 2.

A general finding was that the two cases had developed some characteristics of autism after surgical operations. To specify these characteristics in greater detail, we compared those items to items identified in a two-factor structure model (Hoekstra, Bartels, Cath, & Boomsma, 2008). Two factors were identified among all 50 items in the AQ, namely “social interaction” factor and “attention to detail” factor. In TO, all 18 items fell into the “social interaction” factor, while in HC, 6 of 7 items fell into the “social interaction” factor (Table 2). The only item falling into the “attention to detail” factor in HC was item 9,

TABLE 2

All items representing development of autistic personality traits after surgical operations in both cases

TO
Items changing from <i>definitely disagree</i> or <i>slightly disagree</i> to <i>definitely agree</i> or <i>slightly agree</i>
(4) I frequently get so strongly absorbed in one thing that I lose sight of other things.
(13) I would rather go to library than a party.
(16) I tend to have very strong interests, which I get upset about if I can't pursue.
(20) When I'm reading a story, I find it difficult to work out the characters' intentions.
(21) I don't particularly enjoy reading fiction.
(22) I find it hard to make new friends.
(35) I am often the last to understand the point of a joke.
(45) I find it difficult to work out people's intentions.
(46) New situations make me anxious.
Items changing from <i>definitely agree</i> or <i>slightly agree</i> to <i>definitely disagree</i> or <i>slightly disagree</i>
(8) When I'm reading a story, I can easily imagine what the characters might look like.
(10) In a social group, I can easily keep track of several different people's conversations.
(14) I find making up stories easy.
(17) I enjoy social chit-chat.
(25) It does not upset me if my daily routine is disturbed.
(38) I am good at social chit-chat.
(44) I enjoy social occasions.
(47) I enjoy meeting new people.
(48) I am a good diplomat.
HC
Items changing from <i>definitely disagree</i> or <i>slightly disagree</i> to <i>definitely agree</i> or <i>slightly agree</i>
(9) I am fascinated by dates.
(42) I find it difficult to imagine what it would be like to be someone else.
(45) I find it difficult to work out people's intentions.
Items changing from <i>definitely agree</i> or <i>slightly agree</i> to <i>definitely disagree</i> or <i>slightly disagree</i>
(8) When I'm reading a story, I can easily imagine what the characters might look like.
(10) In a social group, I can easily keep track of several different people's conversations.
(11) I find social situations easy.
(25) It does not upset me if my daily routine is disturbed.

Notes: The number in the top of each item indicates the item number in the AQ questionnaire (Baron-Cohen et al., 2001).

which showed that he had become fascinated by dates.

In another opportunity separate from the present study, we asked 11 cases with damage to other parts of the brain (orbitofrontal lesion, $n = 3$; basal forebrain lesion, $n = 3$; dorsolateral prefrontal lesion, $n = 2$; medial temporal lesion, $n = 1$; amygdala lesion, $n = 1$; and traumatic brain injury, $n = 1$) to complete the AQ, to compare

scores and possible personality changes detected by the AQ. Mean score for the 11 cases was 17.0 (range 9–25), and median score was 17.0. All cases declared that personality traits identified on the AQ were unchanged after surgical operations or closed-head injuries.

DISCUSSION

In this study, we presented two cases with damage to the medial PFC and reported performance on various theory of mind tests, personality changes, and behavioral disturbances in daily activities. The two cases displayed damage basically limited to the medial PFC and showed mild difficulties in memory performance in daily activities, but no serious problems in language activities and executive functions. These patterns of results are basically consistent with previous case studies regarding damage to the same area of the brain (Baird et al., 2006; Bird et al., 2004). Concerning theory of mind tests, performance in the first- and second-order false belief test was perfect in both cases. Performance in the advanced theory of mind tests in TO was slightly impaired regarding the provision of appropriate explanations in the strange stories test and was considerably impaired in the identification of inappropriate verbal expressions for given contexts in the faux pas detection test. In contrast, performance in advanced theory of mind tests in HC was not impaired at all in either test. An interesting finding in both cases was that a faux pas was often reported even in control stories without any obvious faux pas.

The notable finding was that both cases showed some difficulties on the faux pas recognition test. The percentage of detecting faux pas and providing appropriate explanations in HC was 100%, compared to 60.0% in TO. Lower performance by TO may have been caused by deficits in delayed recall performance as found in WMS-R and ROCFT (Table 1). Although TO showed higher scores on the two questions for story comprehension (92.5%), he experienced difficulty in recalling the exact story contents. In fact, TO reported the presence of faux pas for all 10 faux pas stories, but could not recall what the exact contents were in each story. Taking these facts into account, his basic performance for detecting faux pas may not have been greatly reduced.

