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HPA axis dysfunction in unmedicated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions

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Abstract

Dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis is one of the most prominent neurobiological findings in major depressive disorder (MDD). The relationship of regional brain metabolism to HPA axis dysfunction in depressed patients, however, is still unclear. In this study, to examine the clinical pharmacotherapeutic effects on HPA axis function and brain metabolism in MDD patients, we performed the combined dexamethasone (DEX)/corticotropin-releasing hormone (CRH) test on 24 antidepressant-free patients with MDD a few days after positron emission tomography (PET) with a radiotracer, [^{18}F]-fluorodeoxyglucose (FDG). Moreover, 10 patients who responded to pharmacotherapy were re-tested. 75% of unmedicated MDD patients exhibited a heightened cortisol response to the DEX/CRH test, and thus were defined as non-suppressors. Non-suppressors showed a marked hypometabolism in the medial prefrontal cortex as compared with suppressors. After successful pharmacotherapy, enhanced cortisol responsiveness normalized. Prior to treatment of the unmedicated MDD, a significant hypometabolism in various frontal regions and a significant hypermetabolism in the right hippocampus and parahippocampal gyrus were observed compared with controls. Metabolic activity in treatment responders showed a normalizing pattern in almost all the areas that had been characterized by metabolic abnormality at baseline except for the medial prefrontal cortex. These results indicate that depressed patients remitted with antidepressant treatment were accompanied by resolution of HPA dysregulation and alteration of regional glucose metabolism in the prefrontal cortical, limbic and paralimbic regions.

Keywords: Hypothalamic-pituitary-adrenal axis; Dexamethasone; Corticotropin-releasing hormone; Positron emission tomography; Major depressive disorder; Antidepressant

1. Introduction

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is the one of the most prominent neurobiological findings in major depressive disorder (MDD).

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Its clinical manifestations include basal hypercortisolemia at baseline (Halbreich et al., 1985), elevated cortisol secretion with the dexamethasone suppression test (DST) (Stokes et al., 1984), and increased Adrenocorticotropic hormone (ACTH) and cortisol release in the combined dexamethasone suppression/corticotropin releasing hormone (CRH) stimulation (DEX/CRH) test (Heuser et al., 1994; Holsboer et al., 1987). Previous DST results on Japanese patients with MDD, as noted in the WHO Collaborative Study (1987), the percentage of non-suppression was 21% (Nagasaki) and 23% (Sapporo), which are low frequencies compared with the Caucasian rate, 50–70%, as reviewed by Schuckit (1988), and thus may suggest ethnic differences. A recent multicenter study in Japan (Kunugi et al., 2006), however, revealed that the DEX/CRH test is a highly sensitive state-dependent marker and can also be used to monitor HPA axis abnormalities in MDD in Japan. Kunugi et al. discovered that pituitary-adrenocortical responses to the DEX/CRH test were significantly enhanced in MDD patients on admission compared with healthy controls, and were significantly reduced after successful antidepressant treatment and electroconvulsive therapy (ECT). Furthermore, Oshima et al. (2001) demonstrated that acute stress is unlikely to affect the outcome of the DEX/CRH test in healthy volunteers, suggesting that the augmented cortisol response to the DEX/CRH test, as seen in MDD, may reflect the intrinsic pathophysiology of disease rather than acute stress effects.

Functional brain-imaging studies also indicated that the regions most commonly found to be abnormal in MDD are the prefrontal cortex (PFC), anterior cingulate gyrus (AC) and temporal lobe. Relatively consistent findings in unmedicated MDD patients are decreased cerebral metabolic rates and blood flow in dorsolateral PFC (Biver et al., 1994; Buchsbaum et al., 1997; Brody et al., 1999; Mayberg et al., 1999, Drevets et al., 2002b) and increased metabolic rates and blood flow in ventral PFC (Drevets and Raichle, 1992; Biver et al., 1994; Brody et al., 1999; Drevets et al., 2002b). Moreover, recent reports on the clinical correlation between antidepressant drug treatment outcome and changes in cerebral metabolic rate demonstrated that treatment responders showed increases in PFC metabolism and decreases in limbic regions' metabolism (Mayberg et al., 2000; Kennedy et al., 2001; Drevets et al., 2002b). Thus, metabolic aberrations in the PFC and the limbic regions can be associated with HPA axis dysfunction in MDD, and alterations in brain metabolism after clinical improvement can also be associated with the resolution of HPA dysfunction. Drevets et al. (2002a) reported positive correlations between plasma cortisol levels and regional glucose metabolism in the left amygdala in mood disorders. In general, however, evidence has been limited thus far.

In animal studies, secretary cells in the paraventricle nucleus of the hypothalamus (PVN) receive neural inputs from many brain regions, including the hippocampus and parahippocampal regions (Sapolsky et al., 1986). Herman et al. (1989) reported that rat hippocampectomy causes a marked increase in the CRH mRNA expression level in PVN, resulting in HPA axis hyperactivity. These results suggest that the hippocampus regulates the HPA axis in an inhibitory manner, supporting the view that dysregulation of the HPA axis in MDD may be partly caused by metabolic dysfunction of the hippocampus and parahippocampal regions. This hypothesis, although based on preclinical studies, needs to be tested using clinical samples.

The purpose of this study was to evaluate the specific brain regions that may be associated with HPA dysfunction in unmedicated patients with MDD. The DEX/CRH test in addition to positron emission tomography (PET) scan with [^{18}F] fluorodeoxyglucose (FDG) as a radiotracer (FDG-PET) were performed over 2 days on MDD patients. We expected to find a correlation between non-suppression on the DEX/CRH test in depressed patients and cerebral glucose metabolic rate in PFC and limbic/paralimbic regions, which are involved in HPA axis function regulation. Additionally, we examined, in a naturalistic and prospective manner, the changes in HPA axis function and cerebral glucose metabolic rate in antidepressant responders in order to explore the specific brain regions that may be associated with the resolution of HPA axis abnormalities.

2. Methods

2.1. Subjects, treatments, and rating scales

All subjects were inpatients or outpatients of the Department of Neuropsychiatry, Gunma University Hospital in Japan. Twenty-four right-handed patients (9 men and 15 women; mean age 52.4±13.4 years), who met the DSM-IV criteria for major depressive episodes in the context of MDD, and were free from antidepressant medications, were recruited for the initial FDG-PET scan and the DEX/CRH test. The psychopathology of each patient was monitored using the 21-item Hamilton Depression Rating Scale ($HDRS_{21}$) and the 14-item Hamilton Anxiety Rating Scale ($HARS_{14}$). The exclusion criteria were comorbid axis I conditions including substance abuse according to DSM-IV criteria, or current

Table 1
Characteristics of 10 depressed subjects who responded to antidepressant treatment

Case no.	Age (year)	Sex	No. of previous depressive episodes	Duration of current depressive episode (months)	Duration of pre- to post-treatment (days)	$HRDS_{21}$ score		Dose of antidepressants (mg/day)	The DEX/CRH results	
						Before treatment	After treatment		Before treatment	After treatment
1a)*	72	F	0	1	100	33	7	FVM (75)	NS	S
2	29	F	0	1	75	20	9	FVM (100)	NS	NS
3	56	M	0	1	153	36	7	FVM, AMT (100, 100)	S	S
4	51	M	0	1.5	52	42	5	FVM (100)	S	S
5	24	M	0	5	106	36	7	FVM (125)	S	S
6b)	56	M	0	5	133	31	5	AMT (20)	NS	NS
7c)	54	F	0	1	168	34	1	AMT, SPD (110, 100)	NS	S
8d)	75	F	1	5	112	21	8	AMT (30)	NS	S
9	58	F	1	2	259	31	3	AMT (100)	NS	S
10	67	F	0	1	147	33	1	MAS (30)	NS	NS
Mean	54.2		0.2	2.5	130.5	32.0	5.3			
SD	16.6		0.4	1.9	57.6	6.8	2.8			

1) *Abbreviations.* $HRDS_{21}$: 21-item Hamilton Depression Rating Scale, FVM: fluvoxamine, AMT: amitriptyline, SPD: sulpiride, MAS: mianserin, NS: non-suppressor, S: suppressor.
2) *: treated with ECT in addition to antidepressant drug treatment.
3) Cases 1 and 2 were recurrent. Case 1 had shown psychotic features in this study.
4) Comorbid axis III conditions: a) gastric cancer, b) breast cancer. All were post-operative and had not received chemotherapy and radiation therapy.

medical conditions that lead to global cognitive impairment or cerebrovascular risk factors. Eight patients had been diagnosed as having comorbid axis III conditions (i.e., carcinoma). However, as all of them were remitted after successful treatment with surgery and had not experienced chemotherapy and radiation

