Left Hippocampal Volume Inversely Correlates With Enhanced Emotional Memory in Healthy Middle-Aged Women

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The authors investigated the effect of hippocampal volume on enhanced emotional memory in 27 healthy women. Irrespective of age, education, intracranial volume, cognitive function, delayed recall, and neuroticism, left hippocampal volume showed a significant negative correlation with enhanced emotional memory.

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Studies have shown that a considerable number of cancer survivors (11% to 45%) meet the criteria for intrusive recollections related to their cancer experiences rather than criteria for full-blown posttraumatic stress disorder (3% to 6%).[1] Furthermore, it has been indicated that intrusive recollections are associated with the presence of persistent depression or anxiety, poor psychological adjustment, and poorer quality of life.[1] Intrusive recollection is a certain formation of strong emotional memory, a mechanism of which may overlap with posttraumatic stress disorder (PTSD). However, little is known about its neurobiological basis. We previously studied magnetic resonance image (MRI) volumes of the hippocampus and amygdala in women who survived for 3 years or more after breast cancer surgery.[2,3] Women with a history of cancer-related intrusive recollections showed smaller left hippocampal and total amygdalar volumes compared with those without such history. But the fundamental question still remained as to whether the volumetric differences represented the neurotoxic effect of several years of persistent intrusive recollections or a preexisting trait that predisposed people to pathological stress reactions to cancer experiences (predisposition theory). A meta-analysis of MRI studies has shown that severe chronic PTSD is associated with a smaller hippocampal volume in adult patients.[4] Gilbertson et al.[5] suggested in their monozygotic co-twin study that the smaller hippocampal volume in combat-related PTSD represents a preexisting familial vulnerability factor rather than the neurotoxic product of trauma exposure per se. They also found the significant negative correlation between hippocampal volume of combat-unexposed healthy co-twins and the PTSD severity of their combat exposed brothers. Although a possible negative correlation between the hippocampal volume and the emotional memory in humans can be hypothesized, no direct evidence exists. In this experimental study, we examined whether the enhanced emotional memory could be predicted by hippocampal volume.

METHOD

This study was approved by the Institutional Review Board of the National Cancer Center. Twenty-seven healthy women were recruited by advertisements in newspapers and municipal information papers. They were between the ages of 35 and 61 (mean age=51.6 [SD=7.2]) and had 12 to 16 (mean education=13.9

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[SD = 1.7]) years of education. All gave written informed consent.

Most individuals were right-handed (N = 24, 91.4%; mean handedness score = 77.0 [SD = 41.8]), as assessed by the Edinburgh Inventory. They were free of major medical illnesses and traumatic brain injury, free of psychopathology as determined by the Mini-International Neuropsychiatric Interview,[6,7] free of cognitive impairment as assessed by the Mini-Mental State Examination (MMSE),[8] free of gross abnormalities as assessed by MRI, free of potentially psychoactive medications, and free of a family history of psychiatric illness. After the experiment, all of the participants were given a gift voucher (4,000 JPY) for their participation.

On the first experimental day, participants viewed 11 slides[9,10] depicting an emotionally arousing short story. The story consisted of three phases. Phase 1 (images 1 to 4) depicted a mother taking her son to visit his father at work. In phase 2 (images 5 to 8), the boy was badly hurt in a motor vehicle accident and surgeons struggled to save his life. In phase 3 (images 9 to 11), the mother was shown leaving the hospital. Thus, the emotionally arousing narration occurred in phase 2. Participants returned 1 week later for a second day of experiments and were given a surprise memory-recall test consisting of five to nine multiple-choice questions per slide.[11] Recall achievement was expressed as a percentage of the maximum score for each phase because of the different numbers of questions given for each phase. The enhanced emotional memory was defined as the difference [Δ2–1] between percent recall achievement of the emotionally arousing story part (phase 2) and percent recall achievement of the neutral story part (phase 1).

MRI scans were obtained by using a 1.5-T General Electric Signa scanner (GE Medical Systems, Milwaukee) prior to the experiment with an identical protocol[2,3] and MRI-assessed brain volume measurement techniques of the hippocampus and amygdala[2,3,12] previously described. Intrarater and interrater reliabilities were determined by using the intraclass correlation coefficients (>0.90 for all measures). Intracranial volume measurements were made by using a semiautomatic volumetric procedure described in detail elsewhere.[13]

Declarative memory ability was assessed using the Wechsler Memory Scale–Revised (WMS-R)[14] prior to the present experiment. We used the delayed recall indexes. Personality traits were measured using the revised Eysenck Personality Questionnaire (EPQ-R).[15] Since neuroticism refers to a general emotional overresponsiveness and a liability to develop stress-related psychiatric disorders, we used the EPQ-R neuroticism score.

We used the volumes of the left and right hippocampus and of the amygdala for the analysis. To analyze the specific effects of the amygdalar and hippocampal volumes on the enhanced emotional memory, a multiple linear regression partial correlation was used, with Δ2–1 as the dependent variable and the hippocampal and amygdalar volumes as the independent variables. We controlled the possible confounding effects of age, education, and variability in intracranial volume by entering these variables into the model. To eliminate the effect of cognitive function and personality, we subsequently entered the WMS-R delayed memory index, the MMSE score, and the EPQ-R neuroticism score into the model. All statistical analyses used two-tailed tests. The alpha levels of significance of all statistical analyses were $p<0.05$. The statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago).

RESULTS

The mean percent recall achievements for phases 1, 2, and 3 were 51.98 (SD = 8.82), 57.28 (SD = 8.08), and 47.56 (SD = 11.81), respectively. A one-way analysis of variance for repeated measures revealed a significant phase effect on recall achievement ($F = 11.21$, $df = 2, 52$, $p<0.01$). Regarding cognitive function and personality, the mean WMS-R delayed recall index was 103.26 (SD = 14.54), the mean MMSE score was 29.19 (SD = 0.83), the mean EPQ-R neuroticism score was 4.48 (SD = 2.87). No significant correlation between these potential covariates and Δ 2–1 was noted (age, $r = -0.104$, $p = 0.61$; delayed recall index, $r = 0.086$, $p = 0.67$; MMSE, $r = -0.137$, $p = 0.50$; neuroticism, $r = -0.61$, $p = 0.72$). The mean intracranial volume was 1284.4 cm^3 (SD = 106.7) and no significant correlation between intracranial volume and Δ2–1 was noted. The left and right hippocampal volumes were 3326.2 mm^3 (SD = 292.3) and 3423.4 mm^3 (SD = 290.0), respectively. The left and right amygdalar volumes were 1125.4 mm^3 (SD = 130.1) and 1208.5 mm^3 (SD = 145.4), respectively. We found a significant Pearson's correlation between the left hippocampal volume and Δ2–1 ($r = -0.407$, $p = 0.035$). The hippocampal volume was significantly correlated with Δ2–1 irrespective of age, education, and intracranial volume (Table 1). The effects of hippocampal volume on Δ2–1 remained significant after the effects

of cognitive function and personality traits were controlled.

DISCUSSION

The main finding in this study was that the enhanced emotional memory was predicted by the smaller left hippocampal volume but not the amygdalar volume in healthy middle-aged women. Furthermore, we have also addressed the potential impact of confounding factors in the interpretation of hippocampal volume variations. Our study design uniquely circumvented the impact of the participant's own and familial psychiatric conditions. The enhanced emotional memory was negatively correlated with the left hippocampal volume irrespective of age, educational history, intracranial volume, cognitive function, delayed memory function, and neuroticism. These findings support that smaller left hippocampal volume might predispose women to acquire stronger emotional responses when exposed to an aversive stimulus. These findings also support that smaller left hippocampus in cancer survivors with intrusive recollections represent a preexisting (acquired until cancer experience) vulnerability factor rather than the neurotoxic effect of persistent intrusive recollections. Regarding the amygdala, it was suggested that smaller amygdalar volume in cancer survivors with intrusive recollections does not support a predisposition theory.

Since only left hippocampal volume, and not right, was significantly associated with the enhanced emotional memory, there was laterality in these results. Two previous studies have revealed smaller left hippocampal volume in women with a history of cancer-related intrusive recollections[2] and predominantly smaller right hippocampal volume in men with combat-related PTSD.[5] Taken together with these findings, we may assume the existence of gender difference in the laterality of hippocampal volume on emotional memory.

Since breast cancer, at times, occurs in middle-aged women, these findings have important implications for the understanding of the neurobiological basis underlying intrusive recollections in breast cancer survivors. Any interpretation of our results should take into account following limitations. First, there was a small sample size. Second, different populations, different conditions (healthy versus PTSD), and different stress-induction methods might have affected our findings. Finally, MMSE doses not test executive cognitive function.