In contrast, both subjects sometimes incorrectly reported faux pas even in stories containing no faux pas, although they could correctly recognize faux pas in stories containing faux pas. Various factors could explain this pattern of results. First, this pattern could result from perseveration of response in both cases. The response for detecting faux pas could be a prevailing response, as half of the questions in the faux pas test did contain faux pas. However, no strong evidence of perseveration was found in either case, since we found very few total perseveration errors on WCST. Second, the pattern could result from general difficulty in understanding global contexts in complex situations. If this were the case, the subjects would show some problems in detecting faux pas in stories containing faux pas. However, the results were in direct opposition to this prediction. A final possibility is overcompensation. In a psychiatric sense, this is often defined as an attempt to overcome an actual defect or unwanted trait by exaggerating in the opposite direction. Self-reports from the two cases indicated that personality change extended to abnormal feelings in some emotional dimensions. Unfortunately, we did not perform any questionnaires examining anxiety traits, even though both subjects reported anxiety after surgery. These changes may have resulted in subjects being more sensitive to verbal expressions compared to before surgery. The explanation of overcompensation is considered the most plausible for understanding the over-detection of faux pas.

The most interesting finding in the present study was that the two cases showed personality changes after surgery, resulting in some characteristics of autism. These tendencies were mainly clarified by findings from the AQ questionnaire. According to the self-reports shown in Table 2, both cases showed a lack of theory of mind ability in everyday life, reduced spontaneous seeking to communicate with others after surgery, and obsessive focus on a single subject. To elucidate greater detail of those characteristics, we compared those items to the items identified in a two-factor structure model (Hoekstra et al., 2008). As a result, 25 items among the total 26 items for the development of autistic personality traits after surgical operations in both cases fell into the “social interaction” factor. This basically identified acquired functional deficits following damage to the medial PFC as a lack of social interaction. Surprisingly, HC even reported

becoming fascinated by dates, which is considered a strong characteristic of autism. Our results for the number of cases with damage to other areas besides the medial PFC revealed that these personality changes resulted from damage to the medial PFC alone.

However, there are limitations to the interpretation of the present results. We asked the cases to fill out the same questionnaire (AQ) twice, and requested on the second trial that they answer from the perspective of their previous personality before surgery. This obviously represents a “retrospective report” in the post-operative period, and the data are clearly of questionable validity. However, the second AQ trial based on self-reports revealed that some personality traits identified by the questionnaire matched well with actual personality changes reported after surgery. This suggests that results of the second trials were substantially valid. The results were consistent with previous imaging studies for Asperger syndrome, showing that the medial PFC is highly involved in understanding theory of mind stories compared to understanding control stories in normal control and Asperger syndrome groups, although level of peak activation was lower in the Asperger group (Happé et al., 1996). Another interpretation of the AQ rise in both cases is the effect of increased depression and/or anxiety. TO and HC both mentioned feeling depressive and anxious in everyday life. Depression and/or anxiety alone might increase the AQ score. However, most of our control cases with damage to other areas beside the medial PFC reported feeling more or less depressed and anxious, but did not show any increase in AQ score after the damage. This evidence suggests that depression or anxiety alone may not greatly affect AQ score.

In terms of laterality of damage in the medial PFC, clarifying differences in the extent to which cases show damage in each hemisphere is generally difficult (Gilbert, Williamson, Dumontheil, Simons, Frith, & Burgess, 2007). As mentioned above, some previous results support the notion that right hemisphere damage shows as impaired understanding of materials requiring attribution of mental state (Happé et al., 1999). More precise examinations of the present results in the two cases suggest that left-sided damage (TO) resulted in greater acquisition of autism traits than right-sided damage (HC). In contrast, oversensitivity in faux pas tests was relatively more associated with right-sided damage (HC) than left-sided damage (TO). Whether these dissocia-

tive patterns of results with laterality in the medial PFC are essential remains unclear. This inference is consistent with a previous study that reviewed the effect of laterality on theory of mind deficits and found no clear distinction in terms of the laterality of damage (Bird et al., 2004). Further studies are required to clarify this issue.