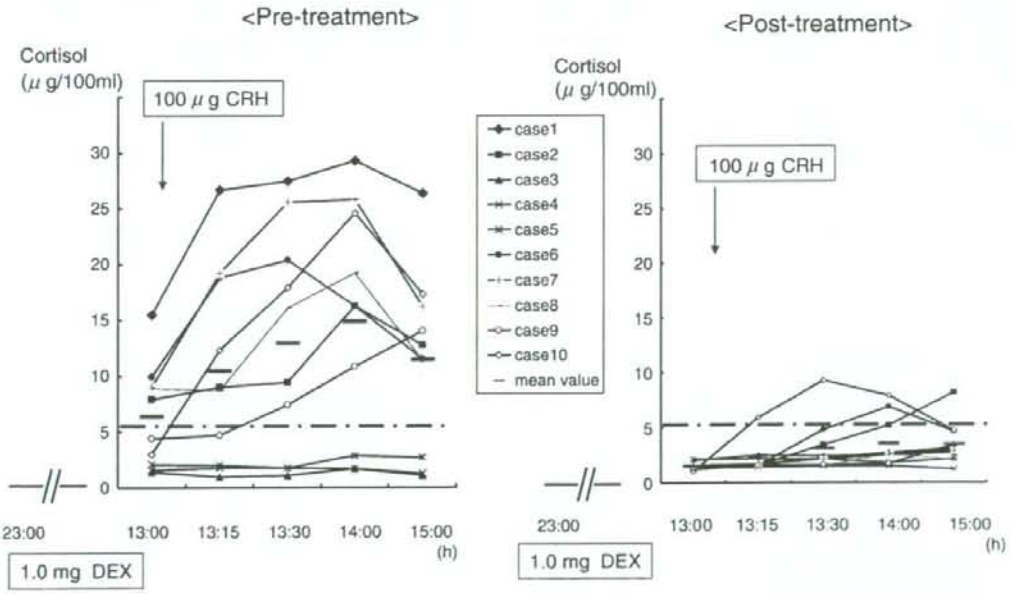

Fig. 1. Individual time course curve of serum cortisol concentration response to DEX/CRH test, where $n = 10$. (a) Time course changes in serum cortisol level after combined DEX/CRH administration before treatment. (b) Time course changes in serum cortisol level after combined DEX/CRH administration after treatment.

therapy, their axis III conditions were not considered to affect their HPA axis function and brain metabolism when they participated in this study. None of the patients took antidepressant medication during the initial FDG-PET scan and the DEX/CRH test. Twenty-three right-handed healthy volunteers (eight men and 15 women; 27–83 years, mean age 54.8±12.6 years), who had no current or past psychiatric history and met the exclusion criteria for the patient group, were recruited as control subjects for the FDG-PET scan.

All the participants, patients and healthy volunteers, gave their written informed consent after receiving a full explanation of the study's purpose and procedure. Consent for this study was obtained using a form approved by the Institutional Review Board of Gunma University School of Medicine.

2.2. Longitudinal observation during treatment

Among 24 MDD patients, 10 patients (4 men and 6 women; mean age 54.2±16.6 years) were defined as treatment responders because their second $HDRS_{21}$ scores were below 10, and reduced at least 50% since the initial FDG-PET scan and the DEX/CRH test. We excluded non-responders ($N=14$) from the analysis because they refused a second PET and DEX/CRH test.

Table 1 summarizes the demographic and clinical characteristics of the subjects. The mean $HDRS_{21}$ scores were 32.0±6.8 points before antidepressant treatment and 5.3±2.8 in remission (U-test, $P=0.0001$). Only one (female) responder received ECT throughout pharmacotherapy. All the responders received a second FDG-PET scan and DEX/CRH test within a week after remission. Dates for PET scanning and DEX/CRH testing were separated by more than 2 days to avoid interference of one test with the other.

2.3. DEX/CRH test

We modified the original method of Holsboer et al. (1995) as follows: 1.0 mg DEX (Banyu Pharmaceutical Corporation, Tokyo, Japan) was administered orally at 2300 h, and around 1230 h the following day, each patient lay in a supine position and a heparinized catheter was inserted into a cubital vein. At 1300 h, the first blood sample was drawn through the intravenous catheter and immediately 100 μg of human CRH (Mitsubishi Pharma Corporation, Osaka, Japan) was administered intravenously. Blood samples were drawn again through the intravenous catheter at 1315 h, 1330 h, 1400 h, and 1500 h. Throughout the test, the patients were encouraged to rest in a quiet room.

Blood samples were immediately centrifuged and stored at −20 °C. Plasma ACTH concentration was measured by radioimmunoassay at the SRL Corporation (Tokyo, Japan), and the plasma cortisol concentration was measured using a radioimmunoassay kit (DiaSorin, Inc., Stillwater, MN). For ACTH assay, the intra-assay coefficients of variation were 4.57 and 2.25% at mean concentrations of 45.9 and 443.4 pg/ml, respectively. The inter-assay coefficients of variation for ACTH were 4.57 and 2.25% at mean concentrations of 45.9 and 443.4 pg/ml, respectively. For cortisol assay, the intra-assay coefficients of variation were 5.0 and 3.5% at mean concentrations of 10.0 and 28.5 μg/100 ml, respectively. The inter-assay coefficients of variation were 8.7 and 4.2 at mean concentrations of 9.9 and 30.6 μg/100 ml, respectively. The detection range of this kit was 1.0–60 μg/100 ml.

The results were evaluated in accordance with the method of Holsboer et al. (1995). "BASAL" concentration was defined as the serum cortisol and ACTH concentration collected at 1300 h, "PEAK" concentration was defined as the maximum serum hormonal concentration after CRH injection (between 1315 and 1500 h), and "DELTA" concentration was defined as the difference between PEAK and BASAL concentrations.

Table 2
Statistical analysis of the DEX/CRH results in 10 treatment responders: comparisons before and after treatment

	Before treatment	After treatment	P
Wilcoxon's signed rank test			
BASAL cortisol (μg/100 ml) mean (S.D.)	6.4 (4.6)	1.5 (0.3)	0.011
PEAK cortisol (μg/100 ml) mean (S.D.)	15.3 (10.4)	4.3 (2.8)	0.009
DELTA cortisol (μg/100 ml) mean (S.D.)	8.9 (7.3)	2.8 (3.0)	0.005
AUC cortisol (μg/100 ml min) mean (S.D.)	743.0 (658.2)	199.5 (233.8)	0.009
BASAL ACTH (pg/ml) mean (S.D.)	11.1 (11.0)	4.3 (3.4)	0.148
PEAK ACTH (pg/ml) mean (S.D.)	50.8 (47.6)	13.7 (7.3)	0.020
DELTA ACTH (pg/ml) mean (S.D.)	39.7 (38.3)	9.3 (5.9)	0.020
AUC ACTH (pg/ml min) mean (S.D.)	2897.5 (2912.9)	708.3 (422.6)	0.012
Two-tailed Fisher's exact test			
Rate of DST non-suppressors % (n)	50.0 (5/10)	0.0 (0/10)	0.016
Rate of DEX/CRH non-suppressors % (n)	70.0 (7/10)	30.0 (3/10)	0.179

The area under the time course curve (AUC) was calculated by trapezoidal integration. BASAL values reflect the suppressive effect of DEX administered the day before, whereas PEAK, DELTA and AUC values reflect the additional effects of the CRH injection. Furthermore, we evaluated the serum cortisol concentration on the basis of the standard cut-off value of DST (5 μg/100 ml) (Carroll et al., 1981). Patients were expediently categorized as "DST non-suppressors" when BASAL values exceeded 5 μg/100 ml and "DEX/CRH non-suppressors" when PEAK values exceeded 5 μg/100 ml. Namely, "DST suppressors" and "DEX/CRH suppressors" were categorized when BASAL values and PEAK values were under 5 μg/100 ml.

Differences between the DEX/CRH test result before and after antidepressant medication were assessed using Wilcoxon's signed rank test, or Fisher's exact test (two-tailed) in the case of dichotomous predictors.

2.4. ^{18}F-FDG PET acquisition and analysis

PET images were obtained using a whole-body PET scanner HEADTOME-V (Shimadzu Corp., Kyoto, Japan) with 64 slices at an interslice distance of 3.17 mm and reconstructed at an in-plane resolution of 3.8 mm. The subjects fasted for at least 8 h before PET. For PET studies, 3–4 MBq/kg of FDG was injected in an intravenous bolus at 1100 h. After the injection, each subject remained in a resting state with their ears and eyes uncovered for a 50-min uptake period. PET was performed for 8 min by the simultaneous transmission–emission method using a rotating external source (370 MBq ^{68}Ge/^{68}Ga at installation). Subsequently, attenuation-corrected transaxial images were reconstructed by ordered subset expectation maximization (OS-EM) algorithm.

For the analysis of PET images, statistical parametric mapping was used (SPM 99, www.fil.ion.ucl.ac.uk/spm).

