delirium and was defined as the 'cause' of delirium in this study. When only criteria 1 and 2 were recognized, that is, when delirium with a possible precipitating factor was encountered, the cause of the delirium was qualified as a 'possible factor'.

The following potential precipitating factors and their definitions were utilized in this study.

Psychoactive Medications and Other Drugs (e.g. Opioids, Benzodiazepines, Steroids, Anti-Cholinergic Agents, H2-blockers and Antiepileptic Agents)

Patients received a new psychoactive medication or an increased dosage of a medication known to cause delirium. The use of opioids, benzodiazepines and steroids was examined in each patient, since these drugs are frequently utilized.

Dehydration or Sodium Level Abnormality

A creatinine level higher than 1.3 or a urea nitrogen level of >20 mg/dL in the absence of bleeding into the gastrointestinal tract with hydration. Sodium levels of >150 mmol/L and <130 mmol/L were defined as hypernatremia and hyponatoremia, respectively.

Structural Brain Lesion

Evidence of CNS problems detected during the episode of delirium was obtained by checking for the occurrence of stroke or the presence of brain tumors, although patients with delirium superimposed on obvious dementia or confirmed intracranial lesions had been excluded from the study.

Alcohol or Other Substance Abuse

Withdrawal from alcohol or other drugs is a known cause of delirium, producing clinical evidence of autonomic hyperreactivity or seizure within 7 days of withdrawal.

Hypoxia

Oximetry levels of <90% while receiving room air or requiring an oxygen flow of at least 2 L/min to maintain oxygen saturation levels of at least 90% were regarded as evidence of hypoxic encephalopathy.

Metabolic Factors Like Liver or Renal Failure, Hypoglycemia

The following laboratory reference values were used for specific metabolic factors: aspartate aminotransferase levels of >40 U/L, alanine aminotransferase levels of >50 U/L, bilirubin levels of >1.1 mg/dL (hepatic impairment), a persistent creatinine level of >1.7 mg/dL (renal insufficiency) and a glucose level of <72 mg/dL (hypoglycemia).

Hypercalcemia

Hypercalcemia was recorded if the calcium levels (corrected for the albumin level) were >10.4 mg/dL.

Anemia

A hemoglobin level of <10 g/L was regarded as indicating anemia.

Clotting Abnormality

Laboratory evidence consisting of low platelet levels, prolonged prothrombin and partial thromboplastin times, and D-dimer levels of >0.5 mg/L.

Inflammation

Laboratory evidence consisting of a high white blood cell count or an elevated C-reactive protein level >0.4 mg/dL.

Reversibility of Delirium

Patient response to treatment for delirium was assessed using the DELIRIUM RATING SCALE REVISED 98 (DRS-R-98) (33) 1 week after the baseline assessment. The DRS-R-98 is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items. The severity scale has a possible range of 0–39 and the diagnostic scale has a range of 0–7. Although the DRS-R-98 is more suitable for diagnostic aims, the quantification of symptom severity using this scale is widely accepted in clinical settings. Using a DRS-R-98 severity score of 15/16 points as the cutoff for distinguishing delirium from other psychiatric disorders, a sensitivity of 92% and a specificity of 93% were obtained. According to this cutoff, a 'reversible case' was defined as a patient whose severity score had dropped to 15 or less at the time of the follow-up examination.

Motor Subtypes of Delirium

The motor subtypes of delirium (15–18) were evaluated using available data from clinical interviews, a review of the case records and information obtained from the medical staff. Clinical information used to determine the subtypes was gathered with regard to the mental status of the patient over several days and nights. The clinical subtypes were evaluated using the phenomenological subtypes initially described by Liptzin and Levkoff in 1992 (34). Using this standard, patients were classified as 'hyperactive' subtype if they had 3 or more of 16 items (such as hypervigilance, restlessness), patients were classified as 'hypoactive' subtype if they had 4 or more of 7 items (such as unawareness, decreased alertness) and patients were classified as 'mixed' subtype if they met the criteria for both hyperactive and hypoactive subtypes.

Statistical Analysis

When investigating the relation between cause and reversibility, we regarded the existence of each 'possible factor' as an independent variable and the reversibility of delirium as the dependent variable. We could not take 'cause of delirium' as independent variable in this analysis because its definition included judgment of reversibility (see the criteria used to identify the cause of delirium). When investigating the relation between the cause and the motor subtypes, we regarded the existence of each investigated factor as an independent variable and the subtype of delirium as the dependent variable. Patients with mixed-type delirium were excluded from these analyses to compare the two distinct delirium conditions.

In both analyses, the association between each possible independent and dependent factor was tested using an appropriate univariate analysis to determine the potential factors. Associated factors ($P < 0.10$) were retained. Then, we used a multivariate analysis to investigate these factors. Similarly, a univariate analysis was conducted using demographic data, such as age, sex, stage of cancer (we divided it into I–III and IV or recurrence, and treated it as category data) and performance status (PS) (we divided it into 0–2 and 3–4, and treated it as category data), and significant variables ($P < 0.1$) were entered into a stepwise multivariate logistic regression analysis to adjust potential confounding factors. A χ^2 test or Fisher exact test was used for the univariate analysis of categorical data. The relation between the number of causes and the reversibility of delirium was analyzed using a Mann–Whitney *U*-test. A Kaplan–Meier analysis was used to calculate the survival period from the beginning of psychiatric consultation until death. A two-tailed *P* value of <0.05 was regarded as significant in all of the statistical analyses. The statistical analysis was conducted using the SPSS ver.11.5 Japanese version for Windows.

RESULTS

Patient Characteristics

Among the 112 delirious patients who met the inclusion criteria, 12 patients were excluded from the analysis (10 cases died soon after entry and 2 moved within 1 week of entry). The characteristics of the remaining 100 patients are summarized in Table 1. The mean patient age was 68 years (SD = 12 years), and 69% of the patients were male. About three-quarters of the patients had metastatic or recurrent cancer. More than three-quarters of the subjects had serious physical impairments (PS = 3–4). The median survival time after the diagnosis of delirium was 39 days (inter-quartile range = 124 days). Fifty-eight percent, 26% and 14% of the patients had hyperactive, mixed and hypoactive delirium subtypes, respectively.

Table 1. Demographic data ($N = 100$)

	N	%
Age (years)	Mean 68 (SD = 12), median 70	
Male	69	69
Clinical stage		
I	3	3
II	1	1
III	8	8
IV (metastasis)	48	48
Recurrence	27	27
Other	13	13
Performance status (ECOG)		
1	7	7
2	15	15
3	46	46
4	32	32
Primary cancer site		
Lung	24	24
Esophagus	15	15
Malignant lymphoma	10	10
Stomach	9	9
Colon	8	8
Survival time (days)	Median 39 (IQR = 124)	
DRS-R-98 severity score (points)	Mean 20 (SD = 6)	
Subtype of delirium		
Hyperactive delirium	58	58
Hypoactive delirium	14	14
Mixed type delirium	26	26
Others (unspecified)	2	2

DRS-R-98, Delirium Rating Scale-Revised-98; ECOG, Eastern Cooperative Oncology Group; IQR, inter-quartile range; SD, standard deviation.

Prevalence of Precipitating Factors

The most common cause of delirium was opioids (29%) (Table 2). The use of benzodiazepines and steroids was also identified in 14% and 9% of the subjects, respectively, and the use of psychoactive drugs accounted for ~50% of all causes of delirium. Inflammation reaction, dehydration and sodium abnormality, and metabolism abnormality were recognized in 27%, 15% and 15% of the cases, respectively. Hypercalcemia, anemia, hypoxemia and a clotting abnormality were also observed in <10% of the patients.

Association between the Reversibility of Delirium and the Presence of Each Precipitating Factor

The delirium of 56 patients (56%) who underwent standard treatment improved within 1 week after the baseline examination (Table 2). Delirium caused by opioids was significantly

Table 2. Causes of delirium and reversibility ($N = 100$)

Precipitating factors	Identified cause		Including possible factors[a]		Reversed ($N = 56$)		Non-reversed ($N = 44$)		OR (95% CI)	P value
	N	%	N	%	N	%	N	%		
Opioids	29	29	36	36	15	27	21	48	2.5 (1.1–5.3)	0.03
Inflammation	27	27	43	43	29	36	23	52	2.0 (0.9–4.4)	0.10
Dehydration and sodium abnormality	15	15	24	24	12	21	12	27	1.4 (0.55–3.5)	0.50
Metabolism abnormality	15	15	22	23	9	16	13	30	2.2 (0.84–5.7)	0.10
Benzodiazepines	14	14	19	19	11	20	8	18	0.90 (0.33–2.5)	0.85
Steroids	9	9	14	14	8	14	6	14	0.95 (0.30–3.0)	0.93
Hypercalcemia	8	8	13	13	7	13	6	14	1.1 (.34–3.6)	0.87
Anemia	7	7	15	15	6	11	9	21	2.1 (0.70–6.6)	0.18
Hypoxemia	6	6	8	8	3	5	5	11	2.3 (0.51–10)	0.30
Clotting abnormality	6	6	10	10	3	5	7	16	3.3 (0.81–14)	0.10
No cause apparent	20	20	—	—	17	30	3	15	0.17 (0.05–0.62)	0.005

[a]Divided into two groups of reversible and non-reversible and then analyzed by independent variable 'possible factors'.
OR, odds ratio; 95% CI, 95% confidence interval.

Table 3. Number of precipitating factors and reversibility ($N = 100$)

Number of causes	All cases		Reversed ($P < 0.001$)[a] ($N = 56$)		Non-reversed ($P < 0.001$)[a] ($N = 44$)	
	N	%	N	%	N	%
Unidentified[b]	20	20	17	85	3	15
1	38	38	26	68	12	32
2	23	23	9	39	14	61
3	14	14	3	21	11	79
4	5	5	1	20	4	80

[a]Mann–Whitney U-test.
[b]Unidentified data were analyzed as missing data.

more unlikely to respond to treatment than delirium caused by other factors, as shown using a univariate analysis ($P = 0.03$). However, this significant difference disappeared after adjustments for PS, clinical stage and demographic data were made using a multivariate analysis. The results indicated that only poor physical functioning was a significant predictor of a poor prognosis for delirium.

Number of Causes and Reversibility of Delirium

The reversibility of delirium was significantly influenced by the number of causes (Table 3).

Association between Motor Subtypes of Delirium and the Presence of Each Precipitating Factor

No significant relations between motor subtypes of delirium and causes of delirium were seen (Table 4).

DISCUSSION

This is the first study to investigate the causes of delirium and their associations with reversibility and motor subtype in cancer patients who were admitted to a general ward. Medicines, such as opioids, and inflammation were the most common causes of delirium. None of the investigated factors showed a significant association with reversibility or clinical subtype.

Medicines, including opioids, were the most frequently identified causes of delirium in cancer patients hospitalized in general wards, consistent with the findings of previous studies performed in different clinical oncology settings. Since pain is a prevalent symptom and opioids are widely used to alleviate pain in cancer patients, opioid-induced delirium is probably the most common cause of delirium in an oncology setting. Infection, dehydration and sodium level abnormality were the next most common causes of delirium.

Table 4. Relation between causes of delirium and clinical subtype

	Hyperactive ($N = 58$)		Hypoactive ($N = 14$)		P value
	N	%	N	%	
Opioids	13	22	6	43	0.16
Inflammation	16	28	2	14	0.49
Dehydration and sodium abnormality	9	16	1	7	0.68
Metabolism abnormality	8	14	1	7	0.68
Benzodiazepines	11	19	2	14	1.00
Steroids	4	7	1	7	1.00
Hypercalcemia	3	5	1	7	1.00
Anemia	4	7	1	7	1.00
Hypoxemia	5	9	0	0	0.58
Clotting abnormality	2	3	2	14	0.17

Fisher's exact test was performed using the hyperactive and hypoactive conditions.

These factors have also been previously reported as potentially important causes of delirium in cancer patients. Thus, the current study, as well as previous studies, demonstrates that opioids, infection, dehydration and mineral imbalances are common causes of delirium in cancer patients, regardless of the clinical setting. In this regard, opioid-induced delirium (76%) was commonly observed in a study by Lawlor et al. (2) (see the Introduction section). On the other hand, we cannot claim, based on the present findings, that these factors, when present, will commonly cause delirium.

The cause of delirium could not be identified in ~20% of the cases. Although we utilized a structured assessment of the causes of delirium in the current study, a more comprehensive evaluation may be necessary. Because some recent studies have suggested other possible causes of delirium, such as vitamin B1 deficiency (35), in cancer patients, our method might have failed to recognize the causes of delirium comprehensively. Antagonistically, high rate of unknown cause was may reflect the quite stringent criteria for attribution of cause in the methods. Some delirium might occur in cancer patients as a result of the accumulation of multiple mild abnormalities or potential factors. Furthermore, 1 week follow might not be long enough to see a reversal in delirium. On the other hand, multiple causes were identified in ~40% of the cases. According to data obtained in palliative care settings, Lawlor et al. and Morita et al. reported that the causes of delirium could not be identified in 1% and 7% of the cases, respectively. And, they also reported that the median number of identified factors were 3 and 2, respectively. These findings suggest that the causes of delirium observed in a general medical ward setting may vary to a greater extent than those in a palliative care setting, and medical staff members should pay attention to a broader range of possible causes.