We were also able to determine the exact location of damage in the medial PFC. Amodio & Frith (2006) reported that the more posterior region of the rostral medial PFC is activated by cognitive tasks (e.g., action monitoring and attention), whereas the more anterior region of the rostral medial PFC is activated by emotional tasks (e.g., rating emotional responses to pictures of varying valence) according to a meta-analysis of task-related neural activations observed in the medial PFC. From these perspectives, TO displayed major damage in the more posterior region of the medial PFC, whereas HC showed major damage to the more anterior region of the medial PFC. Although TO's scores on neuropsychological tests showed no declines in executive functions, scores for attention and concentration and for delayed memory in WMS-R were mildly declined. This suggests that TO experienced some minor deficits in attention functions, consistent with the notion expressed by Amodio & Frith (2006), and also suggests that his amnesic syndrome resulted in lower scores in advanced theory of mind tests. Moreover, the result that TO showed greater acquisition of autism traits than HC seems to be explained by greater declines in social interaction, caused by reduced higher cognitive functions and the following reduced motivation to social communications. This explanation is consistent with some previous studies suggesting that dorsal areas within the PFC are highly involved in social behavior, along with the orbitofrontal cortex (Hornak et al., 2003; Mah, Miriam, & Grafman, 2004; Rudebeck, Bannerman, & Rushworth, 2008).

However, performance in theory of mind tests was less impaired for HC, who displayed major damage to the more anterior region of the medial PFC, than for TO. This is consistent with the previous study (Bird et al., 2004) and is inconsistent with the concepts of Amodio and Frith (2006). The anterior medial PFC is presumably required for efficient realization in theory of mind reasoning, but such reasoning may receive support from other brain areas besides the medial PFC in adults. If the anterior medial PFC plays an important role in theory of mind reasoning

through development, we then need to examine whether adults with early-onset damage to the anterior medial PFC show any deficit in theory of mind performance.

Previous studies have reported functional abnormality in the medial PFC in autism-spectrum disorders during social task performance like theory of mind reasoning (Di Martino et al., 2009). Based on the model by Hoekstra et al. (2008), autism personality traits detected in AQ were divided into "social interaction" and "attention to detail" factors. Considering our result that nearly all items for the development of autistic personality traits in both cases fell into the "social interaction" factor, the medial prefrontal area does not seem to be involved in the personality trait for "attention to detail". Functional abnormality in the medial PFC in autism-spectrum disorders is likely to be associated with a lack of social interaction.

The present study remains preliminary, but some essential implications help in understanding the possible roles of the medial PFC. More research is evidently required to confirm the hypotheses discussed in this study. Besides theory of mind functioning, several recent neuroimaging studies have shown that the medial PFC is involved in moral judgment (Greene, Sommerville, Nyström, Darley, & Cohen, 2001), self-referential processing (Kelley et al., 2002; Schaefer, Berens, Heinze, & Rotte, 2006), memory for self (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004), and detecting the communicative intentions of others (Kampe, Frith, & Frith, 2003). If we expand our discussion by extending the region of interest from the medial PFC to the adjacent anterior cingulate cortex, arguments can be made from the perspectives of cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000), error detection or online monitoring (Carter et al., 2000). Furthermore, the influence of damage to other "social brain" areas needs to be examined. As a recent meta-analysis indicated, the right anterior insula was found to be hypoactive in autism-spectrum disorders compared to the neurotypical control (Di Martino et al., 2009). This area is known to be involved in empathy processing (Singer et al., 2004, 2006). As well as the superior temporal sulcus, amygdala, and posterior cingulate, further examination of the influence of selective damage to these areas on theory of mind performance is required.

Finally, from a comparative neurocognitive perspective, the medial PFC is sure to be an essential area in reaching a full understanding of

the development or evolution of social communications (Rushworth, Walton, Kennerley, & Bannerman, 2004). A morphological study indicated large spindle-shaped cells in layer Vb of the anterior cingulate cortex in pongids and hominids, but not in any other primate species or mammalian taxa (Nimchinsky et al., 1999). Although the ways in which spindle cells contribute to social functions of the anterior cingulate cortex remain unclear, this observation is obviously of great interest in attempts to clarify the mechanisms of possible evolutionary changes to adapt to social worlds.

In sum, we have reported two neurological cases with damage to the medial PFC, focusing on theory of mind performance and personality change. Following damage to this area, both cases showed no impairment on standard theory of mind tests and mild impairments on advanced theory of mind tests. Interestingly, personality changes were found in both cases after surgical operations, leading to characteristics of autism mainly presenting as a lack of social interaction. Recent studies have shown that the medial PFC is involved in various kinds of theory of mind tests. The medial PFC is presumably required for efficient realization in theory of mind reasoning, but such reasoning may receive support from other brain areas in adults. If the medial PFC plays an important role in theory of mind reasoning through development, the critical question in understanding its functions would be whether adults with early-onset damage to the medial PFC show any deficit in theory of mind performance.

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