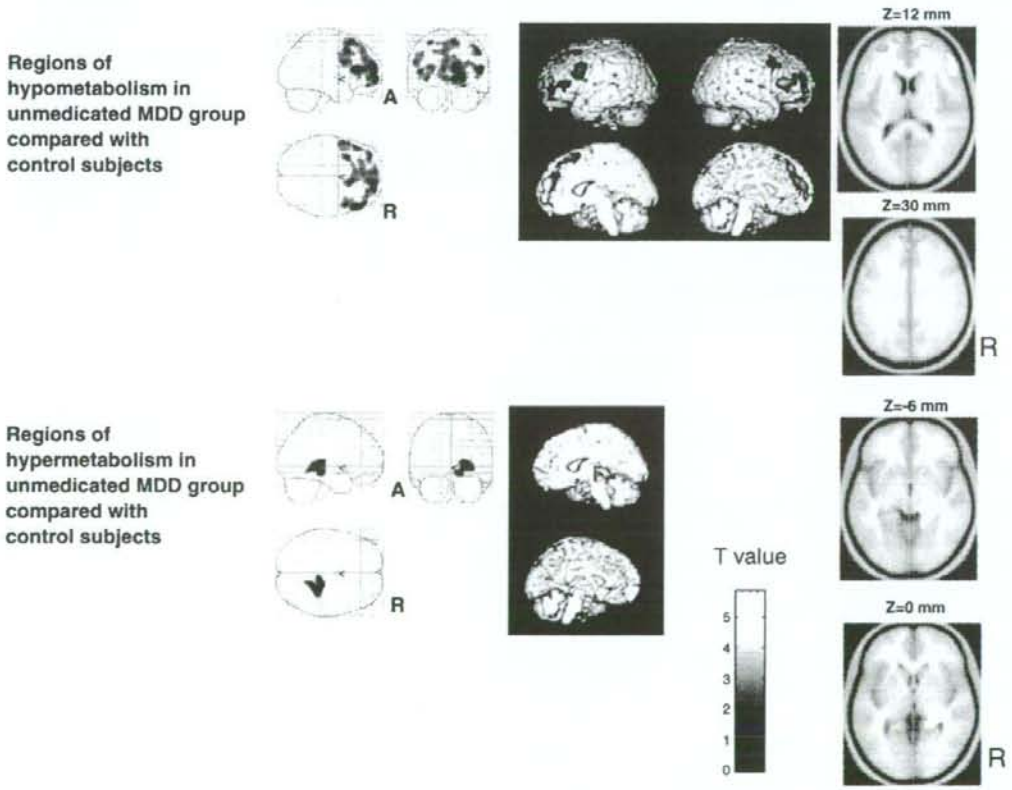

Fig. 2. Visualization of SPM comparison between 24 unmedicated MDD patients and 23 control subjects ($P<0.001$, uncorrected for multiple comparisons). 'Z' indicates Talairach coordinate. 'A' and 'R' indicate anterior and right side, respectively.

For spatial preprocessing of the data, individual PET images were adjusted in accordance with the anterior commissure. Images were spatially normalized to a standard space using the Montreal Neurological Institute (MNI) template. The normalized images were smoothed with an isotropic Gaussian kernel of 10 mm FWHM. Prior to voxel-based statistical analysis, the global cerebral metabolic rate for glucose was normalized to a fixed mean value (50 μmol/100 ml/min) by proportional scaling to remove the confounding effect of global activity. A two-sample *t*-test was performed between 24 unmedicated MDD patients and the control group, between the 10 responders before treatment (first PET) and the control group, between the 10 responders after treatment (second PET) and the control group, and between DEX/CRH non-suppressors and suppressors. A paired *t*-test was carried out within the 10 responders (first PET vs. second PET). Activities of brain regions that were identified as having 100 or more contiguous voxels were defined as significant at a threshold of $P<0.001$ (uncorrected for multiple comparisons) for an unpaired *t*-test between the patient and the control groups and for a paired *t*-test within patient group (first PET vs. second PET). Since the resulting *t*-values are known to closely approximate the standard Gaussian distribution (Worsley et al., 1992), the values were described as *Z*-scores. For anatomical identification, the coordinates derived from the MNI template were transformed using the appropriate algorithm (cf. www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml) to comply with the original grid of Talairach and Tournoux.

3. Results

3.1. DEX/CRH test

The mean $HDRS_{21}$ score of all the patients was 26.9±7.5 points and the mean $HARS_{14}$ score was 21.4±6.2 points. As shown in Fig. 1, 75% ($n=18$, 4 males and 14 females) of the 24 patients who underwent the DEX/CRH test were classified as DEX/CRH non-suppressors because PEAK values exceeded 5 μg/100 ml and 25% ($n=6$, 5 males and 1 females) as DST non-suppressors because BASAL values exceeded 5 μg/100 ml. The mean age, the mean $HDRS_{21}$ score and the mean $HARS_{14}$ score were 55.1±12.4, 26.7±7.2 and 20.7±5.9, respectively, for DEX/CRH non-suppressors, and 44.3±13.9, 27.5±9.7 and 23.7±7.2, respectively, for DEX/CRH suppressors. There were no significant differences in these values between DEX/CRH non-suppressors and suppressors. Based on the results of the AUC (area under the concentration time curve minus linear background, determined by the trapezoidal rule) value of serum ACTH (AUC_{ACTH}) level during the DEX/CRH test, the mean AUC_{ACTH} values of non-suppressors and suppressors were 54.45 pg/ml min and 8.96 pg/ml min, respectively. The mean AUC_{ACTH} of DEX/CRH non-suppressors differed significantly from that of DEX/CRH suppressors ($P<0.005$).

The results of the DEX/CRH test of each patient who responded to pharmacotherapy are shown in Fig. 1, and the statistical analysis of the DEX/CRH test results are shown in Table 2. Before treatment, 50% of the patients (5 of 10) were DST non-suppressors and 70% of the patients (7 of 10) were DEX/CRH non-suppressors. After successful treatment, the proportion of DST non-suppressors and DEX/CRH non-suppressors were 0% (0 of 10) and 30% (3 of 10), respectively. There was no significant difference in the proportion of DEX/CRH non-suppressors before and after treatment (Fisher's exact test with a two-tailed significant level, $P=0.179$), while the proportion of DST non-suppressors significantly decreased after treatment (Fisher's exact test with a two-tailed significant level, $P=0.016$). However, the

Table 3-1
Comparison of glucose metabolism between 10 responders to treatment with antidepressants and 23 healthy volunteers before treatment

Talairach coordinate[a]						
Brain region	Brodmann's area	Side	*x*	*y*	*z*	Z-score
Regions of hypometabolism						
Inferior	9	L	−55	7	24	4.07
frontal gyrus	47	R	48	33	−3	3.91
	46	R	53	26	13	3.70
	47	L	−46	31	−3	3.41
Middle	9	L	−34	31	30	3.38
frontal gyrus	10	L	−40	46	−4	3.32
Medial	10	L	−6	57	14	3.71
frontal gyrus	9	L	−4	46	23	3.53
Superior	8	L	−22	39	39	4.01
frontal gyrus	6	R	10	22	56	3.52
Precentral gyrus	6	L	−57	−1	9	3.40
Middle temporal gyrus	37	R	44	−66	7	3.88
Regions of hypermetabolism						
Thalamus		R	20	−25	6	3.66
Hippocampus		R	30	−31	0	3.46
Parahippocampal gyrus		R	24	−18	−13	3.42

$P<0.001$, uncorrected for multiple comparisons.
[a]Coordinates, mm relative to anterior commissure; *x*, right (+)/left (−); *y*, ant (+)/post (−); *z*, sup (+)/inf (−).

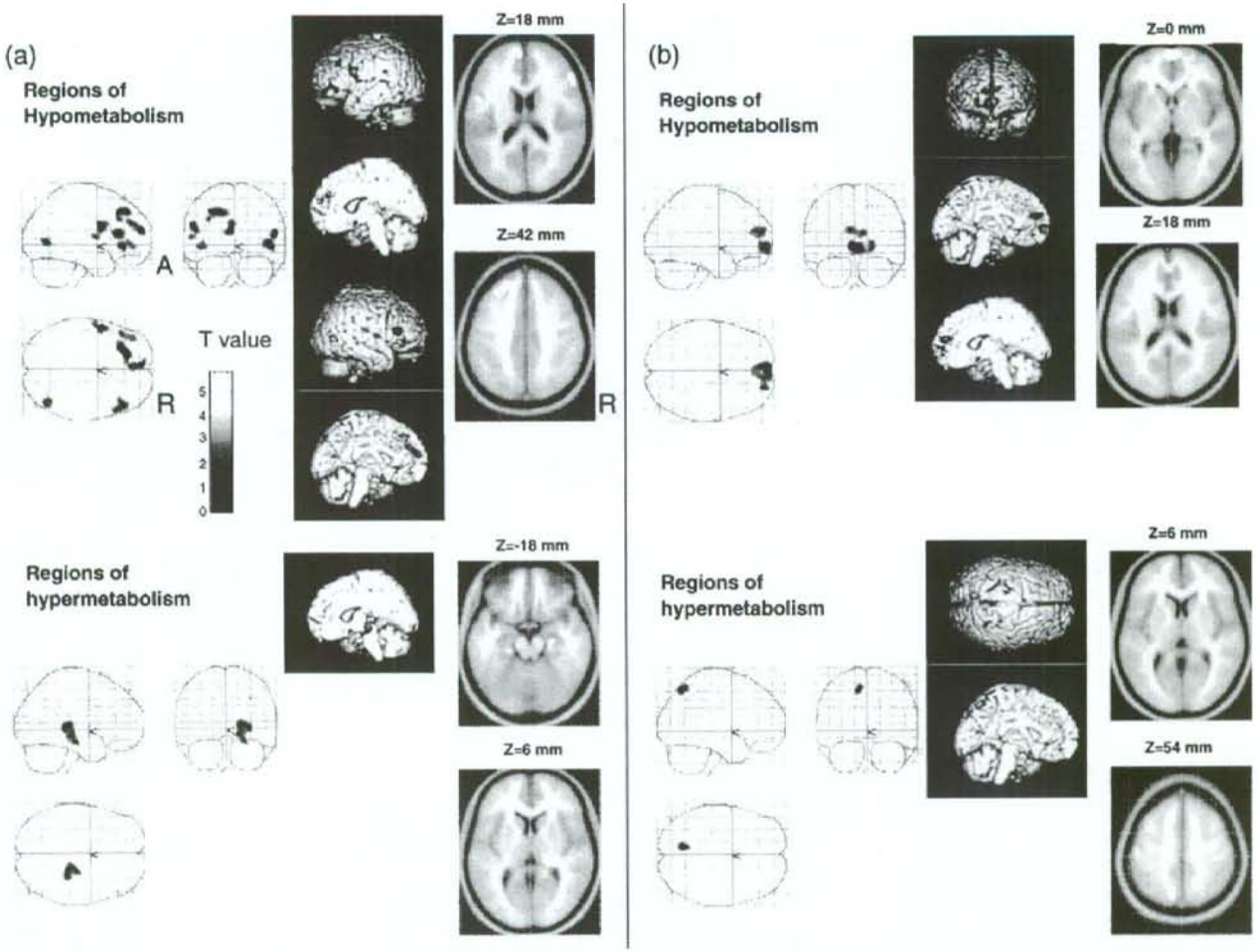

Fig. 3. Visualization of SPM comparison between 10 responders to treatment and 23 control subjects. (a) Regions of significant hypometabolism and hypermetabolism in depressed patients compared with control subjects and (b) in remitted patients compared with control subjects ($P<0.001$, uncorrected for multiple comparisons). 'Z' indicates Talairach coordinate. 'A' and 'R' indicate anterior and right side, respectively.

