# Quantification of Tc-99m-ethyl cysteinate dimer brain single photon emission computed tomography images using statistical probabilistic brain atlas in depressive end-stage renal disease patients
## *Correlation with disease severity and symptom factors*☆

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## Abstract

This study adapted a statistical probabilistic anatomical map of the brain for single photon emission computed tomography images of depressive end-stage renal disease patients. This research aimed to investigate the relationship between symptom clusters, disease severity, and cerebral blood flow. Twenty-seven patients (16 males, 11 females) with stages 4 and 5 end-stage renal disease were enrolled, along with 25 healthy controls. All patients underwent depressive mood assessment and brain single photon emission computed tomography. The statistical probabilistic anatomical map images were used to calculate the brain single photon emission computed tomography counts. Asymmetric index was acquired and Pearson correlation analysis was performed to analyze the correlation between symptom factors, severity, and regional cerebral blood flow. The depression factors of the Hamilton Depression Rating Scale showed a negative correlation with cerebral blood flow in the left amygdale. The insomnia factor showed negative correlations with cerebral blood flow in the left amygdala, right superior frontal gyrus, right middle frontal gyrus, and left middle frontal gyrus. The anxiety factor showed a positive correlation with cerebral glucose metabolism in the cerebellar vermis and a negative correlation with cerebral glucose metabolism in the left globus pallidus, right inferior frontal gyrus, both temporal poles, and left parahippocampus. The overall depression severity (total scores of Hamilton Depression Rating Scale) was negatively correlated with the statistical probabilistic anatomical map results in the left amygdala and right inferior frontal gyrus. In conclusion, our results demonstrated that the disease severity and extent of cerebral blood flow quantified by a probabilistic brain atlas was related to various brain areas in terms of the overall severity and symptom factors in end-stage renal disease patients.

## Key Words

single photon emission computed tomography; end-stage renal disease; depression; statistical probabilistic brain atlas; disease severity; cerebral blood flow; symptom; brain; neural regeneration

## Research Highlights

(1) Depression factor of Hamilton Depression Rating Scale (HDRS) was negatively correlated with statistical probabilistic anatomical map (SPAM) results regarding the left amygdale from patients with end-stage renal disease. (2) Insomnia factor of HDRS was negatively correlated with SPAM results regarding the left amygdala, right superior frontal gyrus, right middle frontal gyrus, and left middle frontal gyrus. (3) Anxiety and psychomotor factor of HDRS was positively correlated with

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SPAM results regarding the cerebellar vermis but was negatively correlated with SPAM results regarding the left globus pallidus, right inferior frontal gyrus, both temporal poles, and left parahippocampus. (4) The overall severity of depression evaluated by HDRS was negatively correlated with SPAM results regarding the left amygdala and right inferior frontal gyrus in patients with end-stage renal disease.

### Abbreviations

ASI, asymmetric index; ECD, ethyl cysteinate dimer; FDG, fluorodeoxyglucose; HDRS, Hamilton Depression Rating Scale; PET, positron emission tomography; SPECT, single photon emission computed tomography; SPAM, statistical probabilistic anatomical map; VOI, volume of interest

## INTRODUCTION

Depression has been identified as the most common psychiatric illness in patients with end-stage renal disease, but its prevalence has varied widely[1-5]. In end-stage renal disease, the neuropsychiatric effects range from subtle, nonspecific changes to gross, distinct abnormalities according to stage and chronicity of kidney disease and patient condition. Recent studies of a hemodialysis population have estimated a 20−30% incidence of depressive disorders in this patient group[5-6].

Among patients with end-stage renal disease, depression and cognitive impairment are the most common causes of neuropsychiatric illness[6]. In particular, depression is considered to be an important factor for determining patient survival[7-8].

A recent study has shown that the 12-month prevalence of major depression in individuals with chronic medical conditions ranges from 7.9 % to 17 %, and that the age-/sex-adjusted odds of major depression for this population range from 1.96 to 3.56[9]. Among the various chronic medical conditions noted in this study, individuals with end-stage renal disease had the highest 12-month prevalence and odds of major depression[9].