The current study did not find an association between specific delirium-precipitating factors and delirium reversibility, and only physical functioning independently influenced the reversibility of delirium. Insomuch as patients receiving opioids in general wards may have a more critical physical condition, the influence of opioids on delirium may have been indirect. On the other hand, some previous studies conducted in palliative care settings have reported that delirium induced by medicines, such as opioids, is more likely to be reversible than delirium induced by other causes (2,4,16,17). Several possible explanations for the observed difference exist. First of all, the treatment interventions after the cause of the delirium had been identified may have differed. Namely, we only notified each patient's physician of the precipitating factors of delirium; whether any intervention was subsequently provided depended on the physician's practice. On the other hand, previous studies in palliative care settings applied more active and structured interventions, such as opioid rotation. The fact that delirium could not be improved in patients with multiple identified causes of delirium may indicate that delirium resulting from multiple causes is more difficult to recover from. In addition, more opioid-induced delirium occurred in a PCU setting study, suggesting that if opioids are widely used, the reversibility of delirium may increase.

The delirium which had many causes was hard to recover in this study. It may be because in the delirium developing from complicated causes, namely the delirium with many causes, it was difficult to treat its precipitating factors. In addition, the patients with delirium developing from complicated causes had such bad physical conditions that the condition was hardly reversible.

No specific delirium-precipitating factors were associated with the motor subtypes of delirium in the present study. Morita et al. (4) only just reported that hyperactive symptoms were significantly associated with drug-induced delirium, whereas dehydration-related pathologies were significantly associated with hypoactivity in a palliative care setting. Thus, the findings regarding the association between the cause of delirium and the motor subtype are inconsistent. In addition, the motor subtype of delirium may result from other factors (e.g. complicated clinical factors, biological factors, the patient's condition and the interaction of factors), rather than the causes that were investigated. Furthermore, the definition of delirium subtypes is problematic, and the operational definitions of the subtypes vary among study (36). To clarify the association between causal factors and the delirium subtype, further studies that overcome these issues are needed. On the other hand, the sample in this study had a high percentage of hyperactive cases contrasts with other studies of cancer patients. The exclusion of cases with dementia may also have reduced the frequency of hypoactive delirium. In addition, the reversibility of delirium was higher than other studies, again possibly related to high frequency of hyperactive delirium where prognosis seemed better.

The current study has several advantages. One advantage was the investigational setting, as our study was performed in a general ward. Thus, our findings may be easier to generalize than those obtained in palliative care settings. Additionally, with regard to identifying the cause of the delirium, the time–dosage relation was judged more strictly than in other studies. Furthermore, clear subtype criteria that were independent of severity-of-illness evaluations and evaluations of cognitive function were used for the subtype evaluation.

This study also has several limitations. First, the referred patient sample may have been influenced by a physician bias. In particular, hypoactive delirium can be easily overlooked by physicians, and this may have led to a selection bias among the subjects. Second, the sample size is relatively small which may account for the lack of positive findings. In particular, the relation between the cause of delirium and the delirium subtype may have been distorted as there were very few cases of hypoactive delirium; consequently, significant features may have been overlooked. Furthermore, in our study, the treatment protocol was not standardized and approaches to delirium depended on the physician's practice or interest. This may have biased the assessment of its reversibility.

In conclusion, medication-induced delirium, especially opioid-induced delirium, is commonly observed in cancer patients hospitalized in general wards. Although opioids are a very important medication for cancer patients, their use must be carefully observed when medical examinations are performed in psychiatric consultation service. In addition, the causes of delirium were not association with delirium reversibility or the motor subtype of delirium. Additional research and biological classification are needed in the future.

Funding

This study was supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Labor, Health and Welfare.

Conflict of interest statement

None declared.

References

1. Bruera E, Miller L, McCallion J, Macmillan K, Krefting L, Hanson J. Cognitive failure in patients with terminal cancer: a prospective study. *J Pain Symptom Manage* 1992;7:192–5.
2. Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000;160:786–94.
3. Massie MJ, Holland J, Glass E. Delirium in terminally ill cancer patients. *Am J Psychiatry* 1983;140:1048–50.
4. Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. *J Pain Symptom Manage* 2001;22:997–1006.
5. Minagawa H, Uchitomi Y, Yamawaki S, Ishitani K. Psychiatric morbidity in terminally ill cancer patients. A prospective study. *Cancer* 1996;78:1131–7.
6. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. *Cancer* 1997;79:835–42.
7. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *Jama* 1990;263:1097–101.
8. Breitbart W, Strout D. Delirium in the terminally ill. *Clin Geriatr Med* 2000;16:357–72.
9. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics* 2002;43:183–94.
10. Morita T, Akechi T, Ikenaga M, Inoue S, Kohara H, Matsubara T, et al. Terminal delirium: recommendations from bereaved families' experiences. *J Pain Symptom Manage* 2007;34:579–89.
11. Morita T, Hirai K, Sakaguchi Y, Tsuneto S, Shima Y. Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. *Psychosomatics* 2004;45:107–13.
12. Gaudreau JD, Gagnon P, Harel F, Roy MA, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. *J Clin Oncol* 2005;23:6712–8.
13. Gaudreau JD, Gagnon P, Roy MA, Harel F, Tremblay A. Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. *Cancer* 2007;109:2365–73.
14. Olofsson SM, Weitzner MA, Valentine AD, Baile WF, Meyers CA. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. *Support Care Cancer* 1996;4:351–7.
15. de Rooij SE, Schuurmans MJ, van der Mast RC, Levi M. Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. *Int J Geriatr Psychiatry* 2005;20:609–15.
16. Meagher DJ, O'Hanlon D, O'Mahony E, Casey PR, Trzepacz PT. Relationship between symptoms and motoric subtype of delirium. *J Neuropsychiatry Clin Neurosci* 2000;12:51–6.
17. Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. *Semin Clin Neuropsychiatry* 2000;5:75–85.
18. Santana Santos F, Wahlund LO, Varli F, Tadeu Velasco I, Eriksdotter JM. Incidence, clinical features and subtypes of delirium in elderly patients treated for hip fractures. *Dement Geriatr Cogn Disord* 2005;20:231–7.
19. Camus V, Gonthier R, Dubos G, Schwed P, Simeone I. Etiologic and outcome profiles in hypoactive and hyperactive subtypes of delirium. *J Geriatr Psychiatry Neurol* 2000;13:38–42.
20. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J, et al. Phenomenology of delirium. Assessment of 100 adult cases using standardised measures. *Br J Psychiatry* 2007;190:135–41.
21. Meagher DJ, O'Hanlon D, O'Mahony E, Casey PR, Trzepacz PT. Relationship between etiology and phenomenologic profile in delirium. *J Geriatr Psychiatry Neurol* 1998;11:146–9. discussion 157-8.
22. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. *Palliat Support Care* 2004;2:171–9.
23. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders—Text Revision. 4th edn. Washington, DC: American Psychiatric Publishing, Inc. 1994.
24. Practice Guideline for the Treatment of Patients with Delirium. Also includes Treating Delirium: A Quick Reference for Psychiatrists. Washington, DC: American Psychiatric Association 1999.
25. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. *Palliat Support Care* 2005;3:227–37.
26. Breitbart W, Marotta R, Platt M, Weisman H, Derevenco M, Grau C, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996;153:231–7.
27. Ozbolt LB, Paniagua MA, Kaiser RM. Atypical antipsychotics for the treatment of delirious elders. *J Am Med Dir Assoc* 2008;9:18–28.
28. Rea RS, Battistone S, Fong JJ, Devlin JW. Atypical antipsychotics versus haloperidol for treatment of delirium in acutely ill patients. *Pharmacotherapy* 2007;27:588–94.
29. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. *J Clin Psychiatry* 2007;68:11–21.
30. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med* 2004;30:444–9.

31. Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics* 2004;45:297–301.
32. Tuma R, DeAngelis LM. Altered mental status in patients with cancer. *Arch Neurol* 2000;57:1727–31.
33. Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci* 2001;13:229–42.
34. Liptzin B, Levkoff SE. An empirical study of delirium subtypes. *Br J Psychiatry* 1992;161:843–5.
35. Onishi H, Sugimasa Y, Kawanishi C, Onose M. Wernicke encephalopathy presented in the form of postoperative delirium in a patient with hepatocellular carcinoma and liver cirrhosis: A case report and review of the literature. *Palliat Support Care* 2005;3:337–40.
36. Meagher DJ, Moran M, Raju B, Gibbons D, Donnelly S, Saunders J, et al. Motor symptoms in 100 patients with delirium versus control subjects: Comparison of subtyping methods. *Psychosomatics* 2008; 49:300–8.

Psychiatry Research: Neuroimaging xxx (2008) xxx–xxx

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder

Tomoaki Yamanishi[a], Shutaro Nakaaki[a,*], Ichiro M. Omori[a], Nobuhiko Hashimoto[a], Yoshihiro Shinagawa[a], Jin Hongo[a], Masaru Horikoshi[b], Junko Tohyama[c], Tatsuo Akechi[a], Tsutomu Soma[d,e], Tetsuya Iidaka[f], Toshi A. Furukawa[a]

[a]Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya City, Japan
[b]Department of Comprehensive Human Sciences, University of Tsukuba Graduate School, Tsukuba City, Japan
[c]Department of Radiology, TOYOTA -kai Medical Corporation Kariya, Toyota General Hospital, Nagoya City, Japan
[d]Clinical Application Technology Group, Fujifilm RI Pharma Company Limited, Tokyo, Japan
[e]Department of Medical Physics and Engineering, Division of Medical Technology and Science, Graduate School of Medicine, Osaka University, Osaka, Japan
[f]Department of Psychiatry, Nagoya University, Graduate School of Medicine, Nagoya City, Japan

ARTICLE INFO

Article history:
Received 17 November 2007
Received in revised form 19 May 2008
Accepted 4 July 2008
Available online xxxx

Keywords:
Single photon emission computed tomography
Statistical parametric mapping
Orbitofrontal cortex
Medial prefrontal cortex
Middle frontal cortex

ABSTRACT

Neuroimaging studies have suggested that behavior therapy (BT) might change abnormal activity in the frontal-subcortical circuits of the brain in patients with obsessive-compulsive disorder (OCD). However, the results of these studies have been rather inconsistent. The aim of the present study was to use statistical parametric mapping (SPM) analysis to explore the effects of successful BT on regional cerebral blood flow (rCBF) in patients with OCD. Forty-five OCD patients who were treatment-resistant to a single serotonin reuptake inhibitor (SRI) trial were examined. Single photon emission computed tomography (SPECT) using 99mTc-ECD was performed before and after the completion of 12 weeks of BT. Although no significant differences in pre-treatment rCBF were observed between responders and nonresponders to BT, the post-treatment rCBF values in the left medial prefrontal cortex (Brodmann area 10) and bilateral middle frontal gyri (Brodmann area 10) were significantly lower in the responders than in the nonresponders. Furthermore, the baseline rCBF in the bilateral orbitofrontal cortex (OFC) was significantly correlated with the change in the Y-BOCS score among the responders. Our results support the hypothesis that while the OFC may be associated with the BT response, BT may result in changes in rCBF in the medial and middle frontal cortex.

1. Introduction

The orbitofrontal cortex (OFC)-striatal circuit plays an important role in the pathogenesis of obsessive-compulsive disorder (OCD). Both the administration of serotonin reuptake inhibitors (SRIs) and behavior therapy (BT), composed of exposure and response prevention (ERP), have been found to be effective for the treatment of OCD (Jenike, 1998). The effects of SRI therapy are thought to be associated with changes in neural activity in either the OFC or the caudate nucleus (Brody et al., 1998; Saxena et al., 1999, 2002, 2003).

In contrast, only six studies have investigated the neural effect of BT in patients with OCD. The first neuroimaging study on patients with OCD was reported by Baxter et al. (1992), who used positron emission tomography (PET) to examine the effects of BT ($n=9$) versus fluoxetine treatment ($n=9$) in OCD patients. Decreased right caudate metabolic rates were found in both groups. In a follow-up study, Schwartz et al. (1996) added nine OCD patients to the previous study group (Baxter et al., 1992) and replicated their previous findings ($n=18$). Brody et al. (1998) analyzed the pre-treatment metabolism of patients who responded to either BT ($n=18$) or fluoxetine treatment ($n=9$); the patients in Brody's study had been previously described in two other studies (Baxter et al., 1992; Schwarz et al., 1996). They found that a higher pretreatment metabolic activity in the left OFC was associated with a better response to BT. In contrast, a lower left OFC pretreatment level of metabolic activity was associated with a better response to fluoxetine. This study suggested that the pre-treatment metabolic activity in the OFC was correlated differently with BT and fluoxetine. Recently, Saxena et al. (2009) reported that the rapid response of OCD patients to intensive cognitive-behavior therapy (CBT) might be mediated by a distinct pattern of changes in regional brain function (decrease in bilateral thalamic activity vs. increase in anterior cingulate cortex [ACC]).