Table 3-2
Comparison of glucose metabolism between 10 antidepressant responders and control subjects after recovery

Talairach coordinate[a]						
Brain region	Brodmann's area	Side	x	y	z	Z-score
Regions of hypometabolism						
Superior frontal gyrus	10	R	24	56	−3	3.52
Medial frontal gyrus	10	L	−2	62	−3	4.25
	9	L	−6	55	16	3.61
	10	R	12	57	14	3.51
Regions of hypermetabolism						
Angular gyrus	39	R	48	−76	35	4.40
Precuneus	7	L	−10	−59	55	3.87

$P<0.001$, uncorrected for multiple comparisons.
[a]Coordinates, mm relative to anterior commissure; x, right (+)/left (−); y, ant (+)/post (−); z, sup (+)/inf (−).

mean BASAL value of serum cortisol level and the mean PEAK, DELTA and AUC values of serum cortisol and ACTH levels significantly decreased after treatment (Wilcoxon's test: $P<0.05$).

3.2. FDG-PET

3.2.1. Comparisons between non-suppressors and suppressors on the DEX/CRH test

DEX/CRH non-suppressors presented a significant decrease in cerebral metabolic rate of glucose (rCMRGlu) in the right medial prefrontal cortex (Brodmann's area 10, Talairach coordinate: $x=12$, $y=66$, $z=4$, Z-score 3.75) when compared with DEX/CRH suppressors ($P<0.001$, uncorrected).

3.2.2. Comparisons between unmedicated depressed patients and control subjects

As shown in Fig. 2, 24 unmedicated depressed patients presented a significant decrease in rCMRGlu in the bilateral dorsolateral prefrontal cortices, namely, bilateral inferior frontal gyrus (Brodmann's area 9, Talairach coordinate: $x=-55$, $y=7$, $z=24$, Z-score 3.98; Brodmann's area 46, $x=51$, $y=30$, $z=11$, Z-score 4.99), bilateral superior frontal gyrus (Brodmann's area 10, $x=12$, $y=57$, $z=16$, Z-score 4.98 and $x=-32$, $y=51$, $z=14$, Z-score 3.72) and bilateral middle frontal gyrus (Brodmann's area 8, $x=48$, $y=14$, $z=42$, Z-score 4.13; Brodmann's area 9, $x=-46$, $y=9$, $z=35$, Z-score 3.48; Brodmann's area 10, $x=-38$, $y=48$ $z=-4$, Z-score 3.73), and the right inferior parietal lobule (Brodmann's area 40, $x=40$, $y=-60$, $z=47$, Z-score 3.79), and a significant increase in the right hippocampus ($x=28$, $y=-33$, $z=2$, Z-score 3.93), parahippocampal gyrus ($x=14$, $y=-30$, $z=-7$, Z-score 3.83) and thalamus ($x=22$, $y=-27$, $z=6$, Z-score 3.84) when compared with 23 control subjects ($P<0.001$, uncorrected).

3.2.3. Comparisons between control subjects and antidepressant responders before treatment

The results of SPM comparisons between control subjects and 10 antidepressant responders before treatment are shown in Table 3-1 and Fig. 3(a). The patients presented a significant decrease in rCMRGlu in the left dorsolateral prefrontal cortices (left middle frontal gyrus, Brodmann's area 9, 10; left inferior frontal gyrus, Brodmann's area 9), bilateral orbitofrontal cortices (Brodmann's area 46, 47), left medial prefrontal cortices (Brodmann's area 9, 10) and right middle temporal gyrus (Brodmann's area 37), and a significant increase in rCMRGlu in right thalamus, hippocampus and parahippocampal gyrus ($P<0.001$, uncorrected).

3.2.4. Comparisons between control subjects and antidepressant responders after treatment

The results of SPM comparisons between control subjects and 10 antidepressant responders after treatment are shown in Table 3-2 and Fig. 3(b). The patients presented a significant decrease in rCMRGlu in bilateral medial prefrontal cortices (Brodmann's area 9, 10) and right dorsolateral prefrontal cortex (Brodmann's area 10), and a significant increase in rCMRGlu in right angular gyrus (Brodmann's area 39) and left precuneus (Brodmann's area 7).

3.2.5. Comparisons between antidepressant responders before and after treatment

As shown in Fig. 4, the antidepressant responders showed a significant decrease in rCMRGlu in the right precuneus (Brodmann's area 7, $x=8$, $y=-59$, $z=56$, Z-score 3.99) before treatment as compared with post-treatment values. The same group exhibited a significant increase in rCMRGlu in the right putamen ($x=20$, $y=3$, $z=15$, Z-score 4.52) and right lentiform nucleus ($x=18$, $y=-10$, $z=-6$, Z-score 3.99) as compared with post-treatment values ($P<0.001$, uncorrected).

4. Discussion

There is cumulative supportive evidence of the involvement of hypothalamic-pituitary-adrenal (HPA) axis abnormalities in major depressive disorder (MDD). The present study confirmed the low frequency of non-suppression estimated by the DST in Japanese patients compared with the Caucasian rate in the WHO collaborative study (1987). Also, the frequency of non-

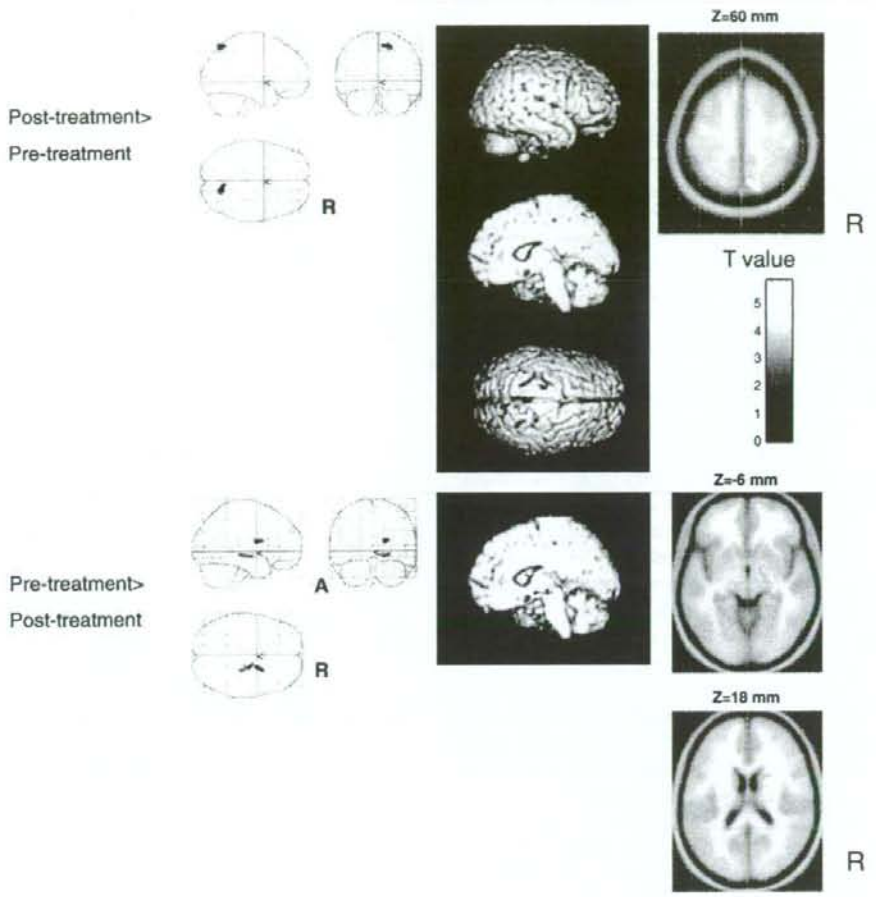

Fig. 4. Visualization of SPM comparison of 10 responders between before and after treatment ($P<0.001$, uncorrected for multiple comparisons). 'Z' indicates Talairach coordinate. 'A' and 'R' indicate anterior and right side, respectively. 'Z' indicates Talairach coordinate.

suppression estimated by the DEX/CRH test in the same Japanese patients with MDD is as high as the DST non-suppression rate in Caucasian patients. Thus, in accordance with previous findings (Kunugi et al., 2006), the DEX/CRH test is a suitable method to investigate the dysregulation of the HPA axis in Japanese patients with MDD.