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TABLE 1. Correlations Between Volumes and Hippocampus and Amygdala and the Enhanced Emotional Memory (Δ2–1) in 27 Healthy Women

Enhanced emotional memory	Hippocampal volume				Amygdalar volume			
	Right		Left		Right		Left	
Controlled Variables	Partial Correlation	p	Partial Correlation	p	Partial Correlation	p	Partial Correlation	p
Age, education	−0.329	0.108	−0.440	0.028	−0.305	0.138	−0.244	0.240
Age, education, intracranial volume	−0.293	0.165	−0.411	0.046	−0.256	0.228	−0.181	0.398
Age, education, intracranial volume, MMSE	−0.293	0.175	−0.419	0.047	−0.256	0.239	−0.185	0.398
Age, education, intracranial volume, delayed recall	−0.303	0.161	−0.425	0.043	−0.256	0.239	−0.212	0.330
Age, education, intracranial volume, neuroticism	−0.303	0.170	−0.420	0.046	−0.276	0.202	−0.173	0.429

MMSE = Score of Mini–Mental State Examination; delayed recall = delayed recall index score of Wechsler Memory Scale revised; neuroticism = neuroticism score of revised Eysenck Personality Questionnaire

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Different Emotional Memory Consolidation in Cancer Survivors With and Those Without a History of Intrusive Recollection

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The study examined emotional memory consolidation among cancer survivors with and without a history of intrusive recollection (IR). Eleven cancer survivors with a history of IR (IR+), 20 cancer survivors without a history of IR (IR−), and 20 healthy women were tested for emotional memory. The participants viewed emotionally arousing slides, and one week later, they were asked to return to the laboratory and were given an unexpected memory test to examine their retention of emotional memory. Only the IR− group did not show any significant enhancement in emotional memory, compared to neutral memory. These findings are discussed in light of possible inhibitory mechanisms of emotional memory consolidation.

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Having cancer is clearly a stressful experience (Cordova, Cunningham, Carlson, & Andrykowski, 2001), and the initial diagnosis of this potentially deadly illness can be sudden and unexpected; furthermore, surgery can be invasive, painful, and disfiguring (Buckley, Green, & Schnurr, 2004). Intrusive recollections (IR), one of the reexperiencing symptoms of posttraumatic stress disorder (PTSD), occur at a relatively high prevalence in cancer survivors. Among studies that have utilized the Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1997), the prevalence of IR has ranged from 11 to 45% (Alter et al., 1996; Andrykowski & Cordova, 1998; Green et al., 1998; Matsuoka et al., 2005). On the other hand, the fact that the other breast cancer patients do not experience IR is also worthy of attention.

Emotional arousing or stressful situations produce several bodily changes, resulting from activation of the (nor)adrenergic system and hypothalamus–pituitary–adrenal (HPA) axis. Considerable evidence suggests that these systems act on consolidation of long-term memory for emotional experiences as well as constitute the neurobiological basis of memory disturbances in PTSD (Elzinga & Bremner, 2002). These stress mechanisms are also appropriate to understand the neurobiological systems activated in cancer-related IR (Matsuoka, Nagamine, & Uchitomi, 2006). Evidence suggests that (nor)adrenaline acts on the amygdala's β-adrenergic receptors to modulate memory consolidation and that the activation of this region is especially important for emotional arousal (McGaugh, 2000). As with noradrenaline, glucocorticoids (cortisol in primates), which are produced by the stress-responsive HPA axis, regulate hippocampal metabolism to enhance memory (McGaugh, 2000). Little is known about the neurobiological basis of IR. We previously used structural magnetic resonance imaging (MRI) to study cancer-related IR and reported that women with a history of cancer-related IR showed a 4.9% smaller left hippocampal volume and 5.7% smaller left amygdala volume as compared with those without such history (Matsuoka, Yamawaki, Inagaki, Akechi, & Uchitomi, 2003; Nakano et al., 2002). Furthermore, women with a history of cancer-related IR showed impaired visual declarative memory as compared with those without such a history (Nakano et al., 2002). Although the memory function (assessed by the Wechsler Memory Scale-Revised [WMS-R]; Sugishita, 2001; Wechsler, 1987) was investigated, the relation with hippocampus volume in our previous study (Nakano et al., 2002), the emotional memory, which relates tightly with limbic function, has not yet been clarified in terms of IR.

The following experimental protocol developed by Cahill, Prins, Weber, and McGaugh (1994) has been widely used to investigate the impact of emotion on memory. Participants are shown a series of slides with an emotionally arousing accompanying narrative; one week later, they are given an unannounced memory test to evaluate their level of story retention. The emotionally arousing story consists of three phases, with the emotional elements introduced during the middle phase (Phase 2). Phase 1 depicts a mother taking her son to visit his father at work. In Phase 2, the boy has a terrible accident, which critically injures him. In Phase 3, the mother is shown leaving the hospital. Participants typically demonstrate heightened recall for Phase 2 events compared to Phases 1 and 3 (Cahill, Prins, Weber, & McGaugh, 1994). The role of the amygdala in emotional memory has been highlighted by several positron emission tomography (PET) studies (Cahill et al., 1996; Hamann, Ely, Grafton, & Kilts, 1999). For example, in the study conducted by Cahill et al. (1996), the glucose metabolic rate of the right amygdaloid complex while viewing the emotional films was highly correlated with the number of emotional films recalled. There was no significant correlation with the number of neutral films recalled. Therefore, it is plausible to evaluate the emotional memory enhancement as a surrogate marker of the amygdala's function.

To our knowledge, the relationship between the presence or absence of a history of IR and emotional memory enhancement in experimental sessions has not yet been directly investigated. The aim of this study was to examine differences in the enhanced retention of emotional memory related to emotionally stressful stimuli, but not to cancer-related stimuli (Cahill et al., 1994), among female healthy controls and female cancer survivors with or without a history of IR. We believe that IR itself is a consequence of

increased arousal; therefore, we hypothesized that cancer patients with a history of IR would show an accentuated enhancement of memory with emotional arousal, but that no difference would be seen between healthy control participants and cancer survivors without a history of IR.

METHOD

Participants

Women were recruited from among the participants of a primary MRI volumetric study that investigated the association between postcancer psychological distress and brain structure. For the primary MRI study, cancer survivors were recruited from the regular follow-up outpatient clinic of the Division of Breast Surgery, National Cancer Center Hospital East in Kashiwa, Japan, between March 1999 and February 2002. The inclusion criteria for the present study were as follows: (a) completion of a cranial MRI scan and participation in the primary study; (b) age between 20 and 60 years old; (c) an educational history of more than 10 years; (d) no current diagnosis of Axis I psychiatric disorders, as evaluated by Mini-International Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998); (e) no cognitive impairment, defined as having a score of less than 24 on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975; Mori, Mitani, & Yamadori, 1985); (e) no chemotherapy in the past; and (f) no gross abnormalities, as assessed by MRI. The exclusion criteria were (1) under medication (such as antidepressants, antipsychotics, benzodiazepine, beta blockers, steroids) within the previous month; (2) a history of any neurological disorder or traumatic brain injury with loss of consciousness; (3) apparent evidence of recurrent cancer during regular medical checkups conducted by an attending oncologist (the co-author Shigeru Imoto); and (4) currently being pregnant or taking antipregnancy drugs.

The presence of IR related to the experience of having had cancer was investigated using semistructured interviews conducted 3 to 15 months after surgery in the primary study. Intrusive recollection was defined, based on a modification of criterion B1 of the PTSD module in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994), as "recurrent and intrusive distressing recollections of the cancer-related event, including images, thoughts, or perceptions" with a duration of one month or more and that had been present within the previous month. We used sentence F42 from the criteria for PTSD in the administration booklet of the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1997). The subjects were asked by a trained psychiatrist (the first author Yutaka Matsuoka), "During your life, from the day when you were diagnosed as having breast cancer to date, did you think about disclosure of your cancer diagnosis when you did not want to, or did thoughts about disclosure of your cancer diagnosis come to you suddenly when you did not want them to?" (details in Matsuoka et al., 2005). Of the 159 breast cancer survivors, 56 candidates met the eligibility criteria. The others were excluded because they did not complete a cranial MRI scan ($n = 20$); had a history of chemotherapy ($n = 82$), had a recurrence of cancer ($n = 1$). Of the remaining 56 eligible cancer survivors, 21 candidates met the criterion for presence of cancer related IR (IR+) and others not ($n = 35$, IR−). Of the 21 candidates with IR, 11 (60%) participated, 4 could not be contacted during the investigation period, and 6 refused. Of the 35 candidates without IR, 20 (57%) participated, 7 could not be contacted during the investigation period, and 8 refused. There were no significant differences between the participants and the nonparticipants in age, education, clinical stage, and type of surgery within each group, IR+ and IR−.