Several neuroimaging studies of psychotherapy in Japanese patients with OCD have recently been conducted. One study (Nakatani et al., 2003) used xenon-enhanced computed tomography (Xe-CT)

* Corresponding author. Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Tel.: +81 52 853 8271; fax: +81 52 852 0837.
E-mail address: hzi05510@nifty.com (S. Nakaaki).

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doi:10.1016/j.pscychresns.2008.07.004

and reported a significant reduction in the regional cerebral blood flow (rCBF) in the right caudate nucleus following BT in patients with OCD ($n=22$). Another group (Nakao et al., 2005a,b) used functional magnetic resonance imaging (fMRI) to conduct a provocation study of the BT effect in patients with OCD. After combining the data from both BT ($n=4$) and SRI therapy ($n=6$) groups, they observed changes in broadly activated areas associated with prefrontal-subcortical-cerebellar connections.

However, all previous studies on the neural effects of BT in patients with OCD have several limitations. Firstly, the sample sizes were relatively small: the largest sample number was only 22 patients. Secondly, all previous studies except one (Nakao et al., 2005b) investigated the effect of BT using a region-of-interest (ROI) approach. An ROI approach may increase the effects of statistical artifacts, such as type I errors, if either a large area or only one region is inappropriately chosen (Bonne et al., 2003). In contrast, a voxel-based analysis using statistical parametric mapping (SPM) has the advantage of a greater statistical power to identify relative changes in significant patterns of rCBF. However, the disadvantage of this technique lies in the possibility of producing type II errors. Another disadvantage lies in the process of spatial normalization, in which each voxel in all the subjects is transformed in the same stereotactic space. A recent study by Saxena et al. (2009) suggested that a magnetic resonance imaging (MRI)-based ROI analysis in each subject may be preferable to an SPM analysis because the normalization process used during SPM analysis can produce errors as a result of anatomic variability among OCD patients. Therefore, the results of both methods (SPM and MRI-based ROI analysis) should be compared in a single study. Thirdly, the neural mechanisms between responders to BT and nonresponders to BT remain unclear.

In the present study, we examined rCBF changes after successful BT treatment in a relatively large number of patients ($n=45$) with OCD using an SPM analysis of 99mTc-ECD single photon emission computed tomography (SPECT) images. The aims of the study were: 1) to compare rCBF between responders versus nonresponders both before and after treatment; 2) determine in which areas baseline rCBF values changed significantly after the completion of BT in responders and nonresponders; and 3) to determine whether pre-treatment rCBF can predict a response to BT in patients with OCD. In addition, we performed an MRI-based ROI approach to confirm the results of the SPM analysis. We hypothesized that changes would occur in the OFC-striatal circuits of patients with OCD who responded to BT.

2. Methods

2.1. Subjects

Japanese patients with OCD were recruited at Nagoya City University Hospital. Diagnoses were made on the basis of structured interviews conducted by trained psychiatrists using the Structured Clinical Interview for DSM-IV Patient Version (SCID-P). Before their enrollment in this study, all the OCD patients had been taking SRIs for at least 3 months. During the 3 months, these OCD patients did not respond to at least one course of full-dose SRI therapy at our hospital (minimum doses: clomipramine, 150 mg/day; fluvoxamine, 200 mg/day; paroxetine, 40 mg/day) (Tolin et al., 2004). Therefore, these OCD patients were regarded as treatment-resistant to SRIs because they had failed one adequate trial of an SRI (Pallanti et al., 2004). In accordance with the criteria used by many pharmacological trials (Kampman et al., 2002; Tolin et al., 2005; Ninan et al., 2006), the treatment was classified as unsuccessful when a decrease of less than 25% in the global Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score was observed.

The SRI dose administered to each patient was not altered during the entire course of BT. The OCD patients were not permitted to use any psychotropic medication other than SRIs during the study. The equivalence of each drug was calculated according to a previously described method (Bollini et al., 1999), in which the recommended therapeutic dose was standardized with respect to the recommended dose of clomipramine (150 mg/day).

The exclusion criteria were presence of a current or past neurological or other significant medical illness, substance dependence, mental retardation, or pregnancy. Patients with other axis I disorders were excluded. Although we did not utilize the SCID-P criteria to exclude patients, trained psychiatrists confirmed these criteria based on a clinical diagnostic interview and the DSM-IV. Patients with other axis I disorders were excluded. Patients with either a current major depressive disorder or a lifetime history of bipolar disorder were also excluded.

The study's protocol was approved by the Ethics Committee of Nagoya City University Graduate School of Medical Sciences, and all the subjects provided their written informed consent.

2.2. Clinical assessments

OCD severity was assessed using the clinician-rated 10-item Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989a, b). An improvement in the global Y-BOCS score of 40% or greater was considered to represent a clinical response because a recent study suggested that patients whose Y-BOCS scores decreased by 39% or less were still rated as moderately ill at post-treatment (Tolin et al., 2005). Furthermore, Tolin et al. (2005) suggested that treatment responders, as defined by a Y-BOCS reduction cutoff of 40% to 50%, were in remission. Therefore, we adopted a more stringent criterion for the clinical outcome of BT than for SRI therapy. Two trained clinical psychiatrists assessed the Y-BOCS independently. The intraclass correlation was 0.87 (95% IC: 0.75 to 0.93) for the pretreatment Y-BOCS scores and 0.85 (95% IC: 0.70 to 0.92) for the post-treatment Y-BOCS scores, suggesting an excellent inter-rater reliability. The clinical subtypes of OCD were identified using the Y-BOCS symptom checklist. In addition, the severity of depression was assessed using the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), while the severity of anxiety was assessed using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970). These clinical ratings were assessed at baseline and at the completion of BT. However, both the pre-Y-BOCS and the post-Y-BOCS were assessed on the days of the pre- and post-treatment SPECT examinations, respectively.

Two-tailed t-tests were used to compare demographic data between the groups (responders vs. nonresponders). The male/female ratio was compared using the Fisher exact test. In addition, we compared the changes in the clinical treatment effects before and after BT among both the responders and the nonresponders using paired t-tests.

2.3. Procedure

2.3.1. Treatment

Individual BT led by experienced psychiatrists was performed using a detailed treatment manual (Iikura, 1999). This treatment manual has been used successfully in previous outcome trials (Nakatani et al., 2005) The treatments consisted of 45-min sessions one to five times a week for approximately 12 consecutive weeks. The mean time from the first session to the completion of BT was 90.7 ± 5.2 days. All the patients who participated in this study were treated by at least two psychiatrists under the supervision of an ERP expert to monitor the quality of therapy. BT consisted of the following sessions: The first session included psycho-education about the nature of OCD and the BT model for the treatment of OCD. The second session began with treatment-planning based on both the behavior analysis and an exposure hierarchy of anxiety-evoking situations. Following the planning sessions, the ERP sessions began. Exposure exercises were arranged hierarchically, beginning with mild or moderately distressing ones. Patients were encouraged to persist with each exposure until their distress decreased noticeably. All patients received therapist-guided

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behavior therapy sessions at least once a week. Patients received a flexible dose schedule of between one to five visits per week because a recent study (Abramowitz et al., 2003) has suggested that less intensive ERP schedules are as effective as more intensive schedules. However, all patients were assigned to approximately 3 h of ERP homework tasks five times a week with self-management. During the later sessions, the patients were required to reach the highest item on their exposure hierarchy in a naturalistic situation.

2.3.2.. SPECT procedure

Investigations using a SPECT scanner to evaluate rCBF were performed at the Department of Radiology of Nagoya City University Hospital. In the patients with OCD, the first SPECT scan was conducted during a 14-day period prior to the start of BT. The second SPECT scan was completed within 14 days after the last BT treatment. All the OCD patients were studied while in a supine resting position in a quiet room. They were instructed to remain awake with their eyes open and to lie still and not talk. A dose of approximately 600 MBq of 99mTc-ECD was injected intravenously. Fifteen minutes after the injection, the scans were performed using a dual head gamma camera equipped with low-energy, high-resolution parallel hole collimators of ECAM (Siemens Medical Solutions USA, Inc.). The energy window was set at 140 keV with a 20% width. The images were obtained using a 128×128 matrix and a pixel size of 3.3 mm. The acquisition time for each projection was 20 s, with a total imaging time of 15 min for all 36 steps. Images were reconstructed using filtered back-projection (Ramp filters) with Butterworth prefiltering (power factor = 8, cut-off frequency = 0.4 cycles/pixel). Attenuation correction was performed using Chang's algorithm (Chang, 1978), with an attenuation coefficient of 0.1/cm. The spatial resolution at full width at half maximum (FWHM) of the reconstructed images was 9 mm.

Although a positron emission tomography (PET) scan provides a higher resolution and is more sensitive than information obtained by SPECT, SPECT devices are widely applied for supplemental investigations in clinical settings. In addition, a SPECT scan is more cost-effective than a PET scan.

2.3.3. Structural MRI

All brain images were acquired at baseline using a 1.5-T MRI system (Gyoro Scan Interu; Philips). The scanning parameters for the three-dimensional magnetization-prepared, rapid-gradient echo (3D-MPRAGE) sequences were as follows: echo time (TE) = 3.70 ms; repetition time (TR) = 8000 ms; inversion time (TI) = 1000 ms; field of view (FOV) = 256×256 mm^2; resolution = $1.0 \times 1.0 \times 1.0$ mm^3; 160 axial slices covering the whole brain; and slice thickness = 1.0 mm. The digital images were reviewed on a Windows workstation using MRI cro software.

2.3.4. SPECT imaging analysis

All images were transferred from the SPECT imaging units to a Windows workstation, where statistical analyses of all the data were conducted on a voxel-by-voxel basis using SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) software implemented in MatLab 7.0 (Mathworks, Inc., Sherborn, Massachusetts, USA). Using a ^{99m}Tc-ECD template, the SPECT data were transformed into a standard stereotaxic space (Montreal Neurological Institute; MNI) and smoothed using a 12-mm isotropic Gaussian filter. In the SPECT analysis, an isotropic Gaussian filter is recommended for use at the full-width at half-maximum (FWHM) of the SPECT device (Ohnishi, 2004). In most previous SPECT studies, images were smoothed using a 12-mm Gaussian filter (Matsuda et al., 2003, 2004). Thus, we utilized a 12-mm isotropic Gaussian filter to smooth the images.

An SPM 2 analysis for comparisons was performed using a design model consisting of a one-scan-per-condition paired *t*-test. We used a *t*-test to compare responders versus nonresponders both before and after the completion of BT. Next, the pretreatment and post-treatment images were compared in each group. In addition, we also examined the correlation between the baseline rCBF and the change in the Y-BOCS score among not only the responders, but also among all the OCD patients and among the nonresponders. For the correlational analysis, we used Pearson correlation coefficients. Also, we included the total number of BT sessions, the changes in the BDI-II score, and the STAI (state, trait) score in the analysis as covariates. We then subtracted the smoothed images obtained before BT from the corresponding images obtained after BT among not only the responders, but also among the nonresponders and examined the correlations between the changes in the rCBF pattern distribution and the changes in the Y-BOCS scores, the BDI-II score, and the STAI (state, trait) score. In this analysis, the voxel-wise statistical threshold of significance was set at $P<0.01$, corrected for multiple comparisons using the false discovery rate (FDR) approach (Genoverse et al., 2002). Cluster significance thresholds were set at 200 voxels to reduce possible noise. Based on the findings of a previous study (Brody et al., 1998), we expected that the OFC would be associated with a better response to BT. Therefore, for the regions specifically hypothesized to change with treatment, the uncorrected threshold of significance was set at $P<0.001$ for the between-group analysis (responders vs. nonresponders) and the within-group analysis (nonresponders) so as to include important information on rCBF regions in nonresponders. These areas generated statistical parametric maps of the *t*-statistics (SPM {*t*}), which were subsequently converted to a unit-normalized distribution (SPM{*Z*}). The cluster locations were converted from coordinates related to the MNI atlas system to coordinates related to the Talairach atlas.

In addition, we performed an MRI-based ROI analysis using images obtained from the OCD patients who underwent an MRI scan. For this analysis, we used the Brain Easy Analysis Tools (BEAT) (Takeuchi et al., 2005) running on a Windows workstation. This software consists of automated image registration (AIR) and an image calculation program. The BEAT program allowed the optimal co-registration of each patient's pre- and post-treatment SPECT images within a three-dimensional orientation of the patient's MR images. Then, the ROIs were identified and outlined on the horizontal MR images of each MRI scan by one examiner who was unaware of the patients' clinical information or identity. The mean 99mTc-ECD uptake values in each ROI volume were normalized to the mean uptake value of the whole brain. For the statistical analysis, we compared the responders and the nonresponders using Student *t*-tests. We also examined the relationship between the baseline rCBF and the change in the Y-BOCS score. For the correlational analysis, we used Pearson correlation coefficients.