Additionally, antidepressant medication-free patients with MDD showed a significant decrease in rCMRGlu in the bilateral dorsolateral prefrontal cortices and right inferior parietal lobule, and a significant increase in rCMRGlu in the right hippocampus, parahippocampal gyrus and thalamus.

Consistent with our findings, numerous neuroimaging studies have reported "hypofrontality" in the untreated depressive state (Biver et al., 1994; Buchsbaum et al., 1997; Brody et al., 1999; Mayberg et al., 1999; Drevets et al., 2002b) and, while less common, hyperactivity in limbic/paralimbic regions (Videbech et al., 2001). However, previous findings concerning altered neural activity in parahippocampal gyrus in depressed patients have been inconsistent (Perico et al., 2005; Surguladze et al., 2005).

It should be noted that the subset of our unmedicated MDD patients, though determined by the DEX/CRH test as suppressors (i.e. normal suppression status), nevertheless exhibited metabolic dysfunction in the hippocampus and parahippocampal region. Before treatment, DEX/CRH suppressors showed hormonal responses similar to those of the healthy subjects but presented

with an increase in CMRGlu in the right hippocampus and parahippocampal gyrus. The suppressive condition of these patients after remission again equaled that of the healthy controls, indicating that "normalization" had been achieved from a neuroendocrinological viewpoint. The CMRGlu in these regions of DEX/CRH suppressors after clinical recovery was also similar to that of the control group. Therefore, the enhanced metabolism in these regions in untreated DEX/CRH suppressors may reflect over compensatory regional brain activity which suppressed an otherwise augmented neuroendocrine responsiveness to the normal level and may be detrimental to the brain if persistent.

In this study, a significant decrease in rCMRGlu in right medial prefrontal cortices discriminated DEX/CRH non-suppressors from suppressors in unmedicated MDD. Moreover, hypometabolism in the medial prefrontal cortex persisted after clinical recovery. In animal studies, the medial prefrontal cortex modulates HPA axis activity and is involved in glucocorticoid-mediated negative feedback mechanisms (Diorio et al., 1993), where a lesion in this area increases neuroendocrine, autonomic and behavioral responses to stress (Gerrits et al., 2003; Figueiredo et al., 2003a,b). However, some studies (Hurley et al., 1991; Sesack et al., 1989) indicate that the role of the medial prefrontal cortex in HPA axis regulation is complex because the prelimbic/anterior cingulate components of the medial prefrontal cortex project to areas implicated in stress inhibition, whereas the infralimbic components project to areas implicated in stress excitation. In clinical studies, an association between a functional deficit in the medial prefrontal cortex and HPA axis dysregulation is not well established. To date, there is only one clinical report by Tachiteya et al. (2003) who found that patients with cortical brain damage presented higher scores of sadness that frontal cortical damage was associated with higher cortisol levels at the morning peak. Thus, further investigation is necessary to confirm the involvement the medial prefrontal cortex with HPA axis dysfunction in MDD.

It is noteworthy that a significant increase in rCMRGlu in the limbic/paralimbic areas in unmedicated patients with MDD normalized after recovery, as did the serum cortisol concentrations in most cases. Namely, the significant increase in rCMRGlu before antidepressant treatment that was observed in the hippocampus and parahippocampal gyrus before treatment was not observed after recovery. These findings are consistent with previous reports describing a change in rCMRGlu in the hippocampus and in the parahippocampal gyrus before and after antidepressant treatment. Kennedy et al. (2001) reported that paroxetine treatment normalized the areas of increased metabolic activity in the right hippocampus and in the parahippocampal regions in 13 depressed patients. Mayberg et al. (2000) reported that clinical improvement after fluoxetine treatment was associated with subcortical and limbic decreases in rCMRGlu (subgenual cingulate, hippocampus and insula) as well as increases in brainstem and cortical rCMRGlu (prefrontal, parietal, anterior and posterior cinglate cortex) relative to pre-treatment values. These and other results (Brody et al., 1999; Drevets et al., 1992; Smith et al., 1999) suggest that recovery from depression may be, to some degree, dependant on the normalization of rCMRGlu in the limbic/paralimbic regions.

Drevets et al. (2002a) reported correlations between plasma cortisol levels and regional glucose metabolism. They sampled plasma cortisol concentrations in triplicate 10 min prior to FDG infusion at the same time each morning. Left amygdala metabolism correlated positively with plasma cortisol level in the MDD and bipolar depression groups. Although findings of abnormality in the left amygdala were not observed in the present study, longitudinal experiments with a larger number of subjects are needed to clarify the association between these subcortical areas (amygdala, parahippocampal gyrus and hippocampus) and MDD.

Several animal studies explain the effects of antidepressant treatment on HPA axis function. It is well known that antidepressant agents exert their clinical action via the facilitation of corticosteroid receptor gene expression in the brain including the hippocampus (Brady et al., 1991; Seckl and Fink, 1992) and via the activation of corticosteroid receptor function (Reul et al., 1993, 1994; Montkowski et al., 1995) with subsequent normalization of the HPA feedback system. It should therefore be considered that improvement in function of the corticosteroid receptor in the hippocampus correlates with clinical recovery. Clinical and preclinical evidence suggests that the parahippocampal gyrus and the hippocampus may be responsible for the dysregulation in the HPA axis, a finding that may correlate with the pathophysiology of MDD.

Unfortunately, several limitations exist in the present study. Specifically, there were a small number of subjects and a lack of examination of cerebral structural changes through MRI (i.e., a volume reduction in the limbic/paralimbic regions in MDD patients). Moreover, we did not exclude one subject (case 1 in Table 1) who responded to ECT in addition to antidepressant treatment because of the small sample size. To date, preclinical studies indicate the difference in the neuropharmacological effects between ECT and antidepressant drugs on serotonin (5-

HT)-mediated neurotransmission. Thus, repeated electroconvulsive shocks (ECS) increase central 5-HT_2 receptors in rodents as opposed to the down-regulation of the receptor by chronic antidepressant administration. However, Strome et al. (2005) demonstrated repeated ECS significantly decreased cortical 5-HT_2 receptor binding in nonhuman primates, suggesting that there is a common neuropharmacological mechanism in ECT and antidepressants since successful treatment with various antidepressants in humans consistently decreased cortical 5-HT_2 receptor binding back to control levels (Attar-Levy et al., 1999; Mischoulon et al., 2002; Yatham et al., 1999). Further examination is necessary; the relation between the two treatments has not yet been definitively established. Another limitation was that we compared a single PET scan of the healthy subjects to the first and second PET of 10 treatment responders, as it was difficult to obtain consent from healthy subjects to carry out a second PET scan. Therefore, future studies taking intrasubject PET variability into account, are necessary.

In summary, we found that unmedicated MDD patients who exhibited a higher cortisol response in the DEX/CRH test and were deemed non-suppressors showed a marked hypometabolism in the medial prefrontal cortex as compared with suppressors. After remission due to successful pharmacotherapy, HPA axis dysfunction was normalized and the significant baseline hypometabolism in various frontal regions, as well as the significant hypermetabolism in the right hippocampus and parahippocampal gyrus, also normalized in an almost state-dependent manner. The hypometabolic state in the medial prefrontal cortex observed when MDD patients were depressed still remained after clinical recovery, suggesting that this area might be responsible for the development of MDD. Given the limitations of the present study, future longitudinal studies are needed.

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Brain metabolic changes associated with predispotion to onset of major depressive disorder and adjustment disorder in cancer patients –A preliminary PET study

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Abstract

Objectives: To explore neurobiological risk factors for major depressive disorder (MDD) and adjustment disorder in cancer patients by examining regional brain metabolism before psychiatric manifestation using positron emission tomography and by prospectively observing depressive and anxiety symptoms.
Method: Cancer patients who showed no psychiatric symptoms when they underwent ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) were followed up for one year using the Hospital Anxiety and Depression Scale (HADS). Fourteen patients who showed high HADS scores and 14 patients who showed low HADS scores were assessed by a psychiatrist 2 years after the PET scan and grouped into the deterioration group ($n = 10$) and the no-change group ($n = 9$). ^{18}F-FDG PET images were analyzed to examine the difference in local brain glucose metabolism between the two groups.
Results: The deterioration group showed a decreased glucose metabolism in the right medial frontal gyrus (BA6) and an increased glucose metabolism in the right posterior cingulate (BA29), right anterior cingulate (BA25), left subcallosal gyrus (BA25), and left caudate compared with the no-change group.
Conclusion: Cancer patients who later developed MDD or adjustment disorder showed regional brain metabolic changes. These regions may be associated with vulnerability to the onset of MDD or adjustment disorder in cancer patients.

Keywords: Cancer; Depression; Adjustment disorder; Anxiety; Vulnerability; Positron emission tomography

1. Introduction

Cancer patients often suffer from psychiatric comorbidities, thereby significantly decreasing their quality of life. Derogatis et al. (1983) reported that 47% of cancer patients have some psychiatric disorders. Among them, 68% had adjustment disorder, approximately 13% depression, and 8% delirium. In a different study, 20–45% of cancer patients have been shown to suffer from depression (Katon and Sullivan, 1990). In a survey with terminally ill cancer patients in Japan (Akechi et al., 2004), 16.3% and 6.7% of them were diagnosed as having adjustment disorder and major depression, respectively. The incidence rate of depression in cancer patients seemingly depends on the tumor-affected area. Higher incidence rates are observed in pancreatic cancer (50%) and pharyngeal cancer (22–40%), and lower incidence rates in gastric cancer (11%) and leukemia (1.5%) (McDaniel et al., 1995).