The healthy women were recruited by advertisements in newspapers and municipal information papers distributed in the geographic area served by the National Cancer Center Hospital East (Kashiwa, Nagareyama, Noda, Abiko, and Matsudo) between November 2000 and April 2002. The inclusion criteria for the healthy women were similar to those for cancer survivors except for cancer-related criteria. Of the 89 healthy candidates, 50 candidates met the eligibility criteria. The others were excluded because they did not complete a cranial MRI scan ($n = 39$). Of the 50

Table 1. Characteristics of Breast Cancer Survivors and Healthy Control Participants

	BCS IR+[a] $n = 11$		BCS IR−[b] $n = 20$		Healthy control $n = 20$		Test		
	M	*SD*	*M*	*SD*	*M*	*SD*	*df*	*F* or *t*	Fisher's exact (*p*)
Age at time of experiment (yrs)	51.8	4.0	51.9	7.8	52.1	6.4	2,48	<1	–
Education (yrs)	13.4	2.4	13.3	2.2	13.8	1.8	2,48	<1	–
MMSE	29.1	1.4	28.5	1.1	29.3	0.7	2,48	2.98	–
Personality trait score by EPQR									
Neuroticism	7.2	2.4	4.8	2.5	4.0	2.9	2,47	5.39**	–
WMS-R Measure									
Delayed memory index	106.2	10.6	100.9	12.6	102.7	13.2	2,48	<1	–
Time elapsed after surgery to									
Identification of IR (mos)	6.7	2.0	8.0	3.5			28.8	−1.40	–
Experiment (yrs)	4.3	0.8	4.5	1.1	–	–	29	0.61	–
IES Score									
Intrusion subscale	8.8	4.9	3.8	5.3			29	2.62*	–
Avoidance subscale	3.2	2.6	2.9	3.9			29	0.22	–
Clinical stage (UICC)									
I-IIB *n*, %	10	90.9	16	80			–	–	0.6
Breast-conserving surgery *n*, %	6	54.5	14	70			–	–	0.5
Lymph node metastasis (+) *n*, %	2	18.2	2	10			–	–	0.6
Radiotherapy (+) *n*, %	5	45.5	11	55			–	–	0.7
Major depressive disorder									
Precancer onset *n*, %	1	9.1	1	5			–	–	1.0
Postcancer onset *n*, %	2	18.2	1	9.1			–	–	0.5

Note. BCS IR+ = breast cancer survivors with intrusive recollections; BCS IR− = breast cancer survivors without intrusive recollections; MMSE = Mini Mental State Examination; UICC = Union Internationale Contre le Cancer; EPQR = Eysenck Personality Questionnaire Revised; WMS-R = Wechsler Memory Scale-Revised.
*$p < .05$. **$p < .01$.

candidates, 20 (40%) participated, 24 could not be contacted during the investigation period, and 6 refused. There were no significant differences between the participants and the nonparticipants in age and education. Finally, the participants were 11 breast cancer survivors with IR (IR+), 20 breast cancer survivors without IR (IR−) and 20 healthy women (control) matched for age, education, and residency. The characteristics of the cancer patients and healthy control participants are presented in Table 1; analyses revealed no significant differences among the three groups except for the neuroticism score by Eysenck Personality Questionnaire-Revised (Eysenck, Eysenck, & Barret, 1985; Hosokawa & Ohyama, 1993) at the semistructured interviews conducted 3 to 15 months after surgery (the IR+ group had a higher neuroticism score than the IR− and control groups: $p < .01$ and $p < .05$, respectively). All participants were currently free from major medical illnesses and psychopathology. This study was approved by the Institutional Review Board and Ethics Committee of the National Cancer Center, Tokyo, Japan. Written informed consent was obtained from each participant after a complete description of the study. All participants were individually tested.

Materials and Procedures

The stimulus materials (11 slides) and narrative scripts were identical to those used in a previous study (Cahill

et al., 1994), and the participants viewed a Japanese version of an emotionally arousing short story lasting about 5 minutes (Kazui, Mori, Hashimoto, & Hirono, 2003). The story was divided into three phases: Phase 1 (slides 1–4), Phase 2 (slides 5–8), and Phase 3 (slides 9–11). The emotionally arousing narration occurred during Phase 2. Each slide was presented for 20 seconds on a standard 14-inch color monitor located approximately 1 m in front of the subject.

The emotional memory experiment was conducted 2.8 to 6.2 years after surgery. On the first experimental day (Day 1), the participants were interviewed and asked to complete the Mini International Neuropsychiatric Interview (Otsubo et al., 2005; Sheehan et al., 1998) to determine whether they were free from current and past major psychiatric illnesses. The Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Mori et al., 1985) was then administered and afterwards, the participants were asked to sit comfortably in a chair. Prior to viewing the slides, each subject was fitted with electrodes for continuous heart rate (HR) and skin conductance response (SCR) monitoring (BIOPAC MP150 recording system, Monte System, Tokyo). Instructions were displayed 20 seconds prior to the slide presentation, and the participants were told to pay attention to the slides and the narration. The participants were informed that the slide show would last about 5 minutes. Immediately after viewing all slides, the participants then saw the slides again and were asked to rate their valence level (0 = *not unpleasant at all* to 10 = *extremely unpleasant*), arousal level (0 = *not emotionally intense at all* to 10 = *extremely emotionally intense)*, and comprehension level (0 = *not understood at all* to 10 = *understood completely*) of each slide. Participants were asked not to discuss the test with anyone else and were instructed to return 1 week later. On the second experimental day (Day 2), the participants returned to the laboratory and were given an unexpected memory test, consisting of five to nine multiple-choice questions per slide (Cahill & McGaugh, 1995). After the memory test, the participants' valence and arousal level for each slide during the memory recall test was evaluated on a scale of 0–10. The participants also saw each slide again for the evaluation. All the participants received monetary compensation (JPY 4000 or approximately US $35) for their participation.

Data Analysis

The correct memory scores were expressed as percentages for the three different story phases because the number of questions differed for each phase. These scores were analyzed using a repeated-measures analysis of variance (ANOVA), with diagnostic group (IR+, IR−, control) as class variable, and phase (Phase 1–3) as a repeated measure. Additionally these scores were analyzed using a repeated-measures analysis of covariance (ANCOVA), with diagnostic group (IR+, IR−, control) as class variable, phase (Phase 1–3) as a repeated measure, and neuroticism as a covariate because the neuroticism score was significantly different among the three groups at the baseline assessment. When there was a significant interaction effect, the post hoc test was conducted based on the three phase means within each group (IR+, IR−, control). Next, the HR recordings were averaged across the 60 seconds prior to Phase 1 as pre-HR (pre) and across Phases 1, 2, and 3. In each subject, the SCR after viewing each slide was determined by subtracting the baseline conductance level (immediately before a slide was presented) from the peak change from baseline that occurred not less than 1 second and not more than 10 seconds after the slide was presented. The responses of each subject to every phase were then averaged. Taking into account the sphericity assumption, the degrees of freedom were adjusted, employing the Greenhouse–Geisser approach when appropriate. An alpha level of .05 was used for all statistical tests. The data were analyzed using the Statistical Program for Social Sciences (SPSS; Windows version 12.0). One set of control group neuroticism, HR and SCR data was not obtained because of a technical error.