3. Results

3.1. Clinical characteristic of participants

Sixty-five patients were enrolled in this study. Eleven patients dropped out during the waiting-list period because of either a worsening of OCD symptoms or their transfer to another clinic. Nine more patients discontinued treatment prior to the end of BT because of unwillingness to comply with BT. As a result, 45 patients completed the BT. Eleven of the 45 patients did not undergo a brain MRI examination. Comparisons of the clinical or demographic characteristics revealed no significant differences between OCD patients who dropped out or discontinued treatment ($n = 20$) and those who completed the treatment ($n = 45$) (all *P* values > 0.10). Among the 45 patients with OCD, 33 were regarded as responders and 12 were regarded as nonresponders, according to the above-mentioned criteria. Table 1 shows the mean scores and the standard deviations of the clinical or demographic characteristics for the responding and nonresponding OCD patients. No significant differences in the baseline clinical or demographic characteristics were observed between the two OCD groups.

The clinical OCD subtypes of the 45 patients were predominantly contamination/cleaning symptoms ($n = 15$) and aggressive/checking

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Table 1
Demographic and clinical findings of OCD group ($n=45$).

	Responders ($n=33$)	Nonresponders ($n=12$)	P
Age, years	34.7 ± 7.1	32.1 ± 7.1	0.301
Gender ratio (male/female)	14/19	5/7	0.83
Right-handed (%)	100	100	
Years of education	14.1 ± 1.8	14.8 ± 1.3	0.106
Duration of illness (years)	6.6 ± 3.1	5.2 ± 2.8	0.153
SRI mg/day (clomipramine-equivalent dosage)	224.2 ± 31.2	233.3 ± 38.9	0.477
Y-BOCS total score	33.5 ± 4.5	34.4 ± 4.8	0.596
BDI-II	14.8 ± 6.2	13.3 ± 6.5	0.394
STAI			
State anxiety	52.6 ± 11.9	57.7 ± 10.6	0.181
Trait anxiety	54.6 ± 12.1	61.5 ± 11.1	0.083

SRI, serotonin reuptakeInhibitors, Y-BOCS, the Yale-Brown Obsessive Compulsive Scale. BDI-II, the Beck Depression Inventory-II. STAI, the State-Trait Anxiety Inventory.

($n=12$). The remaining OCD patients had two ($n=16$) or three ($n=2$) symptoms.

3.2. Clinical findings before and after treatment

As shown in Table 2, the mean Y-BOCS score drastically decreased after approximately 12 weeks of BT in the responders group ($P<0.001$), and the mean percent reduction in the Y-BOCS score was 51.4% ± 7.1%. Among the nonresponders, on the other hand, although the mean Y-BOCS score significantly decreased after approximately 12 weeks of BT ($P=0.03$), the mean percent reduction in the Y-BOCS score was only 13.7% ± 7.3%.

Furthermore, the mean STAI score also decreased significantly after BT, but only among the responders. The mean BDI-II score, however, did not change significantly before and after BT among either the responders or the nonresponders. The changes in the Y-BOCS score were not correlated with the total number of BT sessions in either the responders ($r=0.03$, $P=0.83$) or the nonresponders ($r=0.01$, $P=0.98$). Also, in terms of the total number of BT sessions, no significant difference ($P=0.92$) between the responders (54.04 ± 5.36, range = 42–60) and the nonresponders (54.41 ± 4.53, range = 46–60) was seen.

3.3. SPECT Results

3.3.1. Comparison of rCBF values in responders versus nonresponders before and after BT

Before BT, no significant differences were observed between the responders and the nonresponders. After the completion of BT, the post-treatment rCBF values in the left medial prefrontal cortex (Brodmann area 10) and bilateral middle frontal gyri (Brodmann area 10) were significantly lower among the responders ($n=33$) than among the nonresponders ($n=12$) ($P<0.001$, uncorrected) (Table 3, Fig. 1). No significantly higher areas of post-treatment rCBF were seen in the responders, relative to the levels in the nonresponders.

Table 2
Clinical findings before and after behavior treatment in the OCD group ($n=45$).

	Before treatment	After treatment	P
Responders ($n=33$)			
Y-BOCS total score	33.6 ± 4.5	16.2 ± 3.7	<0.001
Obsessions	16.8 ± 2.3	8.2 ± 2.1	<0.001
Compulsions	16.6 ± 2.7	8.1 ± 2.2	<0.001
BDI-II	15.9 ± 6.7	15.4 ± 6.1	0.15
STAI			
State anxiety	52.6 ± 11.9	41.1 ± 9.8	<0.001
Trait anxiety	56.1 ± 11.6	49.4 ± 8.4	<0.001
Nonresponders ($n=12$)			
Y-BOCS total score	34.4 ± 4.8	29.6 ± 4.7	0.03
Obsessions	17.5 ± 2.7	15.7 ± 3.5	0.16
Compulsions	16.8 ± 2.5	14.1 ± 2.4	0.02
BDI-II	16.1 ± 7.3	15.1 ± 6.9	0.75
STAI			
State anxiety	57.7 ± 10.6	54.8 ± 11.4	0.52
Trait anxiety	61.5 ± 11.1	53.9 ± 8.5	0.07

A paired t-test was used for the statistical analysis.
Y-BOCS, Yale–Brown Obsessive Compulsive Scale. MOCI, Maudsley Obsessive–Compulsive Inventory. BDI-II, Beck Depression Inventory-II. STAI, State-Trait Anxiety Inventory.

Table 3
Areas with lower post-treatment rCBF values in responders ($n=33$) than in nonresponders ($n=12$) (uncorrected $P<0.001$) (Results of a voxel-wise SPM analysis).

Region	Brodmann's Area	Talairach coordinate			Voxels in cluster	Z value
		x	y	z		
R. middle frontal gyrus	10	46	50	3	1972	3.16
L. medial prefrontal cortex	10	−8	62	14	1972	3.12
L. medial prefrontal cortex	10	−2	66	−5	1972	3.04
L. middle frontal gyrus	10	−38	44	10	1530	3.94
L. middle frontal gyrus	10	−44	48	−2	1530	2.51

R, right; L, left.

3.3.2. Comparison of pretreatment versus post-treatment rCBF values in responders and nonresponders

Among the responders ($n=33$), the post-treatment rCBF values were lower than the pretreatment values in the left middle frontal gyrus (Brodmann area 10), the right medial prefrontal cortex (Brodmann area 10), the right inferior frontal cortex (Brodmann area 46), and the right orbitofrontal cotex (OFC; Brodmann area 11) ($P_{FDR\text{-}CORR}<0.01$, corrected) (Table 4). Fig. 2 shows the reduced rCBF in these specific areas in the responders after BT. In contrast, the post-treatment rCBF values were higher than the pretreatment values in the right fusiform gyrus (Brodmann area 19), the right cuneus (Brodmann area 19) (occipital cortex), and the right angular gyrus (Brodmann area 40) (parietal cortex) ($P_{FDR\text{-}CORR}<0.01$, corrected) (Table 5). Fig. 3 shows the increased rCBF in these specific areas in the responders after BT. Among the nonresponders ($n=12$), the pretreatment and post-treatment rCBF values were not significantly different.

3.3.3. Correlation between baseline rCBF and change in the Y-BOCS score

Among all the OCD patients ($n=45$), the reduction in the Y-BOCS score was negatively correlated with the pre-treatment rCBF in the

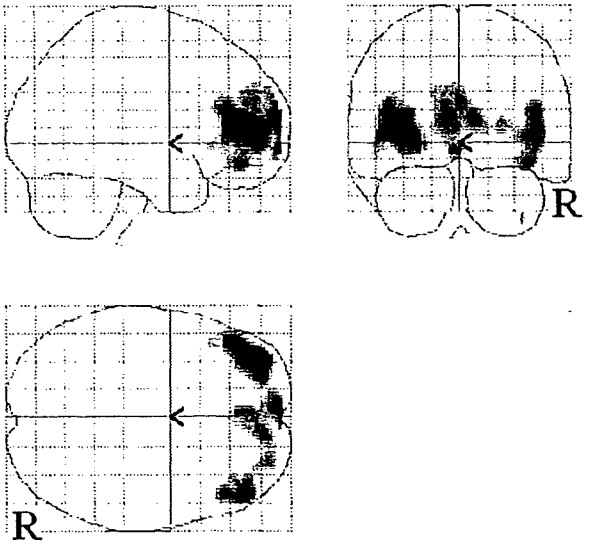

Fig. 1. Results of statistical parametric mapping analyses. Areas with lower post-treatment rCBF values in responders ($n=33$) relative to the values in nonresponders ($n=12$) are shown (uncorrected $P<0.001$). The Talairach coordinates are given in Table 3.

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Table 4
Decreases in rCBF values in responders ($n=33$) after behavior therapy ($P_{FDR\text{-}CORR}<0.01$) (results of a voxel-wise SPM analysis).

Region	Brodmann's area	Talairach coordinate			Voxels in cluster	Z value
		x	y	z		
L. middle frontal gyrus	10	−30	52	2	2078	3.74
L. middle frontal gyrus	10	−40	58	6	2078	3.68
R. medial prefrontal cortex	10	8	56	12	2078	3.4
R. inferior frontal cortex	46	48	44	4	363	3.19
R. inferior frontal cortex	46	46	32	16	363	3.05
R. orbitofrontal cortex	11	30	44	−14	363	2.93

R, right; L, left.

Table 5
Increase in rCBF in responders ($n=33$) after behavior therapy ($P_{FDR\text{-}CORR}<0.01$) (results of a voxel-wise SPM analysis).

Region	Brodmann's area	Talairach coordinate			Voxels in cluster	Z value
		x	y	z		
R. fusiform gyrus	19	30	−60	−4	604	4.12
R. angular gyrus	40	39	−52	24	604	3.97
R. cuneus	19	30	−64	15	604	3.28

R, right.

right OFC (Brodmann area 11) ($P_{FDR\text{-}CORR}<0.01$, corrected) (Table 6, Fig. 4). Among only the 33 responders, the reduction in the Y-BOCS score was negatively correlated with the pre-treatment rCBF in both the right and the left OFC (Brodmann area 11) ($P_{FDR\text{-}CORR}<0.01$, corrected) (Table 6, Fig. 4). In other words, the larger the pre-treatment rCBF in these regions, the greater the decrease in the OCD symptoms. This finding suggests that a higher pretreatment rCBF in the bilateral OFC of responders may predict a greater improvement in OCD severity after BT treatment. For the right OFC, the Pearson product–moment correlation was −0.63 ($P<0.001$) (Fig. 5). In the left OFC, the Pearson product–moment correlation was −0.47 ($P=0.006$) (Fig. 5). These correlations persisted when the total number of BT sessions, the changes in the BDI-II score, and the changes in the STAI (state, trait) score were included as covariates in the analysis.

Among the nonresponders, no significant correlations were observed between the reduction in the Y-BOCS score and the pre-treatment rCBF in any of the brain regions.

3.3.4. Correlation analyses between changes in rCBF and change in the Y-BOCS score

A significant negative correlation was observed between the rCBF in the right OFC (Brodmann area 11) and the changes in the Y-BOCS in responders ($P_{FDR\text{-}CORR}<0.01$, corrected). The reduction in the rCBF in the right OFC was significantly correlated with the reduction in the Y-BOCS. The Pearson product–moment correlation was −0.70 ($P<0.001$). Among responders, no significant correlations were seen between the rCBF in any area and either the changes in the BDI-II score or the changes in the STAI (state, trait) score. Among nonresponders, no significant correlations were seen between the rCBF in any area and either the changes in the Y-BOCS, BDI-II score or the changes in the STAI (state, trait) score.

3.3.5. MRI-based ROI analysis

Among the 45 OCD patients that were examined in this study, 34 OCD patients underwent a brain MRI examination. Twenty-seven of these OCD patients were regarded as responders, and the remaining seven OCD patients were regarded as nonresponders. To confirm the central findings of the SPM analysis of the OCD responders ($n=27$), six bilateral ROIs (three ROIs on each side) were selected: the OFC, the middle frontal gyrus, and the medial prefrontal cortex. A significant negative correlation was observed between the change in the Y-BOCS score and the pre-treatment rCBF in the right OFC in the responders. The Pearson product–moment correlation was −0.49 ($P=0.011$). However, no other significant correlations between the change in the Y-BOCS score and the pre-treatment rCBF values were observed in the responders. In the responders after BT, a significant reduction in rCBF was observed in the right OFC ($t=2.26$, $P=0.028$), the left middle frontal gyrus ($t=2.11$, $P=0.033$), the right medial prefrontal cortex ($t=2.19$, $P=0.039$), and the left medial prefrontal cortex ($t=2.02$, $P=0.046$). No other significant reductions in rCBF after BT were observed in the responders. In the nonresponders, no significant correlations between the change in the Y-BOCS score and the pre-treatment rCBF were observed for any of the six ROI areas. Also, significant reductions in rCBF after BT were not observed in the nonresponders.