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Considering the established efficacy of antidepressants in cancer patients with depression (Massie and Holland, 1990) as well as of psychological interventions for improving the emotional state and quality of life of cancer patients (Fawzy et al., 1993; Goodwin et al., 2001), it is essential to assess the psychiatric state of these patients and intervene, if necessary, at earlier stages. However, only 0.5–3% of cancer patients are referred to psychiatrists (Uchitomi et al., 1993), and many cancer patients with adjustment disorder or depression are presumably overlooked. The prediction, early detection and intervention of depressive and anxiety symptoms would therefore improve the quality of treatment of cancer patients.

The mechanism underlying the development of psychiatric symptoms in cancer patients has not been fully elucidated. Some possible psychosocial factors have been proposed, such as psychological burden and coping with it, and burden from invasive treatments such as chemotherapy (Petty and Noyes, 1981). Putative risk factors for depression in this population also include social isolation, recent losses, a tendency toward pessimism, the presence of pain, socioeconomic pressures, the diagnosis of alcoholism or substance abuse, a history of mood disorders or suicide attempts (McDaniel et al., 1995). Factors like younger age, longer education, lower performance status, severer fatigue, being a burden to others, and loss of independence and dignity are also associated with adjustment disorders and/or major depression in terminally ill cancer patients (Akechi et al., 2004).

By contrast, relatively few studies have been conducted for biological factors potentially predisposing the same population to psychiatric conditions. Although some biological abnormalities such as an altered immune system (e.g., natural killer cell activity) (Levy et al., 1985, 1987) and an increased hypothalamus–pituitary–adrenal (HPA) axis activity (Evans et al., 1986) have been suggested as factors associated with mental distress, recent advances in neuroimaging techniques have led to some interesting data concerning alterations in brain structures and functions in cancer patients with psychiatric symptoms. In a structural MRI study, Nakano et al. (2002) reported that having distressing cancer-related recollections is associated with a smaller left hippocampal volume in survivors of breast cancer, but first major depressive episodes after cancer diagnosis in female cancer survivors do not appear to be associated with hippocampal volume (Inagaki et al., 2004). Yoshikawa et al. (2006) also reported that a smaller amygdala volume is associated with a first minor and/or major depressive episode after cancer diagnosis. A preliminary PET study (Tashiro et al., 2001) showed that cancer patients with high Zung's Self-rating Depression Scale (SDS) scores showed a lower metabolism in the bilateral frontal cortices, bilateral anteroposterior cingulate gyrii, bilateral temporoparietal cortices, insula, anterior temporal cortex and basal ganglia than patients with benign tumor. In all these studies, the brain structure and metabolism after the emergence of psychiatric symptoms were assessed. However, the psychiatrically premorbid examination of the same aspect remains to be performed.

In major depression in the general population, local brain metabolism is reportedly decreased in the prefrontal lobe, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, subgenual prefrontal cortex (subgenual PFC), basal ganglia and temporoparietal cortex (Baxter et al., 1989; Bench et al., 1992; Drevets et al., 1997), and increased in the orbital cortex, amygdala and thalamus (Drevets et al., 1992; Price et al., 1996). Mayberg et al. (1999) reported that depressed patients exhibit a decreased metabolism in the subgenual cingulate and an increased metabolism in the DLPFC, anterior cingulate and posterior cingulate after remission. Although some brain areas that have been shown to have a lower metabolism in major depressive episode overlap between cancer and noncancer patients, it remains unclear whether these two populations share the same biological vulnerability to and the same pathophysiology of depressive symptomatology.

The objectives of the present study were to investigate the onset of major depressive disorder (MDD) and adjustment disorder in cancer patients prospectively and to explore the mechanisms underlying its onset by brain imaging, in the search for neurobiological changes associated with vulnerability to developing MDD or its milder form, adjustment disorder.

2. Subjects and methods

2.1. Subjects

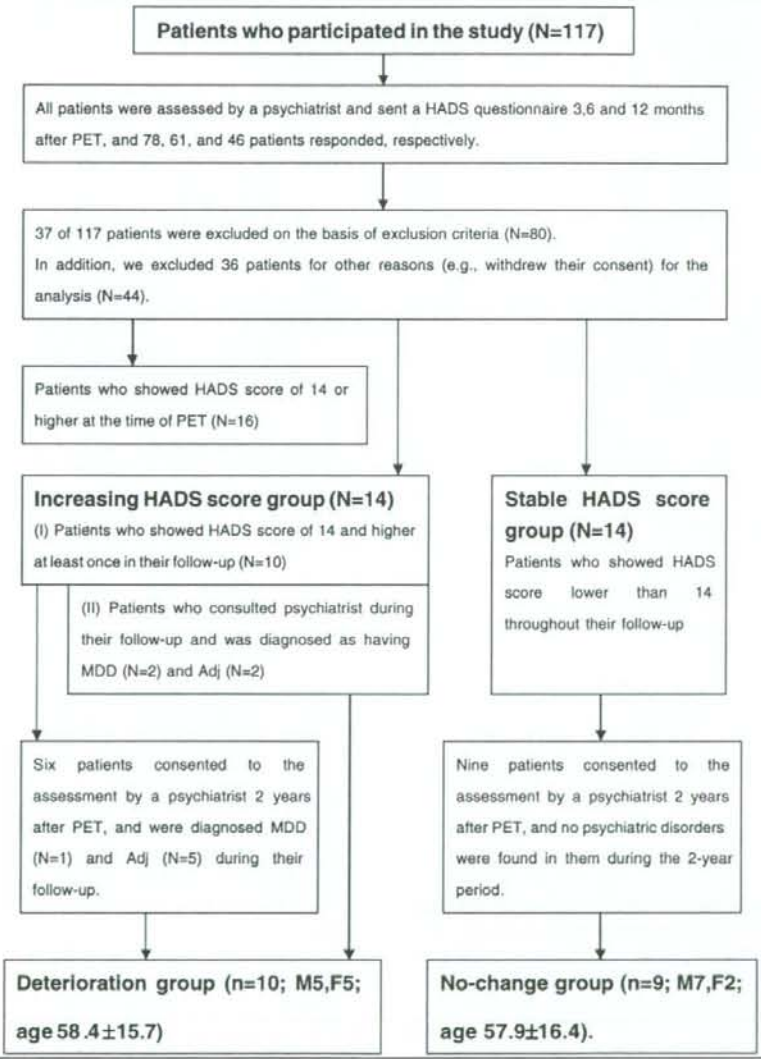
One hundred and seventeen outpatients and inpatients of the Department of Gunma University Hospital in Japan consented to participate in this psychooncological study. The participants were patients who were scheduled to undergo head or whole-body ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) on a clinically routine basis to detect cancer metastasis after being diagnosed as having malignant cancer or to monitor the therapeutic process after treatment for malignant cancer.

All the patients who consented to participate in this study were assessed by a psychiatrist for psychiatric symptoms and also submitted a self-completed report instrument, the Japanese version of Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983; Kitamura, 1993) after the PET scan. The same questionnaire was sent 3, 6, and 12 months after the PET scan, and 78, 61, and 46 patients responded, respectively. We used 14 as the HADS cut-off score for grouping patients for psychiatric screening. Previous studies showed that HADS scores of 13 and higher often indicate adjustment disorder or MDD (Hosaka et al., 1999); HADS scores of 13 and higher have a 75% sensitivity and 15 and higher have a 90% positive predictive value (Razavi et al., 1990) for MDD and adjustment disorder. Thus, it is appropriate that we interpreted HADS scores of 14 and higher to indicate a high possibility for the psychiatric diagnosis of MDD or adjustment disorder for screening.

Table 1 shows the flow chart of the patients' selection for the analysis. Patients with a history of brain infarction and a psychiatric history before the onset of cancer, and those who were on prednisolone, interferon, or any other medications for diabetes at the time of the examination were excluded from the analysis. Thirty-seven patients were excluded on the basis of these criteria. In addition, we excluded those patients from the analysis who did not reply at least once to the sent questionnaire ($n = 16$) or withdrew their consent for the study within the 2-year period ($n = 10$) or whose psychiatric status up to the time of the PET scan was uncertain (10). Sixteen patients scored 14 and higher at the time of the PET scan.

Patients who scored lower than 14 and did not present apparent psychiatric symptoms at the time of the PET scan but showed a score of 14 and higher at least once in their follow-up or those who consulted a psychiatrist during the follow-up period and was diagnosed as having a psychiatric disorder were grouped into the increasing HADS score group ($n = 14$; M9, F5; age 63.3 ± 16.3). The remaining 14 patients ($n = 14$; M9, F5; age 60.4 ± 14.4) did not present apparent psychiatric symptoms at the time of the

Table 1
Flow chart of patients' selection for analysis



Note. PET, positron emission tomography; HADS, Hospital Anxiety and Depression Scale; MDD, major depressive disorder; Adj, adjustment disorder.

PET scan and scored lower than 14 throughout the follow-up period, and were grouped into the stable HADS score group.