Advances in neuroimaging techniques have led to some interesting findings concerning alterations in brain structure and functions in several chronic illnesses with psychiatric symptoms[10-12]. In fact, several studies of depression secondary to chronic medical diseases or neurological diseases have shown particular patterns of cerebral blood flow and metabolism can be implicated in the anterior cingulate, paralimbic areas, parietal, and temporal areas[13-15].

Among the various functional imaging modalities and analytic methods used for assessing brain activity and function, the atlas-based volume of interest (VOI) statistical probabilistic anatomical map (SPAM) is used to obtain regional counts from the spatially normalized individual brain images for translation to the standardized brain templates[16-20]. This multifunctional imaging-and-analysis technique modality serves many purposes, including the diagnosis and quantification of temporal lobe epilepsy and the classification of disease prognosis[16-18]. Also, post-surgical hemodynamic changes could be quantified in cerebrovascular diseases[19-20]. Moreover, a 2007 study by Choi *et al* [21] demonstrated that quantitative brain perfusion single photon emission computed tomography (SPECT) using SPAM can help in evaluating subcortical aphasia in a striatocapsular infarction because it provides functional information that cannot be obtained by morphologic imaging such as magnetic resonance imaging.

We hypothesized that the probabilistic brain atlas could be useful in evaluating depressive-mood disease severity of pre-dialytc chronic kidney disease patients. Therefore, we adapted SPAM to Technetium 99m (Tc-99m) ethyl cysteinate dimer brain SPECT images of depressive end-stage renal disease patients to investigate the relationship between separate symptom clusters, disease severity, and cerebral blood flow. Also, patients' Hamilton Depression Rating Scale (HDRS) items were grouped into three separate factors on the basis of the clustering described by Fleck *et al* [22], and analyses were performed to confirm the presence of the relationships between regional cerebral perfusion and symptom clusters of depressive mood and to quantify depressive mood-related lesions in end-stage renal disease patients.

## RESULTS

### Quantitative analysis and characteristics of patients and controls

All 27 end-stage renal disease patients and 25 controls were included in the final analysis. Baseline data of all subjects are shown in Table 1.

### Correlation of SPAM results with symptom clusters

In the statistical software program used in this study, we performed a "create correlation table" option to obtain statistically significant VOIs between SPAM results and to separate symptom cluster scores evaluated by HDRS in end-stage renal disease patients. We found

depression to be significantly negatively correlated with SPAM results from the left amygdala ($r = -0.429$ 8, $P = 0.025$ 3). The insomnia factor was significantly negatively correlated with SPAM results from the left amygdale ($r = -0.461$ 4, $P = 0.015$ 4), right superior frontal gyrus ($r = -0.381$ 7, $P = 0.049$ 5), right middle frontal gyrus ($r = -0.412$ 5, $P = 0.032$ 5), and left middle frontal gyrus ($r = -0.413$ 9, $P = 0.031$ 8). The anxiety and psychomotor factor was positively correlated with SPAM results from the cerebellar vermis ($r = 0.408$ 6, $P = 0.034$ 3) and negatively correlated with SPAM results from the left globus pallidus ($r = -0.418$ 1, $P = 0.03$), right inferior frontal gyrus ($r = -0.401$ 0, $P = 0.038$ 2), both temporal poles (right: $r = -0.446$ 5, $P = 0.019$ 6; left: $r = -0.383$ 5, $P = 0.048$ 3), and left parahippocampus ($r = -0.439$ 7, $P = 0.021$ 7). The details are shown in Table 2.

### Correlation of SPAM results with disease severity of depression

The total HDRS score of end-stage renal disease patients was negatively correlated with SPAM results

from the left amygdala ($r = -0.489$ 6; 95% confidence interval (*CI*): $-0.733$ 2 to $-0.134$ 6; $P = 0.009$ 5) and right inferior frontal gyrus ($r = -0.385$ 6; 95% *CI*: $-0.667$ 8 to $-0.000$ 6; $P = 0.047$).