4. Discussion

A number of neuroimaging studies have linked the OFC to OCD symptoms. In the present study, however, reductions in rCBF in responders to BT were observed using an SPM analysis in not only the right OFC (BA 11), but also the left middle frontal gyrus (BA 10), the right

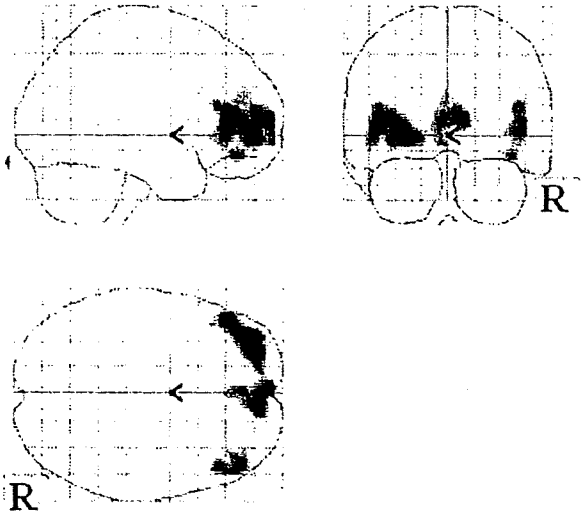

Fig. 2. Results of statistical parametric mapping analyses. Areas with significantly reduced rCBF values after BT in responders ($n=33$) are shown ($P_{FDR\text{-}CORR}<0.01$). The Talairach coordinates are given in Table 4.

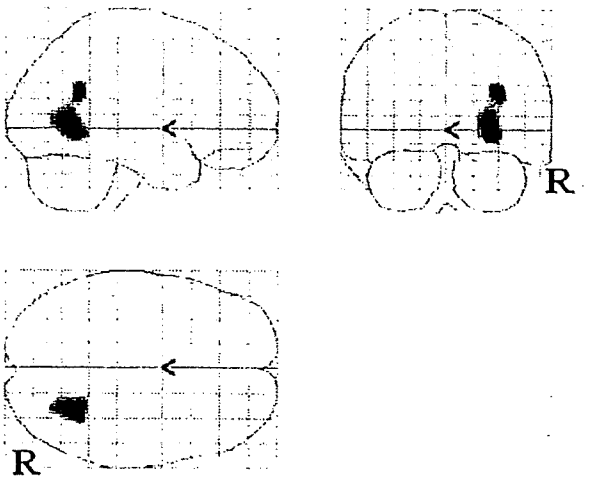

Fig. 3. Results of statistical parametric mapping analyses. Areas with significantly increased rCBF values after BT in responders ($n=33$) are shown ($P_{FDR\text{-}CORR}<0.01$). The Talairach coordinates are given in Table 5.

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Table 6
Significant correlations between elevated pretreatment rCBF values and the reduction in the Y-BOCS score after BT in (a) all OCD patients ($n=45$)/(b) responders ($n=33$) ($P_{FDR\text{-}CORR}<0.01$) (results of a voxel-wise SPM analysis).

(a) Significant correlations between pretreatment rCBF values and the reduction in the Y-BOCS score after BT in all OCD patients ($n=45$)

Region	Brodmann area	Talairach coordinate			Voxels in cluster	Z value
		x	y	z		
R. orbitofrontal cortex	11	24	28	−12	1226	4.24
R. orbitofrontal cortex	11	22	36	−14	1226	3.91
R. orbitofrontal cortex	11	24	40	−16	1226	3.35

(b) Significant correlations between pretreatment rCBF values and the reduction in the Y-BOCS score after BT in OCD responders ($n=33$)

Region	Brodmann area	Talairach coordinate			Voxels in cluster	Z value
		x	y	z		
R. orbitofrontal cortex	11	26	32	−12	567	3.93
R. orbitofrontal cortex	11	28	42	−12	567	3.81
R. orbitofrontal cortex	11	26	34	−14	567	3.46
L. orbitofrontal cortex	11	−30	40	−14	228	4.02
L. orbitofrontal cortex	11	−32	40	−12	228	3.19

R, right; L, left.

medial prefrontal cortex (Brodmann area 10), and the right inferior frontal cortex (Brodmann area 46). These observations were confirmed using an MRI-based ROI analysis. The observed differences in the post-treatment rCBF values for bilateral middle frontal gyri (BA 10) and the left medial prefrontal cortex (BA 10) between responders and non-responders further support the above result. Previous reports (Nakao et al., 2005a,b) have demonstrated that BT was associated with changes in the medial and middle frontal cortex (Brodman areas 9 and 10). This observation might be explained by the interconnection between the OFC and the medial prefrontal cortex, which enable these areas to function together as a neural network. Aouizerate et al. (2004) proposed that the OFC is a large brain region encompassing both rostral and more ventromedial areas. Another possibility is that the reduced rCBF in these areas may reflect lessening in the degrees of both anxiety and depression. With respect to depressive moods, the medial frontal cortex (Brodman areas 9, 10, and 11) is thought to play a critical role in both mood and cognitive interactions (Goldapple et al., 2004). However, our study findings do not support this hypothesis because we did not find any significant correlations between rCBF in any area and either the changes in the BDI-II score or the changes in the STAI (state, trait) score among responders.

Brody et al. (1998) found that higher pre-treatment metabolic predictors in the left OFC were associated with a better response to BT. Consistent with the findings of this previous study, we observed that the left OFC activity was correlated with the BT response. Interestingly, the main difference between the responders and the total group of OCD patients was the association between the left OFC activity at baseline and the change in the Y-BOCS score after BT. Therefore, in the OFC, not only right laterality, but also left laterality may serve as a predictor of the response to BT. The OFC is believed to mediate the expression of OCD symptoms (Milad and Rauch, 2006). Our findings support the hypothesis that the activity in the OFC may be especially important in the neural circuits of subjects with OCD.

OCD patients are thought to exhibit different brain activities depending on their response to SRI treatment. Hendler et al. (2003) reported that while responders to selective serotonin reuptake inhibitors (SSRIs) are characterized by a hypo-active frontal region, non-responders to SSRIs show a hyper-reactive frontal region. Also, a lower pretreatment rCBF in the OFC predicts a better response to SSRIs (Brody et al., 1998; Saxena et al., 1999; Rauch et al., 2002). As Rauch et al. (2002) suggested, the magnitude of OFC activity may be related to not only the severity of the disease, but also the degree of treatment-refractoriness. Recently, Saxena et al. (2009) addressed the neural effect of CBT in patients using SSRIs. In their study, they reported that six out of a total of ten OCD patients taking SSRIs did not respond to SSRIs and still had moderate to severe OCD symptoms at the time of CBT entry. Although they did not observe any metabolic changes in the OFC after CBT, they speculated that the medication-refractory group might be neurobiologically different from the SSRI-responsive OCD patients. In the present study, the neurobiological mechanisms underlying treatment resistance and response to SRIs remain unclear because all the OCD patients ($n=45$) were regarded as being resistant to SRIs. Therefore, future neuroimaging studies are needed to compare the effects of BT in an SRI-responder group and an SRI-nonresponder group to address the potential effect of SRIs on BT treatment.

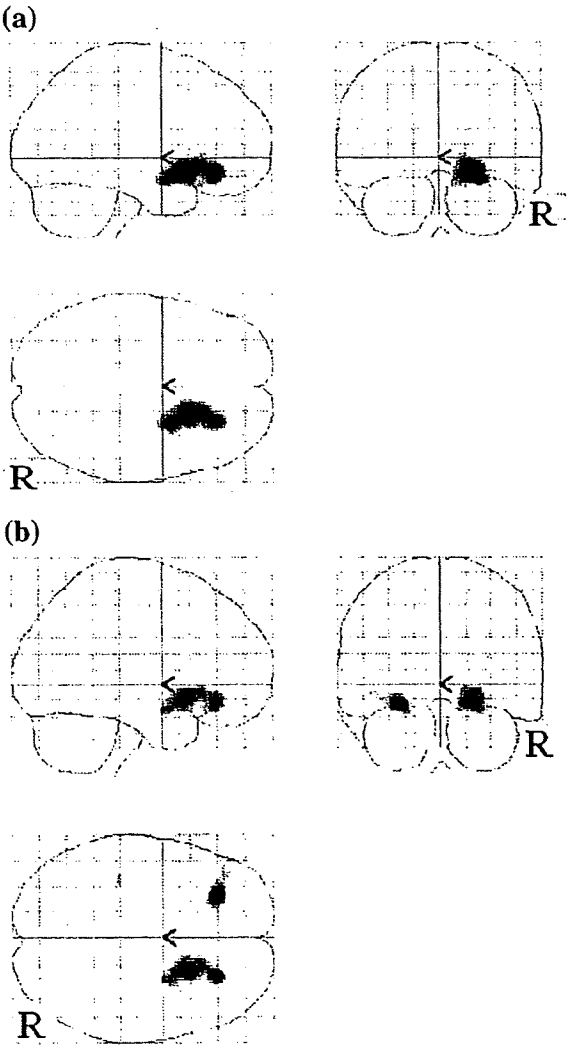

Fig. 4. Results of statistical parametric mapping analyses. (a) The map shows areas with significant correlations between the pretreatment rCBF values and the reduction in the Y-BOCS score after BT in all OCD patients ($n=45$) ($P_{FDR\text{-}CORR}<0.01$). (b) The map shows areas with significant correlations between the pretreatment rCBF values and the reduction in the Y-BOCS score after BT in responders ($n=33$) ($P_{FDR\text{-}CORR}<0.01$). We could not observe any significant correlation between the pretreatment rCBF values and the reduction in the Y-BOCS score after BT in nonresponders ($n=12$). The Talairach coordinates are given in Table 6. (a) Correlation between the pretreatment rCBF values in right OFC and the reduction in the Y-BOCS score after BT in responders ($n=33$). (b) Correlation between the pretreatment rCBF values in left OFC and the reduction in the Y-BOCS score after BT in responders ($n=33$).

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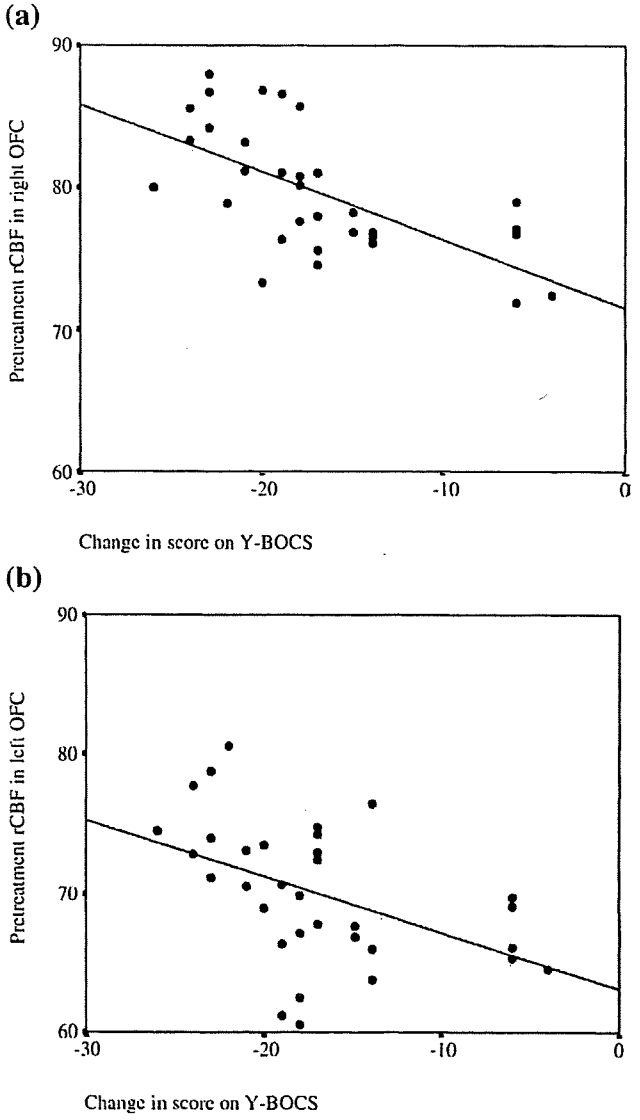

Fig. 5. Results of statistical parametric mapping analyses. A graphical representation of the significant correlation between the change in the Y-BOCS score and the pre-treatment rCBF in (a) the right/(b) left orbitofrontal cortex of responder patients ($n=33$) with OCD is also shown (a) ($r=-0.63$, $P<0.001$)/(b) ($r=-0.47$, $P=0.006$).

In contrast to previous neuroimaging studies, we did not observe a reduction in the activity of the caudate nucleus after BT. This discrepancy is most likely due to differences in the neuroimaging techniques that were used. As Baxter (1995) suggested, the technical limitations of SPECT may prevent the detection of any changes in activity in the caudate nucleus. In addition, an uncoupling of the regional cerebral metabolic rate of glucose observed during PET and the rCBF observed during SPECT has been reported (Whiteside et al., 2004). A recent neuroimaging study has also suggested that different symptoms (washing, checking, hoarding) may be mediated by distinct neural systems (Mataix-Cols et al., 2004). As our study included patients with various OCD symptoms, the heterogeneity of our sample may explain why a reduction in activity was not detected in the caudate nucleus.

We also observed a post-treatment increase in rCBF in both the right occipital lobe (cuneus, fusiform gyrus) and the parietal lobe (angular gyrus). In an fMRI study, Nakao et al. (2005a,b) also observed increased activation in both the occipital lobe and the parietal lobe after treatment. Several studies have suggested that parieto-occipital rCBF abnormalities in patients with OCD might be associated with OCD symptoms (Lucey et al., 1995; Kang et al., 2003). OCD symptoms may suppress parieto-occipital lobe activity prior to BT. However, this area is outside of the fronto-subcortical circuits that have been implicated in OCD. Therefore, further investigation is needed.