A psychiatrist planned to assess the patients in the two groups 2 years after the PET scan to investigate their psychiatric condition within the 2-year period. A depression module of the Mini-International Neuropsychiatric Interview (MINI) and an adjustment disorder module of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), which are semistructured interviews, were administered. Head MRI was carried out to examine any organic changes. In the increasing HADS score group, 2 of 14 patients died during the 2-year period. Of the remaining 12 patients, four consulted psychiatrists during the 2-year period; two of them were diagnosed with adjustment disorder, and the other two with MDD. Six of the remaining 8 patients approved personal interview. Five patients appeared to have adjustment disorder, and one patient MDD, when their HADS score increased. Thus, among the increasing HADS score group, at least 10 patients had adjustment disorder or MDD; thus, these 10 were classified into the deterioration group ($n = 10$; M5, F5; age 58.4 ± 15.7). In the stable HADS score group, 9 of the 14 patients approved personal interview, and the possibility of psychiatric disorders was found to be very low during the 2-year period; thus, these nine patients were classified into the no-change group ($n = 9$; M7, F2; age 57.9 ± 16.4). This two-step research design was chosen to lower patients' burden during clinical interview.

Table 2 shows the summary of the demographics and clinical characteristics of these subjects. At the time of the PET scan, one patient in the deterioration group was on krestin and a normal clinical dose of tegafur uracil (450 mg/day) that rarely cause depression except at a high dose (3000 mg/m^2/day) (Matsui et al., 1991). MRI after 2 years from the PET scan showed no brain infarction or brain metastasis in all the five patients in the deterioration group and six patients in the no-change group who consented to the MRI study. There were no significant differences in age, the time interval between the PET scan and the tumor onset, and HADS score at the time of the PET scan between the two groups ($p = 0.95$, 0.38, 0.075, by t-test respectively). The Institutional Review Board of Gunma University Hospital approved this study, and written informed consent was obtained from all the subjects and/or their family.

Table 2
Demographic and clinical characteristics of subjects

Age (Year)	Sex	Area affected by tumor	Cytological diagnosis, TNM status and stage of tumor before treatment of tumor	Treatment of tumor	Other physical disorders	TNM status and stage of tumor at the time of PET	Time interval between PET and tumor onset (months)	HADS score				Psychiatric diagnosis during 2-year period and consultation	Time interval between psychiatric diagnosis and tumor onset (months)
								At the time of PET	3 months after	6 months after	12 months after		
Deterioration group													
60	M	Lower thigh	Leiomyosarcoma stageIV(T2N0M1)	After OP, RT and CT	Type C hepatitis	StageIV (T1N0M1)	12	10	12	12	27	MDD consult	19
72	M	Colon	Adeno stageIV(TXNXM1)	After OP, RT and CT		StageIV (TXNXM1)	84	11		14		MDD consult	89
65	F	Upper pharynx	Undifferentiated stageIV(T1N3M0)	After RT		R0	30	11	10	15		Adj	41
56	M	Rectum	Adeno StageII(T3N0M0)	After OP	AT	R0	60	7	10		14	Adj	72
67	M	Lung	Unclassified stageIII (T4N0M0)	After RT and CT, Using Kre and TU	Arrhythmia	StageIII (T4N0M0)	3	0		1	7	Adj consult	5

2.2. ^{18}F-FDG PET

PET images were obtained using a SET 2400W instrument (Shimazu Corp., Kyoto, Japan) with a 59.5 cm transverse field of view and a 20 cm axial field of view. The plane of data acquisition was spaced 3.125 mm apart and 63 contiguous images were produced by two-dimensional data acquisition. The transverse spatial resolution was 4.2 mm full-width half-maximum (FWHM) at the center of the field of view, and the axial resolution was 5.0 mm FWHM.

	74	F	Uterus body	Adeno StageI(T1N0M0)	After OP and RT		R0	83	8	6	9	15	MDD	95
	59	F	Lower thigh	Liposarcoma stage I(T1N0M0)	After OP and RT	HT	StageI (T1N0M0)	2	10	16	16		Adj	6
	21	M	Back	PNET StageII(T2N0M0)	After OP and CT		R0	30	7	20			Adj	33
	66	F	Under right armpit	Malignant schwanoma stageII(T2N0M0)	After OP and RT. OP and RT after PET	HT, DM	StageIV (TXN1M0)	25	9	9	12	19	Adj	36
	44	F	Bone metastasis of unknown origin	SCC (TXNXM1)	After RT		TXNXM1	24	11	4	17	13	Adj consult	38
Mean	58.4	M5/F5						35.3	8.4	10.9	12.0	15.8		43.4
SD	15.7							30.3	3.3	5.2	5.1	6.7		32.0
No-change group														
	71	M	Esophagus	SCC StageII(TXN1M0)	After OP. RT after PET		StageII (TXN1M0)	68	5		7		No	
	63	M	Larynx	SCC StageII(T2N0M0)	After OP	HT, DM, AS	R0	8	4	4			No	
	61	M	Pancreas	Duct-islet cell StageI(T1N0M0)	After OP	Type C hepatitis	R0	163	0	2	2	0	No	
	62	F	Uterus	Leiomyosarcoma StageIV(TXN0M1)	After OP	Uterus myoma, HT	R0	3	3		1		No	
	55	M	Upper jaw	Adenoid cystic carcinoma stageIII (T3N0M0)	After OP and RT. OP after PET	Angina	StageIII (TXN1M0)	15	6	2	5		No	
	16	M	Thigh	Fibroblastic osteosarcoma StageIV (TXN0M1)	After OP and CT		R0	27	8	2	1	1	No	
	64	M	Thyroid	Papillary carcinoma StageIV (T4N1M1)	After OP, CT and RT. OP and RT after PET		StageIV (T4N1M1)	85	3	4	0	4	No	
	69	M	Esophagus	SCC StageII (T1N1M0)	After OP	HT	R0	39	11	10	10	3	No	
	60	F	Uterus body	Adeno StageI (T1N0M0)	After OP and RT		R0	67	9	6		4	No	
Mean	57.9	M7/F2						52.8	5.4	4.3	3.7	2.4		
SD	16.4							50.5	3.4	2.9	3.7	1.8		

Note. PET, positron emission tomography; adeno, adenocarcinoma; SCC, squamous cell carcinoma; PNET, primitive neuroectodermal tumor; OP, operation; CT, chemotherapy; RT, radiotherapy; Kre, krestin; TU, tegafur uracil; AT, arteriosclerosis; HT, hypertension; DM, diabetes mellitus; R0, no residual tumor; HADS, Hospital Anxiety and Depression Scale; MDD, major depressive disorder; Adj, adjustment disorder; consult, under regular consultation by a psychiatrist.

Table 3
Summary of SPM comparison between no-change group and deterioration group

Lobe	Structure	Brodmann's area	Hemisphere	Talairach coordinate			Z-score	Cluster size (voxels)
				X	Y	Z		
Hypometabolic area[a]								
Frontal	Medial frontal gyrus	6	R	18	3	59	4.01	81
Hypermetabolic area[a]								
Frontal	Subcallosal gyrus	25	L	−4	9	−12	3.71	198
Limbic	Anterior cingulate	25	R	2	11	−7	3.38	SCAA
	Caudate head		L	−4	2	2	3.68	SCAA
Limbic	Posterior cingulate	29	R	6	−46	8	4.04	113

Note. [a]Significant in deterioration group compared with no-change group. ($p < 0.001$, uncorrected). Cluster size is represented by the number of voxels (voxel size: 2.0 × 2.0 × 2.0 mm/voxel). SCAA, the same cluster as above.

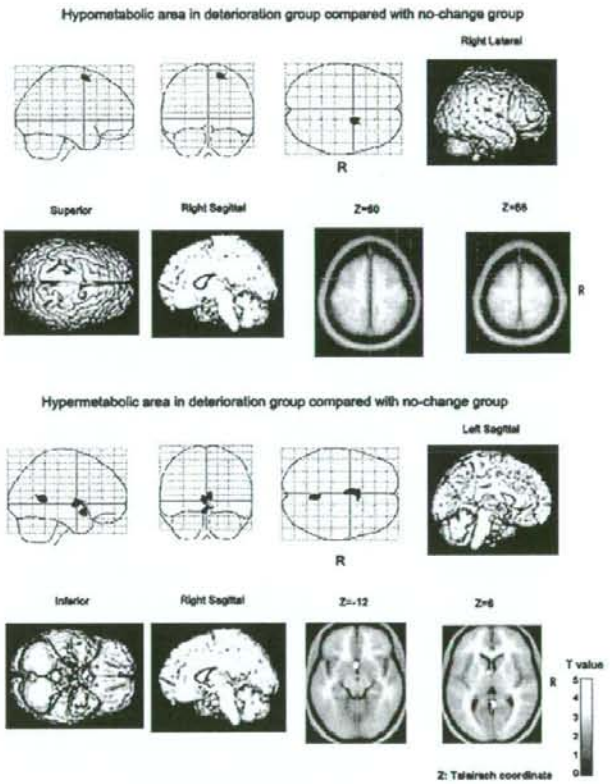


Fig. 1. Visualization of SPM comparison between no-change group and deterioration group. *Note.* 'R' indicates the right side.