RESULTS

Valence, Arousal, and Comprehension Level

The means for each phase among IR+, IR− and control groups are shown in Table 2. Significant main effects of

Table 2. Ratings of the Valence, Arousal, and Comprehension Level of the Story, HR, and SCR Among Breast Cancer Survivors and Healthy Controls

		BCS IR+				BCS IR−				Control				*F*			
		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2		Phase		Group	
		M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	Day 1	Day 2	Day 1	Day 2
Valence	Phase 1	0.9	1.2	1.1	1.5	0.5	1.1	0.5	0.7	0.3	0.6	0.2	0.6	74.30***	40.14***	5.80**	4.59*
	Phase 2	5.1	2.2	4.9	3.2	4.1	2.3	3.0	2.5	2.5	1.6	2.7	2.3				
	Phase 3	2.3	2.5	3.8	2.5	1.6	2.3	1.7	2.8	0.6	1.1	1.2	2.3				
Arousal	Phase 1	1.5	1.4	1.0	1.5	0.7	1.2	0.4	0.7	0.4	0.7	0.3	0.6	49.80***	49.43***	2.32	3.27*
	Phase 2	5.5	2.9	5.1	3.2	3.9	3.1	2.8	2.7	3.2	2.8	3.3	2.7				
	Phase 3	3.4	2.6	4.2	2.7	2.1	2.5	2.0	2.7	2.3	2.5	2.1	2.6				
Comprehension	Phase 1	10.0	0.0			9.7	1.1			10.0	0.0			<1			<1
	Phase 2	10.0	0.0			9.9	0.6			10.0	0.0						
	Phase 3	10.0	0.0			9.9	0.5			10.0	0.0						
HR (bpm)	Pre	72.3	14.8			73.5	10.6			73.0	9.2			4.18*			<1
	Phase 1	72.6	12.3			74.8	10.1			76.2	11.0						
	Phase 2	71.4	11.0			74.4	10.6			74.4	10.2						
	Phase 3	70.9	11.5			73.8	10.8			74.1	10.2						
SCR (μ mhos)	Phase 1	0.04	0.04			0.03	0.04			0.02	0.01			4.32*			1.14
	Phase 2	0.03	0.03			0.03	0.03			0.02	0.01						
	Phase 3	0.03	0.03			0.02	0.02			0.02	0.01						

Note. BCS IR+ = breast cancer survivors with intrusive recollections; BCS IR− = breast cancer survivors without intrusive recollections; HR = heart rate; SCR = skin conductance response.
*$p < .05$. **$p < .01$. ***$p < .001$.

phase on the level of valence and arousal emerged. A post hoc analysis showed, as expected, Phase 2 events produced a higher level of valence and arousal than Phase 1 and 3 events (all $ps < .001$). The significant main effect of group was found only on the level of valence, and a post hoc analysis showed a significantly higher level in the IR+ group than in the control group ($p < .01$). There were no significant main effect of phase or group on comprehension and also no significant group × phase interactions were observed for valence, arousal, or comprehension levels, $F(4, 96) = 2.09$, 0.84, <1, respectively, all *ns*. Thus, all the groups rated Phase 2 events as being more emotional and arousing than Phase 1 events; in addition, the IR+ group rated the events in all the phases as being more emotional, compared with the ratings made by the control group.

One week later, a change in subjective appraisal comparable to Day 1 was found. Significant main effects of phase on the level of valence and arousal were found, and post hoc analysis showed that Phase 2 events produced higher levels of valence and arousal than phase 1 and 3 events (all $ps < .001$). Significant main effects of group on the level of valence and arousal were also found, and a post hoc analysis showed that the valence score of the IR+ group was significantly higher than that of the control group. No significant group × phase interactions were observed for the level of valence or arousal, $F(4, 96) = 1.19$, *ns*, $\varepsilon = .84$, $F(4, 96) = 1.22$, *ns*, $\varepsilon = .78$, respectively.

Emotionally Influenced Memory Test

The mean and adjusted memory scores (and *SD*s) for each phase for the IR+ group were as follows: Phase 1: 53.9 (9.5), 52.4 (10.1); Phase 2: 61.4 (9.0), 60.9 (8.0); and Phase 3: 53.6 (12.2), 54.9 (11.3). For the IR− group, the

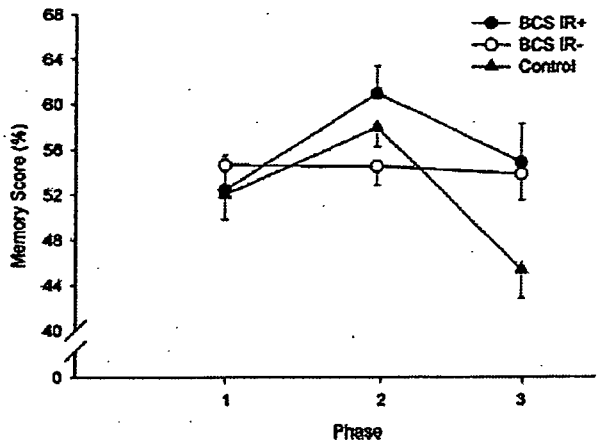

Figure 1. Adjusted mean memory scores (±*SE*) for the three phases in BCS IR+ (breast cancer survivors with intrusive recollections), BCS IR− (breast cancer survivors without intrusive recollections), and control groups.

scores were Phase 1: 54.5 (9.3), 54.6 (9.4); Phase 2: 54.5 (7.5), 54.5 (7.5); and Phase 3: 53.9 (9.9), 53.8 (10.5). For the control group, the scores were Phase 1: 52.0 (9.7), 52.0 (9.9); Phase 2: 58.6 (7.2), 57.9 (7.9); and Phase 3: 46.1 (9.8), 45.4 (11.1) (see Figure 1). The ANOVA revealed significant main effects of phase, $F(2, 96) = 9.08$, $p < .001$, and group × phase interaction, $F(4, 96) = 3.08$, $p < .05$, $\varepsilon = 0.88$, but not a main effect of group, $F(2, 48) = 1.45$, *ns*. The simple main effect revealed a significant difference between Phase 2 events and Phase 1 and 3 events in the control group ($p < .01$ and $p < .001$, respectively) and a significant difference between Phase 1 events and Phase 2 events in the IR+ group ($p < .05$). Next, the repeated ANCOVA revealed the group × phase interaction for memory scores adjusted for neuroticism score was significant, $F(4, 92) = 3.26$, $p < .05$. Neither the main effect of group, $F(2, 46) = 1.40$, nor phase, $F(2, 92) = 1.88$, was significant. The simple main effect revealed a significant difference between Phase 2 events and Phase 1 and 3 events in the control group ($p < .05$ and $p < .001$, respectively) and a significant difference between Phase 1 events and Phase 2 events in the IR+ group ($p < .05$).

Thus, only the IR- group did not exhibit a memory score difference among the three phases.

The relationship of time elapsed after surgery to experiment and the enhanced emotional memory score was also tested. The enhanced emotional memory was defined as the difference [Δ2 − 1] between memory score of the emotionally contrasted story part (Phase 2) and of the neutral story part (Phase 1). There was no significant correlation ($r = .13$, *ns*).

Heart Rate and Skin Conductance Responses

As shown in Table 2, only a main effect of phase on HR was found. A post hoc analysis showed that HR during Phase 1 was significantly higher than Phase 3 ($p < .05$). The HR and SCR were not significantly correlated with the memory scores. No significant group × phase interactions were observed for HR or SCR, $F(6, 138) = 1.17$, *ns*, $\varepsilon = .69$, $F(4, 94) = 1.03$, $\varepsilon = .71$, respectively.

DISCUSSION

To the best of our knowledge, the present findings are the first to show the relation between the presence or absence of a history of IR and emotional memory enhancement during experimental sessions. In contrast to our hypothesis, cancer survivors with a history of IR and healthy control participants showed significant enhanced memory for Phase 2 events of the story compared to Phase 1, whereas cancer survivors without a history of IR did not. This result, in which the IR+ group showed a significant enhancement in emotional memory but the IR− group did not, may partially support the findings of a previous observational study (Matsuoka et al., 2005). Matsuoka and colleagues sought to identify the determinants of IR related to receiving a cancer diagnosis in women after cancer treatment and found that neuroticism, precancer IR, and the number of relatives by marriage with cancer were significant determinants. In our study, the neuroticism score was controlled to investigate the memory score difference among the three groups; therefore, it would be possible to clarify a more direct relationship between the presence or

absence of a history of IR and emotional memory enhancement that may be related to IR associated with current or novel trauma. In terms of participants' selection, cancer survivors had a similar experience between IR+ and IR− groups. Therefore, no enhanced emotional memory in the IR− group suggests that cancer survivors without a history of IR may have some mechanism that inhibits the consolidation of emotional memory. In the previous study, no emotional memory enhancement was found in the patients with left amygdala damage (Adolphs, Tranel, & Denburg, 2000), thus, no enhanced emotional memory in the IR− group would reflect the difference in amygdala's function. Furthermore, there might be individual differences such as beliefs (e.g., optimism, resilience, human strengths, health) between IR+ and IR− groups. Greater attention has been directed to the positive emotions and beliefs that may promote resilience among survivors of cancer (Aspinwall & MacNamara, 2005). It is speculated that cancer survivors without IR may have greater resilience to overcome the traumatic stress and have a stronger inhibitory mechanism compared to those with a history of IR. Possibly, the IR− group could be less vulnerable to traumatic stress.

