

Original Article

Changes of brain activities in cancer-secondary depression patients: a study based on ^{18}F -FDG PET

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Abstract: Aim: The aim of this study was to investigate the changes of brain activities in cancer-secondary depression patients. Methods: Participants without physical disease and those with diagnosed malignant tumors (brain tumors excluded) were recruited in the PET Center of Huashan Hospital. Depression was assessed by psychiatrists using the Hamilton Depression (HAMD) scale. Eight healthy controls, 8 depression patients, and 8 cancer-secondary depression patients, aged 50-60 years, were included to experience ^{18}F -FDG PET scanning for brain glucose metabolism. Correlation between HAMD scores and brain glucose metabolism was investigated by Pearson's correlation analysis. Results: Cancer-secondary depression patients had higher HAMD scores than both healthy controls ($P<0.01$) and depression patients ($P<0.05$). Compared with healthy controls, cancer-secondary depression patients had significantly decreased glucose metabolism in the right cingulate gyrus, left middle temporal gyrus, left post-central gyrus, and left uncus, along with increased glucose metabolism in the left lentiform nucleus (all $P<0.001$). Compared with depression patients, cancer-secondary depression patients also had significantly increased glucose metabolism in the right lentiform nucleus and left limbic lobe parahippocampal gyrus ($P=0.001, 0.002$, respectively), showing positive correlation with HAMD scores. Conclusion: Depression in cancer patients was more severe than in people without physical disease. Increased activities in the lentiform nucleus and parahippocampal gyrus may serve as specific indicators of secondary depression in cancer patients.

Keywords: Cancer-secondary depression, ^{18}F -fluorodeoxyglucose positron emission tomography, brain activities

Introduction

Depression is an important public health problem and one of the most burdensome diseases worldwide. It is especially common in cancer patients because of the huge psychological stress from cancer diagnosis and poor prognosis. Previous studies have found that depression affects up to 25% of cancer patients, 2-3 times more than the general population [1-3]. Depression can significantly promote cancer metastasis [4], increase healthcare costs [1], and has been associated with elevated cancer mortality [5], risk for suicide [6], and non-adherence to cancer treatment [7]. However, detailed pathogenic mechanisms of depression in cancer patients remain under-researched.

^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG PET) brain imaging is a

technique widely used in clinical and experimental research on neurological and mental disorders, such as depression, Alzheimer's disease, and cognitive disorders [8-10]. As glucose is the most important energy source of the brain and metabolic changes appear much earlier than morphological changes, brain glucose metabolic rates can serve as an early indicator for the pathological processes of neurological diseases [8]. By detecting the positrons emitted by ^{18}F -labeled FDG, PET brain imaging can non-invasively, intuitively, and precisely reflect glucose metabolism in intravital brains, reflecting brain functional activities.

The present study recruited healthy controls, depression patients, and malignant cancer patients with secondary depression and investigated the specific changes of brain activities in cancer-secondary depression patients using

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^{18}F -FDG PET brain imaging. The aim of this study was to supply evidence for indicators of secondary depression in cancer patients from the perspective of brain imaging.

Materials and methods

Participants

Participants were recruited and brain PET scans were performed in the PET Center, Huashan Hospital, Fudan University. Upon arrival, fasting blood glucose, height, and body weight were measured. Medical histories were collected by doctors in the PET Center. HAMD scores were assessed by psychiatrists. They also evaluated their depressive status considering clinical manifestations. Diagnosis of depression was based on depressive manifestations and HAMD scores >8 points. Participants that experienced brain PET scanning were included strictly according to the inclusion and exclusion criteria (detailed in [Table S1](#)). Finally, 8 healthy controls, 8 depression patients, and 8 cancer-secondary depression patients, aged 50-60 years, were included for brain ^{18}F -FDG PET scanning (flow chart in [Figure 1](#)). All PET participants were explicitly asked to give consent for their participation in the study without payment and on a voluntary basis. This study obtained ethical approval from the Institutional Review Board of Fudan University (HIRB number: 2009 M-011).