The subjects fasted for at least 8 h before PET. For PET studies, 4–5 MBq/kg ^{18}F-fluorodeoxyglucose (^{18}F-FDG) was injected in an intravenous bolus. After the injection, each subject remained in the resting state with his or her eyes open for a 45-minute-uptake period. Data acquisition was performed by the simultaneous transmission-emission method using a rotating external source (370 MBq ^{68}Ge/^{68}Ga at installation). Subsequently, attenuation-corrected transverse images were reconstructed by the ordered subset expectation maximization (OS-EM) algorithm into 128 × 128 matrices with pixel dimensions of 2.0 mm in-plane and 3.125 mm axially.

For the analysis of PET images, statistical parametric mapping was used (SPM 99, www.fil.ion.ucl.ac.uk/spm). For the spatial preprocessing of data, individual PET images were adjusted in accordance with the anterior com-

missure. Images were spatially normalized to a standard space using the Montreal Neurological Institute (MNI) template with a voxel size $2 \times 2 \times 2$ mm^3. The normalized images were smoothed with an isotropic Gaussian kernel of 8 mm FWHM. Prior to voxel-based statistical analysis, the global cerebral metabolic rate for glucose was normalized to a fixed mean value (50 μmol/100 ml/min) by proportional scaling to remove the confounding effect of global activity and 80% of the mean global value was applied as default by proportional scaling for threshold masking. A two-sample *t*-test was performed between the deterioration group and the non-change group.

The activities of brain regions that were identified as having 40 or more contiguous voxels were defined as significant at a threshold of $p < 0.001$ (uncorrected for multiple comparisons). Because the resulting *t*-values are known to approximate closely the standard Gaussian distribution, they were described as Z-scores. For anatomical identification, the coordinates derived from the MNI template were transformed using the appropriate algorithm (cf. www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml) to comply with the original grid of Talairach and Tournoux.

3. Results

The results of SPM comparison between the no-change group and the deterioration group are shown in Table 3 and Fig. 1. The comparison between the deterioration group and the no-change group revealed that the deterioration group showed a decreased glucose metabolism in the right medial frontal gyrus (Brodmann's area 6, BA6). An increased glucose metabolism was observed in the right posterior cingulate (BA29), right anterior cingulate (BA25), left subcallosal gyrus (BA25), and left caudate.

4. Discussion

To the best of our knowledge, this is the first study demonstrating that cancer patients who later developed MDD or adjustment disorder showed, before their psychiatric manifestation, a decreased metabolism in the right medial frontal gyrus (BA6) and an increased metabolism in the right posterior cingulate (BA29), right anterior cingulate (BA25), left subcallosal gyrus (BA25), and left caudate in comparison with the no-change group. Some of these regions are reported to be affected in MDD; thus, these regions may be associated with vulnerability to the onset of MDD or adjustment disorder in cancer patients.

Recently, illness vulnerability to depression has been extensively investigated by brain imaging. For patients with familial pure depressive disease, Drevets et al. (1992) concluded that a decreased blood flow in the left prefrontal cortex represents a state abnormality, whereas an increased blood flow in the amygdala might represent a trait marker, as it persists after recovery. Previous studies showed that a possible change associated with the trait marker of depression is an increased blood flow in the angular gyrus (Bench et al., 1995), orbital cortex and medial prefrontal cortex (Drevets et al., 1992), which persists after recovery. Another possible change is a decrease in activity in the subgenual PFC observed in depression, which appears to be accounted for by a corresponding decrease in cortical volume (Drevets et al., 1997). These possible changes, however, might have been caused by an experience of depression, because these studies were all retrospective. Our prospective study provides more direct evidence that the local metabolism changes observed in the deterioration group compared with those in the no-change group might be associated with the later onset of depressive and anxiety symptoms. Whether our findings are also applicable to noncancer population requires further study.

The dorsolateral part of the medial frontal gyrus (BA6) is called the premotor cortex. This region receives projections from somatosensory areas (Dum and Strick, 1991), and an increased blood flow in this region was observed during tactile learning and recognition (Roland et al., 1989). This region is considered to have a role in the initiation of an action based on somatosensory inputs (Wise, 1985). Brody et al. (1999) reported an increased metabolism in the premotor/supplementary area with successful proxitine treatment in depression, which might represent an increase in movement or in tension to move with psychiatric recovery, whereas they failed to observe an increased metabolism in DLPFC, although metabolism in DLPFC is often reported to be decreased in depression and increased after remission (Baxter et al., 1989; Buchsbaum et al., 1997).

The posterior cingulate gyrus appears to serve as a sensory association cortex, and may participate in processing the affective salience of sensory stimuli. The posterior cingulate gyrus sends a major anatomical projection to the anterior cingulate cortex, through which it relays such information to the limbic circuitry (reviewed in Drevets et al., 2002). Several groups reported an abnormally increased blood flow or metabolism in the posterior cingulate cortex in depression (Drevets, 2000; Bench et al., 1992). Many functional imaging studies have shown that exposure to aversive stimuli of various types increases physiological activity in the posterior cingulate gyrus (Maddock, 1999). Nevertheless, Mayberg et al. (1999) reported that script-driven sadness results in a decreased posterior cingulate activity in healthy subjects, and blood flow was decreased in depressed state relative to remitted state in subjects with depression, raising the possibility that this large region is functionally heterogenous with respect to emotional behavior (Drevets et al., 2002).

The subcallosal gyrus (BA25) is located under the subgenual cingulate contiguously, and considered to be part of the limbic system. A meta-analytic study showed that this region is involved in sadness (Phan et al., 2002). Previous studies often showed a decreased metabolism in the subgenual PFC in depression, which is situated ventral to the genu of the corpus callosum (Bench et al., 1992;

Drevets et al., 1997); however, metabolism in this area further decreased in the depressed subjects following sertraline treatment (Drevets et al., 1997; Buchsbaum et al., 1997). The subgenual PFC also shows a decreased metabolism and a decreased tissue volume in depression (Drevets et al., 1997) and a decrement in cortex volume is associated with a reduction in glia (Ongur et al., 1998); however, glucose metabolism in this region increased when reduced tissue volume was corrected in depressed subjects as compared with that in normal control subjects (Drevets, 2000). It appears that, in depressed patients, the actual metabolic activity in the remaining cortex would be elevated, as opposed to reduced, relative to the normative level, and that antidepressant treatment decreased this elevated activity to normal (Meltzer et al., 1999; Drevets, 2000).

The caudate is part of the corpus striatum, and this region shows blood flow changes in various tasks (Roland et al., 1989, 1990). However, there is no consistent pattern of increase or decrease in blood flow in this region and the function of this region appears to be complex. Some studies showed a decreased metabolism in this region in depression (Baxter et al., 1989; Drevets et al., 1992), and a decrease in the volume of the region was also reported (Krishnan et al., 1992). A decrease in blood flow in the caudate was reported in depression induced by tryptophane depletion (Smith et al., 1999), so there is a possibility that a decrease in the volume and function of the caudate are both associated with depression (Drevets, 2000). On the other hand, an increased metabolism in the caudate in the deterioration group was observed in this study. However, we did not search for the metabolic changes in this region after the onset of MDD or adjustment disorder.

In light of these functional anatomical data, hypometabolism in the right medial frontal gyrus as observed in the present study may pose as a risk factor for energy loss and psychomotor retardation. Hypermetabolism in the right posterior cingulate, right anterior cingulate, and left subcallosal gyrus may be regarded as predisposing factors for emotional disturbance. Although it is difficult to interpret the increased metabolism in the caudate in the deterioration group, it is possible that, when an individual is vulnerable to the onset of anxiety and/or depressive symptoms, metabolism in the caudate increases under the chronic stress of cancer and then decreases after the onset of depressive and/or anxiety symptoms. This view is also supported by an fMRI study of healthy volunteers (Sinha et al., 2004) in which the recall of highly stressful life events produced significant activation in the caudate. Longitudinal studies of proper design, however, are required to obtain a definite conclusion.

Limitations in the present study include the limited diagnostic reliability, the lack of a reliable absolute metabolic value ($p < 0.001$ uncorrected), the small sample size, the absence of a noncancer control group, the lack of a controlling task for brain activity, and the heterogeneity of the patients' conditions and treatments such as the stage of cancer and the time interval between the PET scan and the tumor onset.

Regarding the diagnosis, this study was originally planned as a naturalistic clinical study with minimal burden to the patients and did not use a structural clinical interview, which could have burdened patients with psychological stress at the time of the PET scan. The patients with probable psychiatric symptoms based on HADS scores were retrospectively assessed with MINI and SCID by a psychiatrist 2 years after the PET scan. However, the validity of the diagnosis was limited. Similarly, 2 years after the PET scan, MRI was employed to examine organic changes in the brain. However, not all the patients were scanned; thus, the possibility of organic changes during the follow-up period cannot be denied. Despite all these methodological difficulties unavoidable in this kind of naturalistic study, we obtained preliminary positive results in several brain regions that were associated by many researchers with the pathophysiology of MDD. This warrants further investigation using a larger sample size and a more rigorous study design.

5. Conclusion

Cancer patients who later developed MDD or adjustment disorder showed a decreased metabolism in the right medial frontal gyrus (BA6), and an increased metabolism in the right posterior cingulate (BA29), right anterior cingulate (BA25), left subcallosal gyrus (BA25), and left caudate. These regions may be associated with vulnerability to the onset of MDD or adjustment disorder in cancer patients. In the future, the mechanisms underlying the onset of psychiatric disorder in cancer patients should be elucidated, by conducting prospective studies of a large population that will examine the relationship between psychiatric symptoms and organic and/or functional changes in the brain.

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