When the differences in emotional memory enhancement among the three groups were considered together with the results of the subjective appraisals, i.e., the valence and arousal ratings for the slides, the absence of a linear relation between subjective appraisal and emotional memory enhancement was readily apparent. The IR+ group showed an enhancement in emotional memory comparable with that of the control group, but the valence scores for the slides were significantly higher in the IR+ group on both experimental days. This result could be explained by the characteristics of the IR+ group, such as high anxious preoccupation (Matsuoka et al., 2002). Matsuoka et al. found that subjects with a history of cancer-related IR showed significantly higher levels of anxious preoccupation compared to those without a history of cancer-related IR. Therefore, a higher level of anxious preoccupation might affect the subjective appraisal on a novel situation such as an experiment session. Additionally, no significant decrease in the memory score from Phase 2 to Phase 3 in the IR+ group could be related with the higher levels of valence compared to those of the control group on the first experimental day.

The change in the memory score from Phase 2 to Phase 3 in the control group is the largest observed change. This change, the significant decrease of memory score was found in a previous study (Cahill et al., 1994), but the amount of decrease seems to be larger in the present study. However, the amount of increase in the memory score from Phase 1 to Phase 2 in the control group is smaller than the result of Cahill's study (Cahill et al., 1994). It is not clear why this should be, but it may reflect the individual differences in the participants, e.g., age; the participants in the present study are older than those who took part in Cahill's study.

For physiological responses (HR and SCR), no differences were seen among the three groups. The HR and SCR showed a decreasing trend from Phase 1 to Phase 3; however, there was no significant difference among the three groups. Therefore, physiological responses seen in the experimental sessions could not distinguish cancer survivors with or without a history of IR from healthy controls. The stimulus may not be enough for enhancing HR and SCR responses.

In summary, the present findings showed no significant enhancement in emotional memory in cancer survivors without a history of IR, compared to cancer survivors with a history of IR and healthy controls, when examined in experimental sessions. Cancer survivors without a history of IR may have a stronger inhibitory mechanism for emotional memory consolidation and have a greater resilience to overcome the traumatic stress compared to cancer survivors with a history of IR. Whether this stronger inhibitory mechanism and higher level of resilience in cancer survivors without IR develops after experiencing cancer or are preexisting characteristics is uncertain; hence, further studies are needed with a large sample. This study included only participants with a history of IR; therefore, emotional memory enhancement in participants with current IR should also be investigated in a future study. Spiegel (2005) advocates a broader view of outcome assessment in traumatic stress research with attention to coping styles, affect management, resilience, and social reorganization. In keeping with this view, it is important to investigate the

influence of personal resilience in overcoming traumatic stress, especially as it relates to the emotional memory, to chart the course of recovery.

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Structure of orbitofrontal cortex and its longitudinal course in cancer-related post-traumatic stress disorder

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Abstract

The neurobiological basis of cancer-related post-traumatic stress disorder (PTSD) has never been studied. We investigated brain structural alterations and the longitudinal courses in patients with cancer-related PTSD. Baseline scans using magnetic resonance imaging were performed in 14 cancer survivors with PTSD, 100 without PTSD, and 70 healthy subjects. Follow-up scans were performed 2 years later in 76 cancer survivors (PTSD, $n = 9$; non-PTSD, $n = 67$). Using voxel-based morphometry, the gray matter volume (GMV) of the cancer survivors with PTSD was compared with the GMVs of those without PTSD and of the healthy subjects. The effects of the interactions between the diagnosis and the timing of the GMV measurements were examined. The GMV of the right orbitofrontal cortex (OFC) was significantly smaller in cancer survivors with PTSD than in those without PTSD or healthy subjects. The interaction between the diagnosis and the timing of the right OFC's GMV measurement was not significant. The OFC, which is thought to be involved in the extinction of fear conditioning and the retrieval of emotional memory, might play an important role in the pathophysiology of PTSD. Moreover, the OFC's GMV may remain constant after the development of cancer-related PTSD.

Keywords: Post-traumatic stress disorder; Magnetic resonance imaging; Voxel-based morphometry; Orbitofrontal cortex; Longitudinal course

1. Introduction

Breast cancer is a major health burden for women. The incidence of breast cancer has been increasing remarkably in Japan, as in Western countries (Yoshimi and Sobue, 2004). The age-standardized incidence rate of breast cancer was reported to be 43.6% (Yoshimi and Sobue, 2004), and breast cancer is now the fifth leading cause of cancer-related deaths among Japanese women (Tsukuma et al., 2004). Breast cancer is a life-threatening illness, and receiving a diagnosis and/or a distressing anticancer treatment can be traumatic. Previous studies have reported that 3–18% of breast cancer survivors develop post-traumatic stress disorder (PTSD) and 41% suffer from any PTSD symptom (Mehnert and Koch, 2007; Matsuoka et al., 2006; Palmer et al., 2004). PTSD symptoms have been shown to be associated with the presence of prolonged depression or anxiety (Epping-Jordan et al., 1999), psychological maladjustment (Matsuoka et al., 2002), and a poor quality of life (Cordova et al., 1995).

The neurobiological basis of cancer-related PTSD has never been studied, although that of other PTSD such as rape, war, and disaster has been extensively studied. Several previous structural neuroimaging studies on PTSD have focused on the hippocampus as the neurobiological basis of the disease and

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have reported a smaller gray matter volume in patients with PTSD (Kitayama et al., 2005). Moreover, a few recent studies using voxel-based morphometry (VBM) have reported a smaller gray matter volume in the anterior cingulate cortex (ACC), suggesting the usefulness of VBM for exploring structural alterations throughout the brain (Yamasue et al., 2003; Corbo et al., 2005; Chen et al., 2006). Findings of a smaller hippocampal or ACC gray matter volume in patients with PTSD have gradually been accumulated in cross-sectional studies. In contrast, only a few studies have longitudinally examined the influence of PTSD on the longitudinal course of the smaller gray matter volume (Bonne et al., 2001), and whether the gray matter volume decreases, increases, or remains constant under the influence of PTSD remains uncertain. On the other hand, in many functional imaging studies of PTSD using symptom provocation paradigms, the limbic system, including the hippocampus and amygdala, and the prefrontal cortex (PFC), including the ACC and orbitofrontal cortex (OFC), have been found to show dysfunctional activation. Given that functional alterations have been shown to be closely associated with structural alterations (Pezawas et al., 2005), the limbic system and the PFC are likely to play roles in the neurobiological basis of cancer-related PTSD. Therefore, the limbic system and the PFC should be considered when examining the neurological basis of cancer-related PTSD. Moreover, structural alterations throughout the brain should be explored using VBM because structural differences in brain regions other than the limbic system and the PFC may exist. Further, in addition to cross-sectional investigations, a longitudinal structural examination would also be useful for revealing whether brain volumes decrease, increase, or remain constant under the influence of cancer-related PTSD.

With the hypothesis that the gray matter volume of the limbic system or the PFC is smaller in breast cancer survivors with PTSD than in those without PTSD or healthy subjects, we used VBM to explore structural alterations throughout the brains of patients with cancer-related PTSD. Any changes in gray matter volume were then examined longitudinally to investigate the influence of cancer-related PTSD on the longitudinal course of gray matter volume.

2. Methods and materials

2.1. Study design and participants

This study was approved by the institutional review board and the ethics committee of the National Cancer Center (NCC) in Tokyo, Japan. We used a database of brain MRI scans performed in breast cancer survivors; the scans were taken 3–15 months after breast cancer surgery (baseline investigation) and 2 years after the first scan (follow-up investigation). The subjects were recruited from patients regularly seen in the follow-up outpatient clinic of the Division of Breast Surgery, National Cancer Center Hospital East, between May 1998 and December 2002.

At the time of the baseline investigation, we selected the records of all the patients who had undergone breast cancer surgery, excluding those who received only a biopsy, between February 1998 and September 2001 and who survived for 3–15 months. The other inclusion criteria were (1) a female sex and (2) an age between 18 and 55 years during the recruitment periods. To minimize influences of brain atrophy and other geriatric brain changes, we included subjects who are 55-year-old or below. The exclusion criteria were (1) a history of treatment for cancer other than breast cancer or double cancer, (2) bilateral breast cancer, (3) clear evidence of residual or recurrent cancer during regular medical checkups conducted by an experienced oncologist (S.I.), (4) chemotherapy or radiation therapy within the previous month, (5) psychotropic medication within the previous month, (6) a history of any neurological disorder or traumatic brain injury accompanied by periods of unconsciousness, (7) a history of substance abuse or dependence, (8) a family history of early dementia among first- or second-degree relatives, (9) moderate physical symptoms that interfered with daily life, as assessed using the performance status defined by the Eastern Cooperative Groups (Oken et al., 1982), (10) cognitive impairment defined as a score of less than 24 on the Mini-Mental State Examination (Folstein et al., 1975; Mori et al., 1985), (11) left-handedness, and (12) the presence of a current diagnosis of major depression or PTSD other than cancer-related PTSD.