How can we interpret the effect of BT on brain function in OCD patients? Schwartz et al. (1996) suggested that the reduction in caudate activity after BT treatment might be explained by procedural learning to acquire new habits and skills. However, the results of the present study are difficult to explain in terms of procedural learning because no changes in caudate activity were observed in the present study. BT involves various cognitive aspects, including reward-based decision making ability, reversal learning, and the extinction of anxiety stimulation (Schwartz,1998; Milad and Rauch, 2006). Several studies (Cavedini et al., 2002; Remijinse et al., 2006) have reported that patients with OCD have impaired decision-making abilities and reversal learning associated with obsessive-compulsive symptoms. Moreover, an extinction-based mechanism in response to ERP has been postulated to be at the core of BT (Brody et al.1998; Milad and Rauch, 2006). Recently, a growing convergence of evidence has suggested that the OFC plays an important role in processing not only decision-making abilities and reversal leaning, but also in the extinction-based mechanism (Phelps et al., 2004; Milad et al., 2005; Milad and Rauch, 2006; Remijinse et al., 2006). In terms of the extinction-based mechanism, Brody et al. (1998) hypothesized that OCD patients with higher pre-treatment metabolism in the OFC may have a greater ability to extinguish habitual, compulsive responses.

Milad and Rauch (2006) also suggested that a hyperactive OFC might be observed in subjects who are driven to perform repetitive behaviors, such as subjects with OCD. We found that a higher pre-treatment rCBF in the OFC may predict a greater improvement in OCD severity after BT treatment. Moreover, a significant decrease in rCBF in the OFC was observed in responders to BT. Saxena et al. (1999) suggested that a reduction in OFC activity and an improvement in OCD symptoms may reflect a decrease in the effort required to resist instructive thoughts and urges. The effort associated with fear extinction learning may improve both the fear response evoked by BT and obsessional fears and compulsive urges, resulting in a reduction of the higher pre-treatment rCBF in the OFC and ultimately leading to a reduction in rCBF in the OFC after BT. The acquisition of specific new skills through BT may reflect treatment-specific OFC functional changes associated with fear extinction learning. Therefore, in accordance with the speculation by Brody et al. (1998), OCD patients with higher pre-treatment rCBF in the OFC may have the capacity to benefit from BT via an extinction-based mechanism. The reductions in rCBF in the medial and middle frontal cortex after BT treatment suggested that the dysfunction of neural networks associated with the OFC dysfunction was normalized by BT. Interestingly, Goldapple et al. (2004) suggested that Cognitive Behavior Therapy (CBT) plays a critical role in modulating medial frontal activity via a top–down effect in patients with major depressive disorder. Therefore, the change in rCBF in the medial and middle frontal cortex after BT treatment may reflect an improvement in emotional processing through the acquisition of specific new skills during the course of BT.

Finally, we must address several limitations of our study. Firstly, the major limitation of this study is that all the patients with OCD were taking SRIs. However, before the start of BT, none of the patients had responded to standard SRI pharmacotherapy with at least one full-dose SRI for at least 12 weeks. Moreover, the SRI dose was not changed during the course of the BT program. Therefore, SRI therapy was unlikely to have had a major effect on the observed reductions in the Y-BOCS scores. Although several studies have reported that patients with OCD may benefit from a combination of BT and pharmacotherapy, exhibiting either early or late improvements (De Haan et al., 1997), the biological mechanism of combination therapy remains unclear. As suggested by Saxena et al. (2002, 2003), the possibility that serotonergic drugs may affect the OFC in patients with OCD cannot be ruled out. Secondly, our

Please cite this article as: Yamanishi, T., et al., Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder, Psychiatry Research: Neuroimaging (2008), doi:10.1016/j.pscychresns.2008.07.004

study did not include either a waiting list control group or a placebo control group. We relied on within-group changes to examine the effects of BT. Future studies should compare a BT treatment group and a placebo control group. However, the OCD patients in the present study had a long duration of illness (14.3 ± 1.7 years) prior to receiving BT treatment. In addition, significant differences in rCBF were observed between responders and nonresponders, despite their participation in the same BT program. Thirdly, although we performed BT using a treatment manual under the supervison of an ERP expert, we could not control the number of BT sessions. However, the correlation between the reduction in the Y-BOCS score and the pre-treatment rCBF in the right OFC persisted when the total number of BT sessions was included as a covariate. In addition, no significant difference in the total number of BT sessions was seen between the responders and the nonresponders. Lastly, our patients with OCD exhibited various OCD subtypes. Mataix-Cols et al. (1999) suggested that the expression of different symptoms may be associated with different neural systems. Therefore, our series of patients with OCD may be rather heterogeneous. Similar to our study, the majority of OCD patients in the study by Nakao et al. (2005a,b) also had either two or three types of symptoms. Furthermore, Nakao et al. (2005a,b) reported that when a symptom provocation task was used during fMRI, OCD patients showed decreased activation in the OFC after either BT ($n=4$) or SRI therapy ($n=6$). However, the neural effects of treatment among patients with various OCD subtypes remained unclear in their study. Further studies are needed to clarify the effect of BT on different types of symptoms in a larger number of OCD patients.

Despite these limitations, this study is the first to use SPM to examine the neural effects of BT in a relatively large group of patients with OCD. Our results support a prominent modulation of neural function in the OFC and in the medial and middle frontal cortex in response to BT.

Acknowledgments

All authors report no competing interests.

This research was supported by a Health and Labor Sciences Research Grant (Research on Health and Technology Assessment) H13-018 from the Ministry of Health, Labor and Welfare, Japan awarded to the second (S.N) and the last authors (T.A.F).

References

Abramowitz, J.S., Foa, E.B., Franklin, M.E., 2003. Exposure and ritual prevention for obsessive-compulsive disorder: effects of intensive versus twice-weekly sessions. Journal of Consulting and Clinical Psychology 71, 394–398.

Aouizerate, B., Guehl, D., Cuny, E., Rougier, A., Bioulac, B., Tignol, J., Burbaud, P., 2004. Pathophysiology of obsessive-compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology. Progress in Neurobiology 72, 195–221.

Baxter, L.R., 1995. Neuroimaging studies of human anxiety disorders: cutting paths of knowledge through the field of neurotic phenomena. In: Bloom, F., Kupfer, D. (Eds.), Neuropsychopharmacology: The Fourth Generation of Progress. Raven Press, New York, pp. 1287–1299.

Baxter Jr., L.R., Schwartz, J.M., Bergman, K.S., Szuba, M.P., Guze, B.H., Mazziotta, J.C., Alazraki, A., Selin, C.E., Ferng, H.K., Munford, P., Phelps, M.E., 1992. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Archives of General Psychiatry 49, 681–689.

Bollini, P., Pampallona, S., Tibaldi, G., Kupelnick, B., Munizza, C., 1999. Effectiveness of antidepressants. Meta-analysis of dose-effect relationships in randomised clinical trials. British Journal of Psychiatry 174, 297–303.

Bonne, O., Louzoun, Y., Aharon, I., Krausz, Y., Karger, H., Lerer, B., Bocher, M., Freedman, N., Chisin, R., 2003. Cerebral blood flow in depressed patients: a methodological comparison of statistical parametric mapping and region of interest analyses. Psychiatry Research 122, 49–57.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. BDI-II Manual. The Psychological Corporation: San Antonio, TX.

Brody, A.L., Saxena, S., Schwartz, J.M., Stoessel, P.W., Maidment, K., Phelps, M.E., Baxter Jr., L. R., 1998. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder. Psychiatry Research: Neuroimaging 84, 1–6.

Cavedini, P., Riboldi, G., D'Annucci, A., Belotti, P., Cisima, M., Bellodi, L., 2002. Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes. Neuropsychologia 40, 205–211.

Chang, L.T., 1978. A method for attenuation correction in radionuclide computedtomography. IEEE transaction on nuclear. Science 25, 638–643.

De Haan, E., van Oppen, P., van Balkom, A.J., Spinhoven, P., Hoogduin, K.A., Van Dyck, R., 1997. Prediction of outcome and early vs. late improvement in OCD patients treated with cognitive behaviour therapy and pharmacotherapy. Acta Psychiatrica Scandinavica 96, 354–361.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15, 870–878.

Goldapple, K., Segal, Z., Garson, C., Lau, M., Bieling, P., Kennedy, S., Mayberg, H., 2004. Modulation of cortical–limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Archives of General Psychiatry 61, 34–41.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989a. The Yale–Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Archives of General Psychiatry 46, 1006–1011.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Delgado, P., Heninger, G.R., Charney, D.S., 1989.. The Yale–Brown Obsessive Compulsive Scale. II. Validity. Archives of General Psychiatry 46, 1012–1016.

Hendler, T., Goshen, E., Tzila Zwas, S., Sasson, Y., Gal, G., Zohar, J., 2003. Brain reactivity to specific symptom provocation indicates prospective therapeutic outcome in OCD. Psychiatry Research: Neuroimaging 124, 87–103.

Iikura, Y., 1999. Treatment Guide for Obsessive-Compulsive Disorder. Nihei-Sha, Osaka.

Jenike, M.A., 1998. Drug treatment of obsessive compulsive disorders. In: Jenike, M.A., Baer, L., Minichiello, W.E. (Eds.), Obsessive-Compulsive Disorder: Practical Management. Mosby, New York, pp. 469–554.

Kampman, M., Keijsers, G.P., Hoogduin, C.A., Verbraak, M.J., 2002. Addition of cognitive-behaviour therapy for obsessive–compulsive disorder patients non-responding to fluoxetine. Acta Psychiatrica Scandinavica 106, 314–319.

Kang, D.H., Kwon, J.S., Kim, J.J., Youn, T., Park, H.J., Kim, M.S., Lee, D.S., Lee, M.C., 2003. Brain glucose metabolic changes associated with neuropsychological improvements after 4 months of treatment in patients with obsessive-compulsive disorder. Acta Psychiatrica Scandinavica 107, 291–297.

Lucey, J.V., Costa, D.C., Blanes, T., Busatto, G.F., Pilowsky, L.S., Takei, N., Marks, I.M., Ell, P.J., Kerwin, R.W., 1995. Regional cerebral blood flow in obsessive–compulsive disordered patients at rest. Differential correlates with obsessive-compulsive and anxious-avoidant dimensions. British Journal of Psychiatry 167, 629–634.

Mataix-Cols, D., Rauch, S.L., Manzo, P.A., Jenike, M.A., Baer, L., 1999. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. American Journal of Psychiatry 156, 1409–1416.

Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M.J., Speckens, A., Phillips, M.L., 2004. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive–compulsive disorder. Archives of General Psychiatry 61, 564–576.

Matsuda, H., Ohnishi, T., Asada, T., Li, Z.J., Kanetaka, H., Imabayashi, E., Tanaka, F., Nakano, S., 2003. Correction for partial-volume effects on brain perfusion SPECT in healthy men. Journal of Nuclear Medicine 44, 1243–1252.

Matsuda, H., Mizumura, S., Soma, T., Takemura, N., 2004. Conversion of brain SPECT images between different collimators and reconstruction processes for analysis using statistical parametric mapping. Nuclear Medicine Communications 25, 67–74.

Milad, M.R., Quinn, B.T., Pitman, R.K., Orr, S.P., Fischl, B., Rauch, S.L., 2005. Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proceedings of the National Academy of Sciences of the United States of America 102, 10706–10711.

Milad, M.R., Rauch, S.L., 2006. The orbitofrontal cortex and anxiety disorders. In: Zald, D.H., Rauch, S.L. (Eds.), The Orbitofrontal Cortex. Oxford University Press, New York, pp. 523–543.

Nakatani, E., Nakgawa, A., Ohara, Y., Goto, S., Uozumi, N., Iwakiri, M., Yamamoto, Y., Motomura, K., Iikura, Y., Yamagami, T., 2003. Effects of behavior therapy on regional cerebral blood flow in obsessive-compulsive disorder. Psychiatry Research: Neuroimaging 124, 113–120.

Nakatani, E., Nakagawa, A., Nakao, T., Yoshizato, C., Nabeyama, M., Kudo, A., Isomura, K., Kato, N., Yoshioka, K., Kawamoto, M., 2005. A randomized controlled trial of Japanese patients with obsessive-compulsive disorder—effectiveness of behavior therapy and fluvoxamine. Psychotherapy and Psychosomatics 74, 269–276.

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatani, E., Nabeyama, M., Yoshizato, C., Kudoh, A., Tada, K., Yoshioka, K., Kawamoto, M., 2005a. A functional MRI comparison of patients with obsessive–compulsive disorder and normal controls during a Chinese character Stroop task. Psychiatry Research: Neuroimaging 139, 101–114.

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatani, E., Nabeyama, M., Yoshizato, C., Kudoh, A., Tada, K., Yoshioka, K., Kawamoto, M., Togao, O., Kanba, S., 2005b. Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biological Psychiatry 57, 901–910.