Brain ^{18}F -FDG PET scanning

All participants were forbidden to use coffee, cigarettes, wine, and drugs (including antihistamines, aspirin, diazepam) for 24 hours before PET scanning. Ample sleep and 6 hours of fasting were also guaranteed the night before PET scanning. After resting for 15 minutes in a dim room upon their arrival, ^{18}F -FDG (radiochemical purity $>95\%$, 7.4 MBq/kg) was intravenously injected as the tracer. After an uptake period of 40 minutes in a quiet and dimly lit environment, a 20 second CT transmission scan was first performed for attenuation correction. A 10 minute 3-dimensional brain emission scan was then acquired with a PET scanner (Biograph Sensation 64, Siemens, Germany). During the scanning procedure, heads of the participants were immobilized using a head holder. PET image data sets were reconstructed iteratively by FBP to obtain the transverse section, coronal plane, and sagittal plane brain images.

Statistical analysis

Statistical analyses for data were carried out using SPSS 15.0 software (IBM, USA). All data are presented as mean \pm SD. One-way ANOVA was performed if the data of 3 groups followed a normal distribution (Shapiro-Wilk test, $P > 0.10$) and variances were homogeneous (Levene test, $P > 0.10$). Otherwise, a nonparametric test was adopted. Bivariate correlations were analyzed by using Pearson's correlation coefficient if data followed a normal distribution. If not, Spearman's correlation coefficient was used. Data was statistically significant if $P < 0.05$.

Reconstructed images were transmitted from PET workstations into PCs via Microsoft FTP software, which were then converted into Analyze format by using MRIcro software. PET brain images were first spatially normalized to the SPM PET template that was aligned to the Montreal Neurological Institute (MNI) brain space with linear affine transformation and nonlinear iteration, using the SPM5 software package (Wellcome Department of Cognitive Neurology, London, UK) running on MATLAB Version 2009a (Mathworks Inc, Sherborn, MA, USA). Normalized PET images were then smoothed by a Gaussian filter of 8 mm full width of half maximum (FWHM) over a 3D space to increase signal to noise ratio for statistical analysis, with matrix $128 \times 128 \times 63$ and voxel $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$. To identify brain areas displaying different glucose metabolisms, this study compared PET brain images of the 2 groups in SPM5 software. Simple fixed-effects t -tests for each voxel were performed. Clusters with thresholds of 2-tailed uncorrected $P < 0.001$ were considered as significantly different in glucose metabolism. For all statistical analyses, Talairach Client software was used to convert MNI coordinates to Talairach coordinates.

Results

Characteristics of PET participants

As shown in [Figure 1](#), 76 participants without physical disease and 69 patients with diagnosed malignant cancers were initially assessed. As brain glucose metabolism is closely associated with age [11, 12] and participants aged 50-60 years had the highest proportion of

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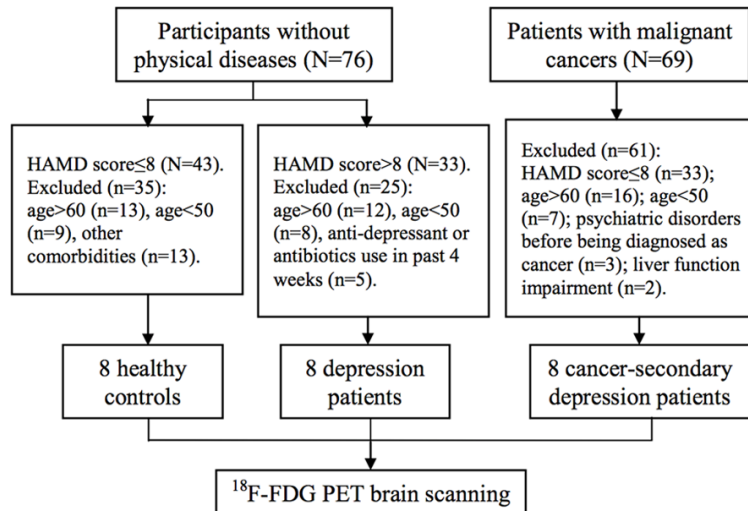


Figure 1. Flow chart of inclusion and exclusion processes.

Table 1. Characteristics of participants

Characteristics	Healthy Control (n=8)	Depression (n=8)	Cancer-secondary depression (n=8)
Age (years)	54.1±3.44	55.1±3.09	55.9±3.00
Gender (male, n, %)	5 (62.5)	2 (25)	4 (50)
BMI (kg/m ²)	26.4±2.28	24.1±1.20	20.6±3.10**.,##
Education (years)	11.0±1.85	11.8±2.25	12.6±2.39
Blood glucose (mmol/L)	5.24±0.63	5.21±0.51	5.06±0.62
HAMD score (point)	3.88±2.53	13.0±3.70**	17.5±4.18**.,#

**P<0.01 vs Healthy Control; ##P<0.01, #P<0.05 vs Depression. BMI: body mass index; HAMD: Hamilton Depression.

the population assessed, this study only included participants aged 50-60 years for brain ¹⁸F-FDG PET scanning, according to inclusion and exclusion criteria.