Of the 603 breast cancer patients who underwent operations between February 1998 and September 2001, 359 patients met the inclusion criteria (244 were excluded because of age). Based on their medical charts, 37 patients were excluded (double cancer: 4; bilateral cancer: 9; residual cancer: 6; recurrent cancer: 1; chemotherapy or radiation therapy within the previous month: 11; and psychotropic medication: 6). Of the remaining 322 patients, 119 refused to participate in the study and 68 could not be contacted. After an interview to screen for the exclusion criteria, 16 of the 135 patients were excluded (psychotropic medication within the previous month: 9; history of any neurological disorder or traumatic brain injury accompanied by periods of unconsciousness: 3; history of substance abuse or dependence: 1; and left-handedness: 3). Of the 119 patients who underwent MRI scans, three were excluded because of MRI acquisition errors and one was excluded because of MRI evidence of cancer metastasis in the brain. The remaining 115 patients were interviewed by a trained psychiatrist (Y.M.) using a semi-structured interview, including the clinician version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997). Another psychiatrist assessed 30 of the same participants, and the κ-value for the current diagnosis of PTSD was 1.0. Definition of cancer-related PTSD was PTSD related to the patient's experience of the disclosure of cancer diagnosis and/or receiving distressing anticancer treatment. After the interview, one patient was excluded because of the presence of current non-cancer-related PTSD. Ultimately, 114 patients participated in the study. Of these 114 patients, 14 (12%) met the criteria for PTSD (current: 4 and past: 10). Of the other 100 patients, 12 (12%) have met 1 or 2 PTSD criteria of reexperience, avoidance, and hyperarousal symptoms in the past. In addition, we used advertisements or flyers in the local newspaper to recruit healthy subjects who live in the geographic area of NCC to exclude the influence of cancer itself on brain structure. The eligibility criteria were the same as those for the cancer patients, except for the requirement of a history of breast cancer surgery. Seventy healthy subjects participated in the study. After a complete description of the study was given to the subjects, written informed consent was obtained. No significant demographic differences between the breast cancer survivors with PTSD and those without PTSD or the healthy subjects were present (Table 1).

At the time of the follow-up investigation, 76 of the cancer survivors who participated in the study (9 with PTSD and 67 without PTSD) could be contacted. At this time point, all the patients with PTSD had recovered naturally without any pharmacological or psychological intervention. No significant differences in the demographics between the breast cancer survivors with PTSD and those without PTSD were observed, except for a history of major depression (PTSD, $n = 7$, 77.8%; non-PTSD, $n = 14$, 20.9%; $\chi^2 = 12.84$, $p = 0.001$).

2.2. Assessment of PTSD symptomatic responses to the cancer experience

To measure the PTSD symptomatic responses to the cancer experience, the Impact of Event Scale (IES), which is used worldwide to assess PTSD symptomatic responses to specific traumatic experiences, was used. The IES is a self-reported questionnaire consisting of 15 items: 7 items assessing intrusion symptoms and 8 items assessing avoidance symptoms. Each item is rated using a 4-point scale ("not at all" = 0, "rarely" = 1, "sometimes" = 3, "often" = 5) (Horowitz et al., 1979).

Table 1
Demographic characteristics of cancer survivors with PTSD and without PTSD or healthy subjects

Characteristics	Cancer survivors, mean (S.D.)		Difference between groups[a]			Healthy subjects ($n = 70$), mean (S.D.)	Difference between groups[b]		
	With PTSD ($n = 14$)	Without PTSD ($n = 100$)	Statistical value, t	d.f.	p		Statistical value, t	d.f.	p
Age (years)	45.6 (6.2)	47.1 (5.7)	0.90	112	0.37	46.0 (6.9)	0.22	82	0.82
Height (cm)	157.4 (6.2)	156.1 (5.4)	0.80	112	0.43	156.5 (5.2)	0.54	82	0.59
Weight (kg)	57.4 (13.6)	55.6 (7.3)	0.75	112	0.45	53.1 (7.3)	1.69	82	0.09
Education (years)	13.9 (1.5)	13.2 (1.9)	1.33	112	0.19	14.3 (1.8)	0.73	82	0.47
Accumulated alcohol consumption ($g \times 10^3$)	26 (42)	30 (72)	0.18	112	0.86	32 (64)	0.32	82	0.75
IES score	17.1 (6.6)	8.2 (7.8)	4.05	112	<0.001	–	–	–	–
Intrusion subscale	10.5 (5.0)	5.0 (4.6)	4.12	112	<0.001	–	–	–	–
Avoidance subscale	6.6 (6.0)	3.2 (4.5)	2.58	112	0.011	–	–	–	–

Characteristics	Cancer survivors, n (%)		Difference between groups[a]			Healthy subjects ($n = 70$), n (%)	Difference between groups[b]		
	With PTSD ($n = 14$)	Without PTSD ($n = 100$)	Statistical value, χ^2	d.f.	p		Statistical value, χ^2	d.f.	p
Smoking habit	0 (0)	12 (12.0)	1.88	1	0.36	3 (4.3)	0.62	1	1.00
Postmenopausal state	6 (43)	60 (60)	1.48	1	0.22	21 (30)	0.88	1	0.36
Partial mastectomy	7 (50)	53 (53)	0.04	1	0.83	–	–	–	–
Clinical stage: 1	9 (64)	64 (64)	0.01	1	1.00	–	–	–	–
Lymph node metastasis: positive	4 (29)	33 (33)	0.11	1	1.00	–	–	–	–
Chemotherapy	7 (50)	48 (48)	0.02	1	0.88	–	–	–	–
Radiation therapy	6 (43)	47 (47)	0.09	1	0.77	–	–	–	–
Hormonal therapy	5 (36)	33 (33)	0.04	1	1.00	–	–	–	–
Days after surgery	266 (96)	288 (106)	0.75	112	0.46	–	–	–	–
History of major depression	7 (50)	10 (10)	15.49	1	0.001	12 (17)	7.20	1	0.013
History of PTSD	4 (29)	4 (4)	11.36	1	0.008	0 (0)	21.00	1	0.001

[a] Comparison between breast cancer survivors with PTSD and those without PTSD.
[b] Comparison between breast cancer survivors with PTSD and healthy subjects.

2.3. MRI image acquisition

The details concerning the MRI acquisition and data analysis were described in our previous study (Nakano et al., 2002; Matsuoka et al., 2003). Briefly, MRI scans were performed using a 1.5-T MRI unit (Signa Scanner; GE Medical Systems, Milwaukee, Wisconsin) with three-dimensional spoiled gradient-recalled acquisition of 1.5-mm contiguous sections under the following conditions: field of view = 230 mm, matrix = 256 × 256 pixels, repetition time (TR) = 25 ms, echo time (TE) = 5 ms, and flip angle = 45°.

2.4. Data analyses

The theory and algorithm for VBM using Statistical Parametric Mapping (SPM) two software (Welcome Department of Cognitive Neurology, London, United Kingdom) have been well documented (Ashburner and Friston, 2000). VBM was performed using an optimized method (Good et al., 2001). First, an optimized study-specific template set consisting of a T1 image and a priori gray, white, and cerebrospinal fluid images was created for the VBM analysis. This template set was constructed from brain scans taken from all the study subjects. All the scans were spatially normalized to the customized template, then smoothed with an 8-mm, full-width maximum (FWHM) smoothing kernel, followed by averaging to create a customized template. The images were then segmented into gray matter and white matter, using customized prior probability maps. These segments were then modulated to correct for volume changes occurring during spatial normalization. Finally, the images were smoothed using a 12-mm FWHM Gaussian kernel. Smoothing was performed to convert the tissue classification images into images of local gray matter density. Gray mater density, in this context, means the proportion of the smoothing kernel that was classified as gray matter. The size of this kernel specifies the spatial scale of the gray matter density changes.