Ninan, P.T., Koran, L.M., Kiev, A., Davidson, J.R., Rasmussen, S.A., Zajecka, J.M., Robinson, D.G., Crits-Christoph, P., Mandel, F.S., Austin, C., 2006. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. Journal of Clinical Psychiatry 67, 15–22.

Ohnishi, T., 2004. SPM. In: Matsuda, H., Asada, T. (Eds.), Imaging Diagnosis for Dementia. Nagai Shoten, Osaka, pp. 73–89.

Pallanti, S., Hollander, E., Goodman, W.K., 2004. A qualitative analysis of nonresponse: management of treatment-refractory obsessive-compulsive disorder. Journal of clinical Psychiatry 65 (Suppl 14), 6–10.

Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E., 2004. Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43, 897–905.

Rauch, S.L., Shin, L.M., Dougherty, D.D., Alpert, N.M., Fischman, A.J., Jenike, M.A., 2002. Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study. Neuropsychopharmacology 27, 782–791.

Please cite this article as: Yamanishi, T., et al., Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder, Psychiatry Research: Neuroimaging (2008), doi:10.1016/j.pscychresns.2008.07.004

Remijnse, P.L., Nielen, M.M., van Balkom, A.J., Cath, D.C., van Oppen, P., Uylings, H.B., Veltman, D.J., 2006. Reduced orbitofrontal–striatal activity on a reversal learning task in obsessive–compulsive disorder. Archives of General Psychiatry 63, 1225–1236.

Saxena, S., Brody, A.L., Maidment, K.M., Dunkin, J.J., Colgan, M., Alborzian, S., Phelps, M.E., Baxter Jr., L.R., 1999. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive–compulsive disorder. Neuropsychopharmacology 21, 683–693.

Saxena, S., Brody, A.L., Ho, M.L., Alborzian, S., Maidment, K.M., Zohrabi, N., Ho, M.K., Huang, S.C., Wu, H.M., Baxter Jr., L.R., 2002. Differential cerebral metabolic changes with paroxetine treatment of obsessive–compulsive disorder vs major depression. Archives of General Psychiatry 59, 250–261.

Saxena, S., Brody, A.L., Ho, M.L., Zohrabi, N., Maidment, K.M., Baxter Jr., L.R., 2003. Differential brain metabolic predictors of response to paroxetine in obsessive–compulsive disorder versus major depression. American Journal of Psychiatry 160, 522–532.

Saxena, S., Gorbis, E., O'Neill, J., Baker, S.K., Mandelkern, M.A., Maidment, K.M., Chang, S., Salamon, N., Brody, A.L., Schwartz, J.M., London, E.D., 2009. Rapid effects of brief intensive cognitive-behavioral therapy on brain glucose metabolism in obsessive–compulsive disorder. Molecular Psychiatry 14, 197–205.

Schwartz, J.M., Stoessel, P.W., Baxter Jr., L.R., Martin, K.M., Phelps, M.E., 1996. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive–compulsive disorder. Archives of General Psychiatry 53, 109–113.

Schwartz, J.M., 1998. Neuroanatomical aspects of cognitive-behavioural therapy response in obsessive–compulsive disorder. An evolving perspective on brain and behaviour. British Journal of Psychiatry (Suppl) 38–44.

Spielberger, C.D., Gorsuch, R., Lushene, R., 1970. Manual for the State-Trait Anxiety Inventory. Consulting Psychologist Press, Palo Alto, CA.

Takeuchi, Y., Tohyama, J., Katano, H., Mase, M., Kanai, H., Yamada, K., 2005. Identification of motor activation brain perfusion SPECT with brain easy analysis tools. Nagoya Medical Journal 47, 57–66.

Tolin, D.F., Maltby, N., Diefenbach, G.J., Hannan, S.E., Worhunsky, P., 2004. Cognitive-behavioral therapy for medication nonresponders with obsessive–compulsive disorder: a wait-list-controlled open trial. Journal of Clinical Psychiatry 65, 922–931.

Tolin, D.F., Abramowitz, J.S., Diefenbach, G.J., 2005. Defining response in clinical trials for obsessive-compulsive disorder: a signal detection analysis of the Yale–Brown Obsessive Compulsive Scale. Journal of Clinical Psychiatry 66, 1549–1557.

Whiteside, S.P., Port, J.D., Abramowitz, J.S., 2004. A meta-analysis of functional neuroimaging in obsessive–compulsive disorder. Psychiatry Research: Neuroimaging 132, 69–79.

Please cite this article as: Yamanishi, T., et al., Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder, Psychiatry Research: Neuroimaging (2008), doi:10.1016/j.pscychresns.2008.07.004

Mental Vulnerability and Survival After Cancer

Naoki Nakaya,[a,b,c] *Pernille E. Bidstrup,*[a] *Lene F. Eplov,*[d] *Kumi Saito-Nakaya,*[a,b] *Shinichi Kuriyama,*[e] *Ichiro Tsuji,*[e] *Yosuke Uchitomi,*[b] and *Christoffer Johansen*[a]

Background: It has been hypothesized that personality traits affect survival after cancer, but studies have produced inconsistent results. This study examined the association between mental vulnerability and survival after cancer in Denmark in a prospective cohort study.
Methods: Between 1976 and 2001, 12733 residents of Copenhagen completed a questionnaire eliciting information on a 12-item mental vulnerability scale, as well as various personal data. Follow-up in the Danish Cancer Registry until 2003 identified 884 incident cases of primary cancer, and follow-up for death from the date of cancer diagnosis until 2003 identified 382 deaths. Mental vulnerability scores were divided into 4 approximately equal-sized groups. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) of all-cause mortality.
Results: Multivariate HR for all-cause mortality for persons in the highest category of mental vulnerability compared with those at the lowest was 1.1 (95% confidence interval = 0.9–1.5).
Conclusion: We found no support for the hypothesis that mental vulnerability is associated with survival after cancer diagnosis.

It has been hypothesized that personality traits affect the risk for cancer incidence by altering immune and endocrine function.[1–3] However, several well-conducted prospective studies have not confirmed this hypothesis.[4–9] The role of personality traits in survival after cancer[10] has been addressed in at least 7 studies.[11–17] Three studies supported an association: higher scores of "lie scale,"[11] introversion,[12] and neuroticism[13] were associated with poor survival after cancer. All studies, however, had important limitations, including failure to control for cigarette smoking or alcohol consumption,[11,12,14,15] clinical status,[15] and comorbidity[11–13,15,17]; personality traits measured prior to the diagnosis of cancer[11,12,14,15,17]; and use of small samples (5 of the 7 studies had fewer than 200 study subjects).[11–15]

Mental vulnerability is defined as a tendency to experience psychosomatic symptoms, mental symptoms, or negative reactions in social interactions.[18–20] Mental vulnerability represents a reaction pattern that is closely related to personality traits such as neuroticism.[21] No study had previously investigated the association between mental vulnerability and survival after cancer. We conducted a large, population-based prospective cohort study in Denmark to explore this relationship.

METHODS

Study Population

The sample was based on 6 studies conducted at the Copenhagen County Research Center for Prevention and Health (eTable 1, http://links.lww.com/EDE/A337). The populations were sampled randomly in southwestern Copenhagen County, and 12,733 men and women participated in a general health examination (eTable 2 and eFigure, http://links.lww.com/EDE/A337).

Health Data

Data on mental vulnerability, sex, age, education, comorbidity, and physical activity, as well as tobacco and alcohol consumption, were obtained from questionnaires. Body mass index in kg/m^2 was calculated from self-reported data on height and weight.[22–24]

Mental Vulnerability Scale

In 1981 Kühl and Martini developed a 22-item scale, which was later reduced to a 12-item scale on the basis of validity tests.[18,25] On the basis of theoretical considerations, 3 new scales (psychosomatic symptoms, interpersonal problems and mental symptoms) were then designed from the 22 items selected.[18] In this study, we used both the 3 newly validated scales and the 12-item scale (eAppendix, http://links.lww.com/EDE/A337).

Linkage to Registries

Data for all members of the study population were linked to the Central Population Register for verification of

Submitted 22 July 2008; accepted 7 January 2009.
From the [a]Department of Psychosocial Cancer Research, Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark; [b]Psycho-Oncology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [c]The Japan Society for the Promotion of Science (JSPS), Tokyo, Japan; [d]Research Centre for Prevention and Health, The Capital Region of Denmark, Denmark; and [e]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan.
Supported by the Foundation for Promotion of Cancer Research (Japan) for the 3rd Term Comprehensive 10-year Strategy for Control, and the Psychosocial Research Committee at the Danish Cancer Society, Denmark.
SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).
Correspondence: Christoffer Johansen, Department of Psychosocial Cancer Research, Institute of Cancer Epidemiology, Danish Cancer Society, Strand boulevarden 49, DK-2100 Copenhagen, Denmark. E-mail: christof@cancer.dk.

ISSN: 1044-3983/09/2006-0916
DOI: 10.1097/EDE.0b013e3181b5f3b0

the personal identification number and for information on vital statistics and migration. Subsequently, the study cohort was linked to the Danish Cancer Registry for information on date of diagnosis of the tumor and details about the tumor.[26] Tumors are coded according to a modified Danish version of the International Classification of Diseases, Seventh Revision.[26] Finally, the study cohort was linked to the Danish Registry of Causes of Death.[27] Cause of death was coded according to a modified Danish version of the International Classification of Diseases, Tenth Revision.[28]

Follow-up

The 12,733 persons in the study cohort were followed for cancer from the date of the interview until the date of first cancer (other than nonmelanoma skin cancer), date of emigration, date of death or 31 December 2003, whichever came first. We identified 1085 incident cases of cancer. We then excluded 33 persons who had not answered the mental vulnerability questions and 168 persons without information on cancer stage, leaving 884 cancer cases for analysis. These persons were followed up for death from the date of cancer diagnosis until date of emigration, date of death or 31 December 2003, whichever came first. A total of 382 deaths were identified (eFigure, http://links.lww.com/EDE/A337).

Statistical Analyses

Analyses were conducted with the 12 item scale as an ordinal variable, and the scores for mental vulnerability (0–12) were divided into 4 approximately equal-sized groups (quartiles). For all 3 subscales, we chose a cut-off point of 0 and ≥1, because the distributions were not normal, and the proportion of persons with score 0 was high (62%–70%). Kaplan-Meier analyses were used to obtain estimates of survival. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed as the death rates among persons in each quartile of mental vulnerability score divided by the death rate among persons in the lowest quartile. Both deaths from all causes and cancer-related death were used as end-points. We conducted a stratified analysis of HR of death according to the duration between mental vulnerability assessment and cancer diagnosis. A Cox proportional hazard model was used to estimate HRs for mental vulnerability.[29] Multivariate HRs were adjusted for sex, age at cancer diagnosis, study cohort, body mass index in kg/m^2, marital status, length of education in years, smoking status, alcohol consumption, physical activity in leisure time, a history of comorbidity, and a history of depression, cancer site, and cancer type.

RESULTS

The 884 incident cases of primary cancer accrued a total of 3736 person-years of follow-up, with a mean follow-up of 4 years (range, 0–23 years). Persons with higher scores of the mental vulnerability were more likely to be women, unmarried, and nondrinkers; to have cancer in hormone-related organs; to have a low level of physical activity; and to have a history of comorbidity and depression (eTable 2, http://links.lww.com/EDE/A337).

Kaplan-Meier plots showed no clear association between score on the 12 item scale and overall survival (Figure). Sex and age-adjusted analyses showed no association between mental vulnerability and the overall risk of death. The HR for death from all causes for persons in the highest category of mental vulnerability, compared with those at the lowest was 1.2 (95% CI = 0.9–1.5) (Table). After control for potential confounders, the association between scores and risk of death was further reduced (HR = 1.1 [0.9–1.5]). When cancer-related death was used as an end-point, the adjusted HR for persons in the highest category of mental vulnerability compared with those in the lowest was 1.1 (0.8–1.5). In multivariate analyses, we found no associations between any mental vulnerability subscale and the risk for death from all causes or from cancer.

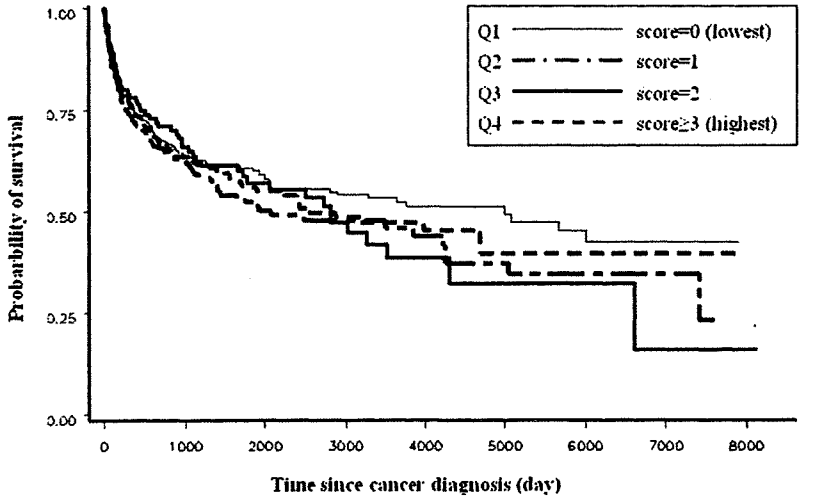

FIGURE. Overall survival according to the 12-item mental vulnerability scale.