The 3 groups of participants had similar age, gender, education levels, and fasting blood glucose (all $P>0.05$, **Table 1**). Compared with both healthy controls and depression patients, cancer-secondary depression patients had significantly lower BMI (both $P<0.01$) and higher HAMD scores ($P<0.01$, $P<0.05$, respectively), indicating cachexia and more severe depression.

Brain regions with different glucose metabolisms among the 3 groups

As shown in **Figure 2** and **Table 2**, compared with healthy controls, cancer-secondary depression patients had significantly decreased glu-

cose metabolism in the right cingulate gyrus (BA24), left middle temporal gyrus (BA21), left postcentral gyrus (BA40), and left uncus (BA20), along with increased glucose metabolism in the left lentiform nucleus (all $P<0.001$, glucose metabolic rates listed in **Table S2**). Compared with depression patients, those with cancer-secondary depression had significantly increased glucose metabolism in the right lentiform nucleus ($P=0.001$), left limbic lobe parahippocampal gyrus (BA28) ($P=0.002$), as well as the right nodule and left inferior semi-lunar lobule in cerebellum ($P<0.001$).

Correlation between HAMD scores and brain glucose metabolism in depression and cancer-secondary depression patients

Pearson's correlation analysis was used to analyze correlation between HAMD scores and glucose metabolic rates in the 4 brain regions with significantly changed glucose metabolisms between depression

and cancer-secondary depression patients. As shown in **Figure 3**, glucose metabolism in the right lentiform nucleus, left parahippocampal gyrus (BA28), and left inferior semi-lunar lobule showed significant positive correlation with HAMD scores ($P=0.031$, $P=0.021$, $P=0.049$, respectively), indicating that glucose metabolic levels in these brain regions could reflect the severity of depression to some extent.

Discussion

Depression is quite common in cancer patients, with a prevalence as high as 25% [2, 3]. It can cause many adverse outcomes, such as cancer metastasis and suicide [4-7]. Incidence of cancer-secondary depression also depends on the location and prognosis of cancers [13], which determine the degree of psychological stress in patients. Therefore, during clinical treatment of cancers, attention should be paid to assess the

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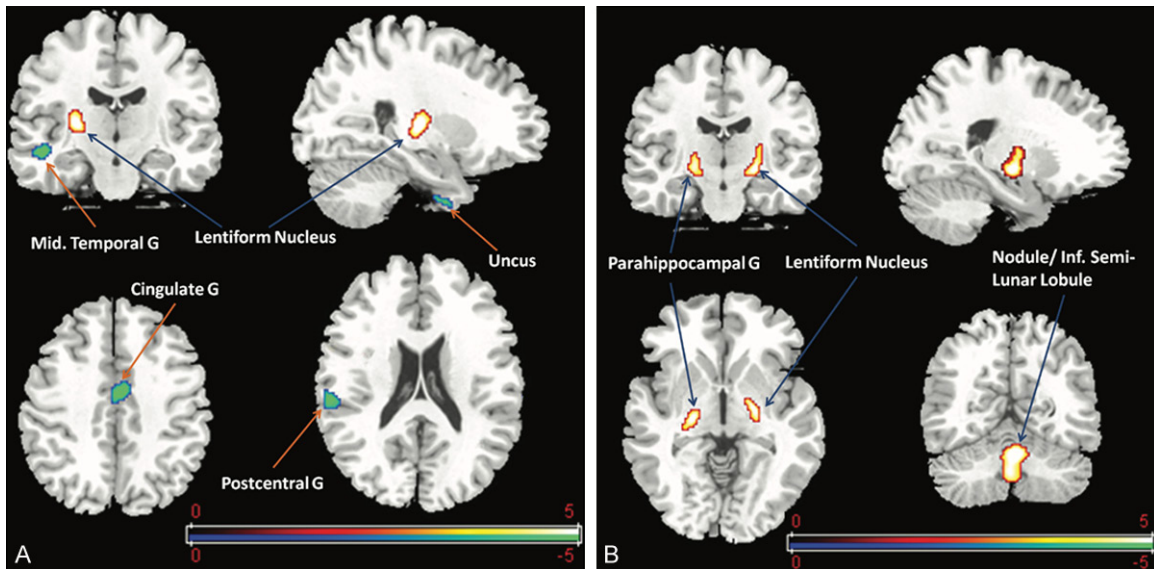