For group comparisons, differences in gray matter volume at the time of the baseline investigation were compared between the cancer survivors with PTSD and those without PTSD or the healthy subjects using an analysis of covariance (ANCOVA) with a basic SPM2 model and age, accumulated alcohol consumption, and total gray matter volume as nuisance variables. Accumulated alcohol consumption was entered into the analysis model because alcohol consumption is known to be associated with the brain atrophy (Mukamal, 2004). Significance levels were set at a p-value of 0.05 and were corrected for multiple comparisons using the false discovery rate (FDR) approach (Genovese et al., 2002) in regions without a hypothesis. For regions with a hypothesis (amygdala, hippocampus, ACC, and OFC), significance was assumed at an uncorrected p-value of 0.001 and a k-value of 100 to suppress the possibility of small clusters arising by chance. As an additional analysis, a small volume correction (SVC) was applied to correct for multiple comparisons at the bilateral ACC and OFC by using custom-made template. As to the amygdala and hippocampus, 4-mm FWHM smoothing was performed and then the same procedure as above was followed.

We also performed a correlation analysis between regional brain volume and the IES score controlling for age, accumulated alcohol consumption, and total gray matter volume. As a value indicating the regional brain volume, the β-value of the brain area within the region of interest (ROI) was extracted using the MarsBaR ROI analysis toolbox. The ROI was set within areas that were detected to be significantly smaller in cancer survivors with PTSD than in those without PTSD at the baseline investigation. Significance levels were set at $p < 0.05$ (two-tailed).

Additionally, to examine the influence of cancer-related PTSD on the longitudinal course of the brain volume within the ROI, a repeated measures mixed model analysis of covariance was performed using SPSS software 14.0J (SPSS, Inc., Tokyo). TIME (baseline vs. follow-up), DIAGNOSIS (PTSD vs. non-PTSD), and TIME × DIAGNOSIS were used as effects on the brain volume within the ROI. As covariates, age, accumulated alcohol consumption, total gray matter volume at baseline, and days from baseline to follow-up were included in the analysis. Significance levels were set at $p < 0.05$ (two-tailed).

Moreover, the repeated measures mixed model analysis of covariance was also performed using SPM2 software, following the procedure which was shown in Draganski et al. (2004, 2006).

Student's t-tests or χ^2 tests were used for comparisons of demographic factors to confirm homogeneity between the groups. Significance levels were set at $p < 0.05$ (two-tailed). The correlational analyses, t-tests and χ^2 tests were performed using SPSS software 14.0J.

3. Results

3.1. Comparison of gray matter volume between breast cancer survivors with PTSD and those without PTSD or healthy subjects at the baseline investigation

The area found to have a smaller gray matter volume in breast cancer survivors with PTSD than in those without PTSD is shown in Fig. 1 {Peak coordinate [x, y, z (mm)] = (17, 48, −38), $k = 295$, $t = 3.60$, d.f. = 109, $p < 0.001$}, and the area found to have a smaller gray matter volume in breast cancer survivors with PTSD than in healthy subjects is shown in Fig. 2 {Peak coordinate [x, y, z (mm)] = (14, 51, −27), $k = 735$, $t = 3.78$, d.f. = 79, $p < 0.001$}. Both areas correspond to the right Brodmann area (BA) 11. Significant difference found in comparison between cancer survivors with PTSD and without PTSD did not survive a SVC {Peak coordinate [x, y, z (mm)] = (13, 50, −29), $k = 110$, $t = 3.43$, d.f. = 109, corrected $p = 0.194$}, but significant difference found in comparison between cancer survivors with PTSD and healthy subjects survived a SVC {Peak coordinate [x, y, z (mm)] = (14, 51, −27), $k = 708$, $t = 3.78$, d.f. = 79, corrected $p = 0.039$}. As a reference comparison between breast cancer survivors without PTSD and healthy subjects, no significantly smaller gray matter volumes were found.

3.2. Correlation of right BA11 gray matter volume with PTSD symptomatic responses

Among the cancer survivors with PTSD ($n = 14$), significant negative correlations were observed between the right BA11 gray matter volume and the total IES score and the Intrusion subscale score, as shown in Table 2.

3.3. Longitudinal course of right BA11 gray matter volume in breast cancer survivors with PTSD compared to the course in survivors without PTSD

The effect of the interaction between TIME (baseline vs. follow-up) and DIAGNOSIS (PTSD vs. non-PTSD) on the right BA11 gray matter volume was not significant in the analysis using SPSS software (Table 3), as well as in the analysis using SPM2 software. On the other hand, the right BA11 gray matter volume of the cancer survivors with PTSD was significantly smaller than that of cancer survivors without PTSD at both the baseline and the follow-up investigation.

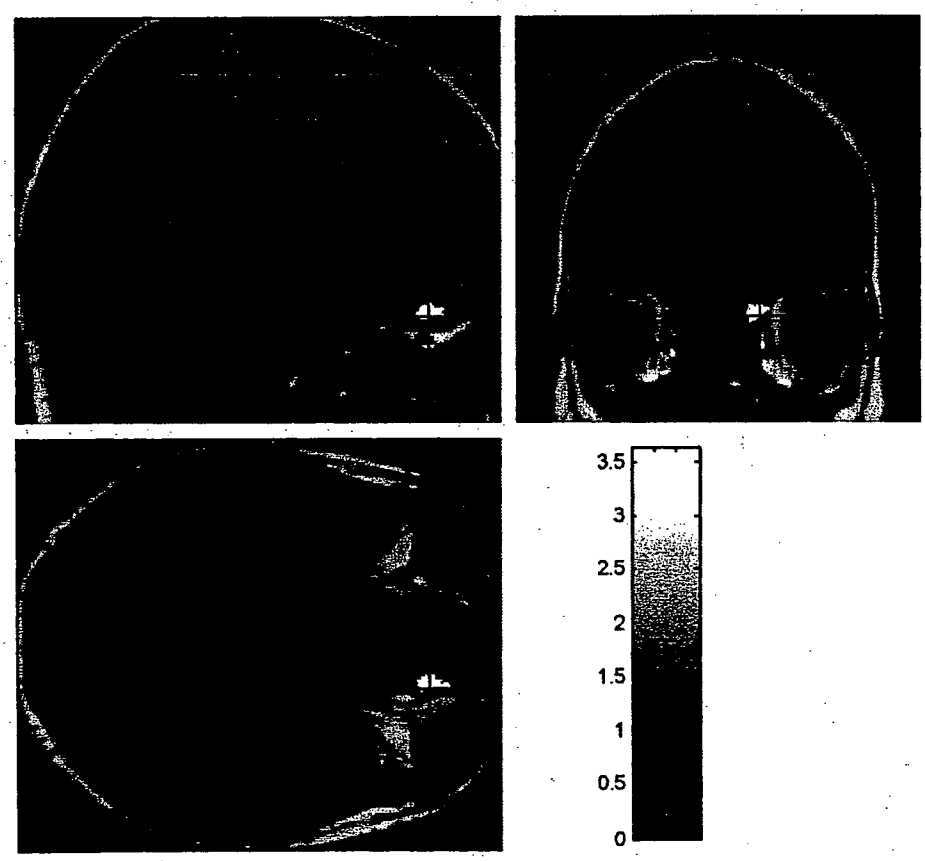

Fig. 1. Smaller right BA11 gray matter volume in breast cancer survivors with PTSD, compared to survivors without PTSD. The color bar indicates the t-value.