TABLE. Hazard Ratio (HR) and 95% Confidence Interval (95% CI) of Death From All-cause and Cancer-related Death According to Mental Vulnerability Among 884 Persons Diagnosed With Cancer, Denmark

	Mental Vulnerability (12-item scale)				Mental Vulnerability, 3-Subscales					
	Q1 (Lowest)	Q2	Q3	Q4 (Highest)	Psychosomatic Symptoms		Interpersonal Problems		Psychological Symptoms	
Score	0	1	2	≥3	0	≥1	0	≥1	0	≥1
All subjects (n = 884)										
No. person-years of follow-up	1575	782	496	883	2374	1362	2374	1362	2696	1040
No. of deaths (death from all-causes/cancer-related death)	143/94	93/63	57/35	89/59	247/164	135/87	247/164	135/87	258/170	124/81
Crude mortality rate (per 1000 person years)	91	119	115	101	104	99	104	99	96	119
Sex- and age-adjusted HR (95% CI) for deaths from all causes	1.0[a]	1.1 (0.9–1.5)	1.2 (0.9–1.7)	1.2 (0.9–1.5)	1.0[a]	1.4 (1.2–1.8)	1.0[a]	0.9 (0.7–1.1)	1.0[a]	1.2 (1.0–1.5)
Multivariate HR[b] (95% CI) for deaths from all causes	1.0[a]	1.0 (0.8–1.3)	1.0 (0.7–1.4)	1.1 (0.9–1.5)	1.0[a]	1.2 (1.0–1.5)	1.0[a]	0.9 (0.7–1.1)	1.0[a]	1.0 (0.8–1.2)
Multivariate HR[b] (95% CI) for cancer-related deaths	1.0[a]	1.1 (0.8–1.5)	0.9 (0.6–1.4)	1.1 (0.8–1.5)	1.0[a]	1.2 (0.9–1.5)	1.0[a]	0.9 (0.7–1.2)	1.0[a]	1.0 (0.7–1.3)
Subjects diagnosed within 3 years of the mental vulnerability assessment (n = 157)[c]										
Multivariate HR[b] (95% CI) for death from all-cause	1.0[a]	1.9 (0.8–4.1)	1.8 (0.7–4.3)	1.2 (0.5–2.9)	1.0[a]	1.4 (0.7–2.8)	1.0[a]	0.9 (0.5–1.6)	1.0[a]	1.1 (0.6–2.1)
Multivariate HR[b] (95% CI) for cancer-related death	1.0[a]	1.7 (0.6–4.5)	2.1 (0.7–6.0)	1.3 (0.4–3.7)	1.0[a]	1.6 (0.6–3.8)	1.0[a]	0.7 (0.3–1.6)	1.0[a]	0.9 (0.4–2.1)
Subjects diagnosed later than 3 years from the mental vulnerability assessment (n = 727)[d]										
Multivariate HR[b] (95% CI) for death from all-cause	1.0[a]	1.0 (0.7–1.3)	1.0 (0.7–1.4)	1.1 (0.8–1.5)	1.0[a]	1.1 (0.8–1.5)	1.0[a]	0.9 (0.7–1.2)	1.0[a]	1.0 (0.8–1.3)
Multivariate HR[b] (95% CI) for cancer-related death	1.0[a]	1.0 (0.7–1.5)	0.8 (0.5–1.3)	1.0 (0.7–1.5)	1.0[a]	1.1 (0.8–1.4)	1.0[a]	0.9 (0.7–1.3)	1.0[a]	1.0 (0.7–1.3)

[a]Reference category.

[b]Multivariate HRs were adjusted for sex and age at cancer diagnosis (continuous variable), study cohort (1936 cohort, MONICA 1, MONICA 3, Allergi 90 Cohort, Allergi 97 Cohort, and DAN-THYR), body mass index in kg/m^2 (<18.5, 18.5–24.9, or 25.0≤), marital status (married, widowed/divorced, or single), length of education in years (≤12 years or 13≤ years), smoking status (never, ex-, or current), alcohol consumption (0, 1–14, or 15≤ units/week), physical activity in leisure time (sit still, walk, or do exercise/sports), a history of comorbidity[b] (any or none), and a history of depression (present or absent), cancer site (hormone-related organs, virus-related and immune-related malignancies, digestive organs [excluding liver], respiratory organs, or other sites), and cancer type (in situ or localized, regional invasion, or distant metastasis). Comorbidity was measured by the following question: "Has a doctor ever told you that you have: coronary thrombosis, heart disease, high blood pressure, cerebral thrombosis, brain hemorrhage, diabetes, or bronchitis?"

[c]69 deaths from all causes and 52 cancer-related deaths.

[d]313 deaths from all causes and 199 cancer-related deaths.

Some differences were seen when analyses were stratified according to the time elapsed between mental vulnerability assessment and cancer diagnosis. Among persons diagnosed within 3 years of the mental vulnerability assessment, those who scored high on mental vulnerability had a slightly increased risk of death from all causes, compared with persons who had low scores. No increased risk was observed among persons diagnosed later than 3 years after the mental vulnerability assessment.

We further conducted analyses stratified by sex, and there was no association between mental vulnerability and risk for death among either men or women (data not shown).

DISCUSSION

In this large prospective cohort study, we found no support for the hypothesis that mental vulnerability is associated with survival after cancer.

Three studies have reported positive associations between personality traits and survival after cancer.[11–13] The design of these studies had some limitations, including small numbers of participants, making chance a possible explanation for the overall results. Furthermore, the mental vulnerability scale and each of the personality traits represent different ways of assessing personality.

In one previous study, Nakaya et al[13] indicated that neuroticism was positively associated with death from all-cause only among women. The present study did not support the hypothesis of a sex difference in the association between personality traits and survival after cancer.

This study had several methodologic advantages over previous studies. First, we had the largest number of cancer cases used yet to explore this question. Secondly, we controlled extensively for potential confounding variables, including cigarette smoking and alcohol consumption, clinical status and comorbidity, which have been shown to be associated with survival after cancer.[30–32] Thirdly, we took into account the duration of time between mental vulnerability assessment and cancer diagnosis, which did seem to play a role. The slightly increased risk of all-cause mortality observed among persons diagnosed within 3 years of the mental vulnerability assessments suggests that mental vulnerability assessments could have been affected by subclinical symptoms of as-yet-undiagnosed cancers.[4] It is also possible that mental vulnerability is not a stable personality trait, resulting in increasing measurement error with increasing time since the measurement. One limitation in the current study is that we had no information on health behavior after the cancer diagnosis or on compliance with treatment, which could have affected survival.

In an earlier prospective study, subjects with high scores on mental vulnerability had increased cancer mortality compared with subjects with low scores among the general Danish populations.[20] Cancer-related death was used as the end-point, and it was difficult to distinguish between mental vulnerability associated with cancer incidence and with the survival. This may explain the differences in results between the previous and present studies.

Although we found no support for the hypothesis that mental vulnerability is associated with survival after cancer, we cannot rule out associations with other personality traits.

ACKNOWLEDGMENTS

We thank Visti B. Larsen of the Department of Psychosocial Cancer Research, Institute of Cancer Epidemiology, Danish Cancer Society, for his assistance with the statistical analyses.

REFERENCES

1. Spiegel D, Kato M. Psychological influences on cancer incidence and progression. *Harv Rev Psychiat.* 1996;4:10–26.
2. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nat Rev Cancer.* 2006;6:240–248.
3. Dalton SO, Boesen EH, Ross L, Schapiro IR, Johansen C. Mind and cancer. Do Psychological Factors Cause Cancer? *Eur J Cancer.* 2002; 38:1313–1323.
4. Nakaya N, Tsubono Y, Hosokawa T, et al. Personality and the risk of cancer. *J Natl Cancer Inst.* 2003;95:799–805.
5. Schapiro IR, Ross-Petersen L, Saelan H, Garde K, Olsen JH, Johansen C. Extraversion and neuroticism and the associated risk of cancer: a Danish cohort study. *Am J Epidemiol.* 2001;153:757–763.
6. Hansen PE, Floderus B, Frederiksen K, Johansen C. Personality traits, health behavior, and risk for cancer: a prospective study of a Swedish twin cohort. *Cancer.* 2005;103:1082–1091.
7. Lillberg K, Verkasalo PK, Kapr J, Teppo L, Helenius H, Koskenvuo M. A prospective study of life satisfaction, neuroticism and breast cancer risk (Finland). *Cancer Causes Control.* 2002;13:191–198.
8. Bleiker EM, Hendriks JH, Otten JD, Verbeek AL, van der Ploeg HM. Personality factors and breast cancer risk: a 13-year follow-up. *J Natl Cancer Inst.* 2008;100:213–218.
9. Everson SA, Goldberg DE, Kaplan GA, et al. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. *Psychosom Med.* 1996;58:113–121.
10. Ross L, Boesen EH, Dalton SO, Johansen C. Mind and cancer: dose psychosocial intervention improve survival and psychological well-being? *Eur J Cancer.* 2002;38:1447–1457.
11. Ratcliffe MA, Dawson AA, Walker LG. Eysenck Personality Inventory L-scores in patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Psychooncology.* 1995;4:39–45.
12. Hislop TG, Waxler NE, Coldman AJ, Elwood JM, Kan L. The prognostic significance of psychosocial factors in women with breast cancer. *J Clin Epidemiol.* 1987;40:729–735.
13. Nakaya N, Hansen PE, Schapiro IR, et al. Personality traits and cancer survival: a Danish cohort study. *Br J Cancer.* 2006;95:146–152.
14. Dean C, Surtees G. Do psychological factors predict survival in breast cancer? *J Psychosom Res.* 1989;33:561–569.
15. Greer S, Morris T, Pettingale KW, Haybittle JL. Psychological response to breast cancer and 15-year outcome. *Lancet.* 1990;335:49–50.
16. Nakaya N, Tsubono Y, Nishino Y, et al. Personality and cancer survival: the Miyagi cohort study. *Br J Cancer.* 2005;92:2089–2094.
17. Nakaya N, Saito-Nakaya K, Akechi T, et al. Negative psychological aspects and survival in lung cancer patients. *Psychooncology.* 2008;17: 466–473.
18. Kühl PH, Martini S, Psykisk Sårbare. *Sociale livsbetingelser, psychically vulnerable persons. Their social and living conditions* [English abstract and summary]. The Danish National Institute of Social Research, Copenhagen, Denmark; 1981. Publication no. 102.
19. Sabroe K, Kousgaard E, Knox-Seith B, Rieneck B, Bratfeldt EL. *P-faktoren i FOUSHIP-klassificerings-systemet* [English summaries].

Vol. 1–4. Copenhagen, Denmark: MPT; 1968–1970: V1, 1–34; V2, 1–74; V3, 1–89; V4, 1–64.
20. Eplov LF, Jorgensen T, Birket-Smith M, Segel S, Johansen C, Mortensen EL. Mental vulnerability as a predictor of early mortality. *Epidemiology*. 2005;16:226–232.
21. Jess P, Jess T, Beck H, Bech P. Neuroticism in relation to recovery and persisting pain after laparoscopic cholecystectomy. *Scand J Gastroenterol*. 1998;33:550–553.
22. Jørgensen T. Gallstones: An epidemiological investigation. *Dan Med Bull*. 1990;37:336–346.
23. Thomsen KK, Larsen S, Schroll M. Cardiovascular risk factors and age: a cross-sectional survey of Danish men and women from the Glostrup Population Studies. *Am J Geriatr Cardiol*. 1995;3:31–41.
24. Hollnagel H. The health structure of 40-year-old men and women in the Glostrup area, Denmark–an epidemiological survey. *Dan Med Bull*. 1980;27:121–130.
25. Andersen EB, Sørensen SL. *Måling af psykisk sårbarhed. En analyse af visse egenskaber ved sårbarhedstesten* [in Danish]. Universitetets Statistiske Institut, Copenhagen 1979. Research report no 58.
26. Jensen OM, Storm HH, Jensen H. Cancer registration in Denmark and the study of multiple primary cancers, 1943–1980. *Natl Cancer Inst Monogr*. 1985;68:245–251.
27. Juel K, Helweg-Larsen K. The Danish registers of causes of death. *Dan Med Bull*. 1999;46:354–357.
28. World Health Organization. *International Statistics Classification of Diseases and Related Health Problems*. 10th ed. Geneva: World Health Organization; 1992.
29. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven;1998:288–300.
30. Battaglioli T, Gorini G, Costantini AS, et al. Cigarette smoking and alcohol consumption as determinants of survival in non-Hodgkin's lymphoma: a population-based study. *Ann Oncol*. 2006;17:1283–1289.
31. Tammemagi CM, Neslund Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. *Chest*. 2004;125:27–37.
32. Tammemagi CM, Nerenz D, Neslund Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. *JAMA*. 2005;294:1765–1772.