Figure 2. Brain regions with significantly changed glucose metabolism in cancer-secondary depression patients. A: Cancer-secondary depression patients had decreased glucose metabolism in the right cingulate gyrus, left middle temporal gyrus, left postcentral gyrus, and left uncus, and increased glucose metabolism in the left lentiform nucleus, compared with healthy controls. B: Cancer-secondary depression patients also had increased glucose metabolism in the right lentiform nucleus, left parahippocampal gyrus, right nodule, and left inferior semi-lunar lobule, compared with depression patients.

Table 2. Brain regions with significantly changed glucose metabolism in cancer-secondary depression patients

Brain Regions	Side	Size (voxels)	Coordinates			Z _{max}
			x	y	z	
<i>Cancer-secondary Depression vs Healthy Control</i>						
<i>Metabolic decrease</i>						
Limbic Lobe, Cingulate G (BA24)	R	138	4	-8	42	4.08
Temporal Lobe, Middle Temporal G (BA21)	L	214	-48	-16	-12	4.07
Parietal Lobe, Postcentral G (BA40)	L	82	-58	-26	18	4
Limbic Lobe, Uncus (BA20)	L	92	-24	-2	-44	3.86
<i>Metabolic increase</i>						
Sub-lobar, Lentiform Nucleus	L	125	-26	-18	6	4.18
<i>Cancer-secondary Depression vs Depression</i>						
<i>Metabolic increase</i>						
Sub-lobar, Lentiform Nucleus	R	243	22	-14	-6	3.92
Limbic Lobe, Parahippocampal G (BA28)	L	163	-22	-20	-4	3.88
Cerebellum, Anterior Lobe, Nodule	R	662	4	-60	-26	4.25
Cerebellum, Posterior Lobe, Inferior Semi-Lunar Lobule	L	662	0	-64	-38	4.09

BA: brodmann area, R: right, L: left, G: gyrus.

possible comorbidity of depression and appropriate psychological interventions and/or antidepressants should be adopted correspondingly.

Since the whole population initially assessed in this study had the highest proportion of people

aged 50-60 years and brain glucose metabolic rates decrease gradually with older age [11, 12], this study only included participants aged 50-60 years for PET brain scanning. The present study found that when participants of the 3 groups had similar age, gender, education levels, and fasting blood glucose, cancer-second-

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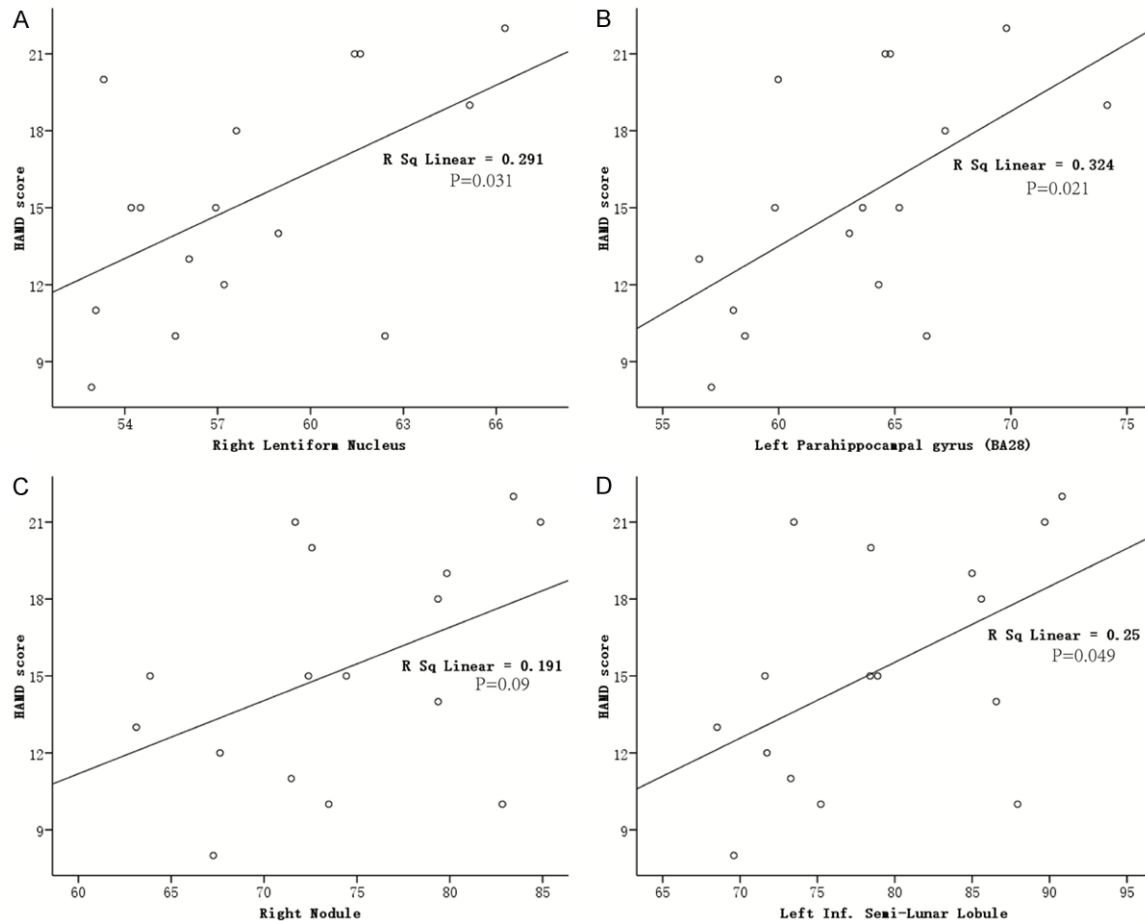