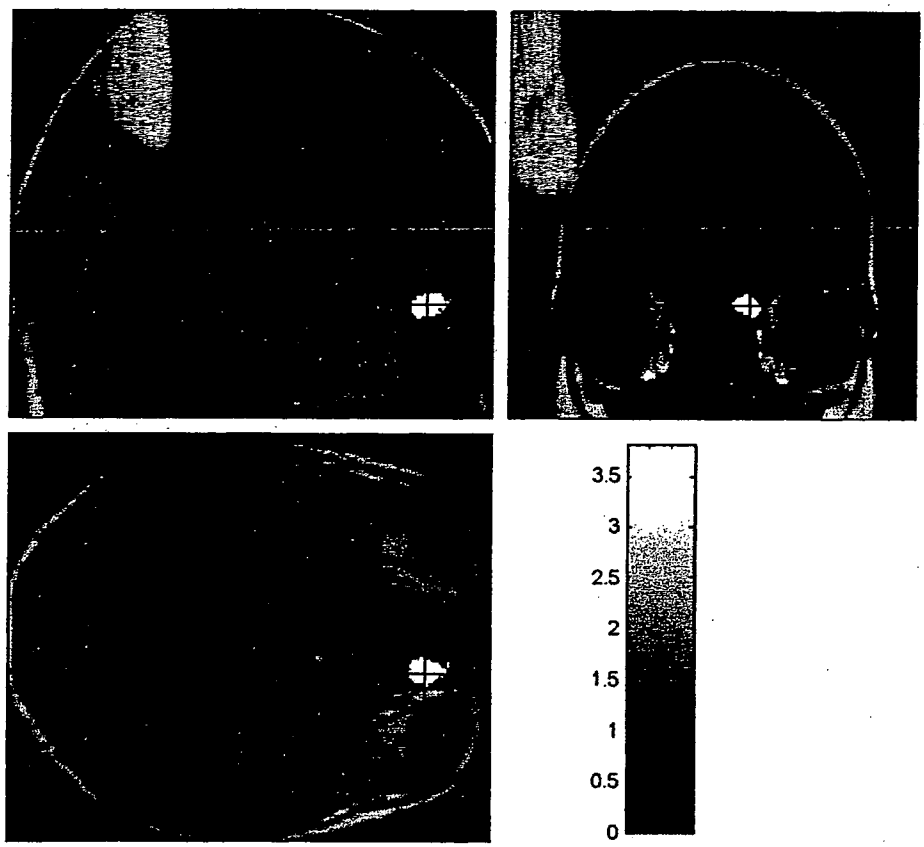

Fig. 2. Smaller right BA11 gray matter volume in breast cancer survivors with PTSD, compared to healthy controls. The color bar indicates the *t*-value.

4. Discussion

The present cross-sectional analysis revealed that the right BA11 gray matter volume of breast cancer survivors with PTSD was significantly smaller than those of breast cancer survivors without PTSD or healthy subjects and exhibited a significantly negative association with PTSD symptomatic responses to the cancer experience, particularly with intrusive responses. BA11 is included in the OFC, which is directly connected to limbic and related structures. Previous functional neuroimaging studies of patients with better understood PTSD have reported the dysfunctional activation of the OFC (Shin et al., 1999; Lanius et al., 2001; Bremner et al., 2005), while no structural neuroimaging study have reported the structural alternation of the OFC. Thus, the smaller OFC gray matter volume found in the present study might indicate a common neurobiological basis for PTSD, rather than a mechanism specific to cancer-related PTSD. However, smaller gray matter volumes in the limbic system or in PFC regions other than BA11, particularly the ACC, were not found in the present study, while previous structural neuroimaging studies have shown such changes. The discrepancies in these findings may be attributed to differences in the demographics or methodologies of the studies. As to the limbic system, including structures like the hippocampus and amygdala, our previous ROI-based volumetric studies found a smaller hippocampal and amygdalar gray matter volume in breast cancer survivors with intrusive recollection but without PTSD (Nakano et al., 2002; Matsuoka et al., 2003). Several possible explanations for these inconsistencies can be made; for example, the detection power of ROI-based volumetry might be higher than that of VBM because ROI-based volumetry

Table 2
Correlation between right BA11 gray matter volume and IES score in breast cancer survivors with PTSD ($n = 14$)

	Right BA11 gray matter volume		
	r	d.f.	*p*
IES total score	−0.201	109	0.034
Intrusion subscale score	−0.249	109	0.008
Avoidance subscale score	−0.088	109	0.361

Controlling for age, accumulated alcohol consumption, and total gray matter volume. Right BA11 gray matter volume is located at {Peak coordinate [*x*, *y*, *z* (mm)] = (17, 48, −38), $k = 295$}.

Table 3
Interaction of TIME and GROUP on right BA11 gray matter volume in breast cancer survivors ($n = 76$)

Effects	*F*	d.f.	*p*
TIME	1.819	1	0.182
GROUP	7.515	1	0.008
TIME × GROUP interaction	0.402	1	0.528

TIME, baseline or follow-up; GROUP, the presence or absence of PTSD diagnosis; PTSD, $n = 9$; non-PTSD, $n = 67$.

performs a statistical analysis within regional brain areas, unlike VBM—which performs a statistical analysis within the global brain area. Because of this, VBM might not detect significant differences in the same brain regions as those detected by ROI-based volumetry. In addition, the breast cancer survivors in the present study had survived for 3–15 months after surgery, while those in our previous studies had survived for 3 years or more. This difference might also be relevant. As to the ACC, three previous VBM studies found smaller gray matter volumes (Yamasue et al., 2003; Corbo et al., 2005; Chen et al., 2006), although one VBM study failed to do so (Jatzko et al., 2006). The difference between the present study and these previous VBM studies might be explained by the confounder of gender; the present study included only female subjects, while previous studies included both female and male subjects. Moreover, the number of controls in our study was relatively large, while those of previous studies were relatively small. These differences might result in inconsistent findings.

The OFC, particularly on the right side, is thought to be related to the integration of affective and non-affective information and in the regulation of motivational and emotional behavior (Happaney et al., 2004). Much research has reported that the OFC is involved in the extinction of learned responses in reinforcement learning, such as fear conditioning. For example, OFC-ablated non-human primates (Butter et al., 1963) as well as human patients with OFC damage (Rolls et al., 1994) have been reported to show resistance to the extinction of fear conditioning. Moreover, a functional magnetic resonance imaging (fMRI) study of healthy subjects has shown that the OFC (BA11) and amygdala were preferentially enhanced during an extinction task (Gottfried and Dolan, 2004). Furthermore, recent structural neuroimaging studies for healthy subjects have revealed that a larger OFC (BA11) gray matter volume was associated with lower skin conductance responses to a fear-conditioned stimulus during an extinction memory task (i.e., greater extinction memory) (Milad et al., 2005; Rauch et al., 2005). On the other hand, many studies have also reported that the OFC is engaged in the recall of subjective feeling states associated with past emotional experiences (Dolan, 2002). For example, in event-related fMRI studies of healthy subjects, OFC (BA11) activity has been shown to increase significantly during the recognition of an emotionally neutral stimulus learned in an emotional context, compared to those learned in a neutral context (Maratos et al., 2001; Smith et al., 2004). Similarly, an fMRI study of healthy subjects showed a significant increase in the activity of the OFC (BA11) during the recollection of emotional autobiographical memory (Piefke et al., 2003). Given these previous findings and the negative association between OFC gray matter volume and intrusive responses that as found in the present study, a smaller OFC gray matter volume might reflect the difficulty of cancer survivors with PTSD in extricating fear-conditioned emotional memories of their cancer experience; as a result, it may be easy for them to retrieve their emotional experiences frequently and repeatedly. In fact, 11–45% of breast cancer survivors have been reported to reexperience symptoms, including intrusive recollections (Matsuoka et al., 2006). Therefore, the OFC might play an important role in the pathophysiology of PTSD, particularly its intrusive symptoms.

An additional longitudinal analysis revealed that the effect of interactions between the diagnosis of cancer-related PTSD and the timing of the MRI examinations on the right BA11 gray matter volume was not significant, while the main effect of the diagnosis was significant. This result might imply that the OFC gray matter volume does not increase or decrease but remains unaltered across time after the development of cancer-related PTSD. Given that no longitudinal alterations in the right BA11 gray matter volume were observed, even though all breast cancer survivors with PTSD had naturally recovered at the time of the follow-up investigation, the smaller size seen among the patients with cancer-related PTSD might have existed before the development of the cancer-related PTSD. However, the smaller size might also have occurred as a result of scarring from the cancer-related PTSD. Future studies are required to examine the brain volume longitudinally in a larger sample both before and after the development of PTSD.

Several weaknesses of the present study should be considered when interpreting these results. First, the severity of the PTSD symptoms was unclear because the Clinician-Administered PTSD Scale (Blake et al., 1995) was not used. Second, our cancer-related PTSD group included breast cancer survivors with a past diagnosis of PTSD in addition to those with a current diagnosis of PTSD. Third, 12% of cancer survivors without PTSD have had partial PTSD symptoms in the past. Forth, our follow-up sample was relatively small in size and may have been biased. Despite these weaknesses, our study also had several strengths. First, our sample was larger than that used in previous studies. Second, none of the subjects in the present study had a history of substance-related disorders and all were antidepressant-naive. Third, we prepared both a traumatized without PTSD group and a healthy subject group to compare with the traumatized with PTSD group, whereas most previous studies prepared only one of these two comparison groups.

In conclusion, the present study revealed the right OFC gray matter volume was significantly smaller in breast cancer survivors with PTSD than in those without PTSD or healthy subjects. These findings provide evidence that OFC, which is involved in the extinction of fear conditioning or the emotional retrieval of autobiographical memory, might play an important role as the neurobiological basis of PTSD, particularly its intrusive symptoms.

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