Figure 3. Correlation between HAMD scores and brain glucose metabolic rates in depression and cancer-secondary depression patients (N=16).

ary depression patients showed lower BMI and higher HAMD scores than both healthy controls and depression patients. This finding indicates that secondary depression caused by cancers was more severe than depression in people without physical disease, reflecting the occurrence of cancers could contribute more to the severity of depression than its common causes.

Previous studies of PET brain imaging have rarely involved the pathogenesis of secondary depression in cancer patients. A former study found that, compared with healthy controls, depression patients had decreased glucose metabolism in the left cingulate gyrus, left superior frontal gyrus, right orbital gyrus, left rectal gyrus, and left inferior semi-lunar lobule [14]. This study further compared brain activities between cancer-secondary depression patients and the same healthy controls/depression patients as those in the former

study [14]. It was found that, compared with healthy controls, cancer-secondary depression patients had significantly decreased glucose metabolism in the right cingulate gyrus, left middle temporal gyrus, left postcentral gyrus, and left uncus, along with increased glucose metabolism in the left lentiform nucleus. Compared with depression patients, cancer-secondary depression patients had significantly increased glucose metabolism in the right lentiform nucleus, left limbic lobe parahippocampal gyrus, right nodule, and left inferior semi-lunar lobule. The above pairwise comparisons showed that lentiform nucleus and parahippocampal gyrus might be specific brain regions with significantly increased glucose metabolism in cancer-secondary depression patients, indicating from a brain imaging perspective that the pathogenesis of cancer-secondary depression is different from depression in the general population.

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The lentiform nucleus is one structural component of the striatum. Parahippocampal gyrus belongs to the limbic system, the structural or functional changes of which are widely involved in the pathogenesis of various mental and neurological diseases, such as depression and Parkinson's disease. Brain PET and functional MRI studies have shown that glucose metabolic rates and functional activities were significantly decreased in lentiform nucleus of depression patients [15, 16] and the severity of depression was negatively correlated with blood flow in the lentiform nucleus and parahippocampal gyrus [17]. The volume of gray matter in lentiform nucleus as well as gray and white matter in parahippocampal gyrus was significantly reduced in patients with delayed-onset depression. Compared with depression patients that did not commit suicide, the volume of gray and white matter in lentiform nucleus was significantly reduced in suicidal depression patients [18, 19]. SPECT studies have shown a significant reduction of blood perfusion in lentiform nucleus of depression patients with cognitive impairment [20] and the severity of depression secondary to chronic physical diseases was negatively correlated with regional cerebral blood flow in the lentiform nucleus [17]. Compared with Alzheimer's patients, the density of lentiform nucleus gray matter was significantly decreased in Alzheimer's patients with late-onset depression [21]. In addition, one study found that patients with Parkinson's disease had significantly increased glucose metabolic rates in lentiform nucleus and parahippocampal gyrus [22]. In the present study, increased glucose metabolism in lentiform nucleus and parahippocampal gyrus found in cancer-secondary depression patients was not consistent with the above depression-related studies, which also indicated the different pathogenesis of depression in cancer patients. The present study also revealed that the glucose metabolic rate in these 2 brain regions could reflect the severity of depression to some extent.

As ^{18}F -FDG PET/CT of the whole body has become a popular and useful technique to assess metastasis and prognosis of many kinds of malignant cancers in clinical practice, brain metabolic rates could be investigated simultaneously as one method to assess depression. Therefore, this study provided imaging evi-

dence, not only for the specific pathogenesis of cancer-secondary depression, but also a new way to assess depression status of cancer patients, displaying a certain clinical significance.

The primary limitation in this study was the small number of participants involved in brain PET scanning. Participants were from only one center and the age range was only 50-60 years, which may have introduced bias. The influence of different types of cancers and treatments of cancer patients on depression status was also not considered, due to the small number. In the future, randomized controlled double-blind clinical trials with large sample sizes, multi-centers, and multi-age groups should be carried out. Blood and saliva indicators should also be involved in further exploration of the mechanisms of cancer-secondary depression, aiming to provide theoretical basis for prevention and treatment.

In conclusion, depression in cancer patients was more severe than in people without physical disease. This should receive high attention. Increased activities in the lentiform nucleus and parahippocampal gyrus may serve as specific indicators of secondary depression in cancer patients, displaying certain clinical significance.

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Disclosure of conflict of interest

None.

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Table S1. Inclusion and exclusion criteria in this study

Inclusion criteria

- (1) Healthy controls: no current organic or psychiatric disorder, no history of mental and physical illness, and no antibiotic drugs use in 4 weeks prior to the screening.
- (2) Depression patients: HAMD score >8 and were recognized as depression by psychiatrists. No antidepressant or antibiotic drug use in 4 weeks prior to screening.
- (3) Cancer-secondary depression patients: had diagnosed malignant cancers, HAMD score >8 and were recognized as depression by psychiatrists. No antidepressant or antibiotic drugs use in 4 weeks prior to the screening.
- (4) All subjects were right-handed; had good cognitive ability, normal thinking ability and memory; agree to sign informed consent for participation.

Exclusion criteria

- (1) Subjects with other psychiatric disorders (e.g., mania, schizophrenia, or sleep disorder), or with any other diseases and conditions that might confound data interpretation (e.g., immune, endocrine, cerebrovascular, cardiovascular, hematologic, hepatic, renal, or neurological diseases, oral contraceptives or pregnancy).
- (2) Subjects that had used antidepressant, antibiotic drugs, opioid analgesics, glucocorticoids or sex hormones in 4 weeks prior to the screening.
- (3) Subjects that refused to sign informed consent or had poor compliance.

Table S2. Glucose metabolic rates in brain regions with significantly changed activities

Brain regions	Healthy Control	Depression	Cancer-secondary Depression	P
<i>Cancer-secondary Depression vs Healthy Control</i>				
Limbic Lobe, Cingulate G (BA24, R)	95.5±3.03	-	81.7±4.27	<0.001
Temporal Lobe, Middle Temporal G (BA21, L)	72.5±4.30	-	60.4±1.97	<0.001
Parietal Lobe, Postcentral G (BA40, L)	93.5±2.17	-	81.8±3.84	<0.001
Limbic Lobe, Uncus (BA20, L)	59.3±3.52	-	49.1±3.19	<0.001
Sub-lobar, Lentiform Nucleus (L)	67.1±2.27	-	76.1±5.29	<0.001
<i>Cancer-secondary Depression vs Depression</i>				
Sub-lobar, Lentiform Nucleus (R)	-	54.9±1.76	61.0±3.88	0.001
Limbic Lobe, Parahippocampal G (BA28, L)	-	59.9±3.20	66.7±3.71	0.002
Cerebellum, Anterior Lobe, Nodule (R)	-	69.0±4.07	79.5±4.51	<0.001
Cerebellum, Posterior Lobe, Inferior Semi-Lunar Lobule (L)	-	73.4±3.74	84.7±5.81	<0.001

Data represent mean ± SD. L, left; R, right.