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**Table 1   Characteristics of ESRD patients and controls**

| Characteristics | ESRD patients | Controls | $P$ |
|---|---|---|---|
| Age (year) | 51.9±14.4 | 50.0±11.8 | 0.630 9 |
| Male/female (*n*) | 16/11 | 13/12 | 0.804 8 |
| ESRD cause (*n*) | | | |
|   HT | 10 | – | |
|   DM | 12 | – | |
|   GN | 2 | – | |
| GFR (mL/min/1.73 m$^2$) | 9.1±4.8 | 113.2±12.6 | < 0.001 |
| HDRS | 16.6±7.2 | | |
|   Depressive factor | 6.0±2.9 | – | |
|   Insomnia factor | 2.4±2.3 | – | |
|   Anxiety and psychomotor factor | 3.1±1.3 | – | |

Measurement values are expressed as mean ± SD. ESRD: End-stage renal disease; HT: hypertension; DM: diabetes mellitus; GN: glomerulonephritis; GFR: glomerular filtration rate; HDRS: Hamilton Depression Rating Scale. Fisher's exact test was used.

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**Table 2   Correlation of Abbreviations results with symptom factors in end-stage renal disease patients**

| Factor | Side | Brain region | 95% *CI* | $r$ | $P$ |
|---|---|---|---|---|---|
| Depression | Left | Amygdala | –0.696 1 to –0.059 4 | –0.429 8 | 0.025 3 |
| Insomnia | Left | Amygdala | –0.715 9 to –0.098 7 | –0.461 4 | 0.015 4 |
| | Right | Superior frontal gyrus | –0.665 2 to –0.001 9 | –0.381 7 | 0.049 5 |
| | Right | Middle frontal gyrus | –0.685 1 to –0.038 4 | –0.412 5 | 0.032 5 |
| | Left | Middle frontal gyrus | –0.686 0 to –0.040 2 | –0.413 9 | 0.031 8 |
| Anxiety & psychomotor | | Cerebellar vermis | 0.033 8 to 0.682 6 | 0.408 6 | 0.034 3 |
| | Left | Globus pallidus | –0.688 7 to –0.045 2 | –0.418 1 | 0.03 |
| | Right | Inferior frontal gyrus | –0.677 7 to –0.024 6 | –0.401 0 | 0.038 2 |
| | Right | Temporal pole | –0.706 6 to –0.080 | –0.446 5 | 0.019 6 |
| | Left | Temporal pole | –0.666 4 to –0.000 4 | –0.383 5 | 0.048 3 |
| | Left | Parahippocampus | –0.702 4 to –0.071 6 | –0.439 7 | 0.021 7 |

Correlation was assessed by Pearson correlation analysis. *CI*: Confidence interval.

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### Comparison of asymmetric index (ASI) detected by SPECT between end-stage renal disease patients and normal controls

Table 3 and Figure 1 demonstrate the differences of ASI of affected cerebral structures between end-stage renal disease patients and normal controls. The affected side of the brain structure showed statistically significant lower values of ASI in end-stage renal disease patients compared to normal controls, with the exception of the inferior frontal gyrus and temporal pole.

### Correlations of ASI detected by SPECT with symptom clusters and disease severity of depression

Figure 2 shows that the depression severity of end-stage renal disease patients (total scores of HDRS) was negatively correlated with ASI of the amygdala ($r =$

$-0.583$ 9; 95% *CI*: $-0.788$ 9 to $-0.262$ 1; $P = 0.001$ 4) and the superior frontal gyrus ($r = -0.427$ 5; 95% *CI*: $-0.694$ 7 to $-0.056$ 7; $P = 0.026$ 1).

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**Table 3   Comparison of asymmetric index in affected brain regions between ESRD patients and normal controls**

| Brain region | ESRD patients | Controls | $P$ |
|---|---|---|---|
| Amygdala | –0.44±8.54 | 4.92±6.37 | 0.038 4 |
| Globus pallidus | –3.82±9.12 | 1.86±7.99 | 0.034 8 |
| Superior frontal gyrus | 0.88±3.05 | 13.8±5.81 | < 0.001 |
| Inferior frontal gyrus | –6.49±6.31 | –17.0±5.66 | < 0.001 |
| Middle frontal gryus | 4.29±4.26 | 12.2±3.37 | < 0.001 |
| Temporal pole | –3.86±6.16 | –35.8±7.29 | < 0.001 |
| Parahippocampus | –1.47±5.14 | 13.4±6.23 | < 0.001 |

ESRD: End-stage renal disease. The comparison of groups was performed using the Mann-Whitney test.
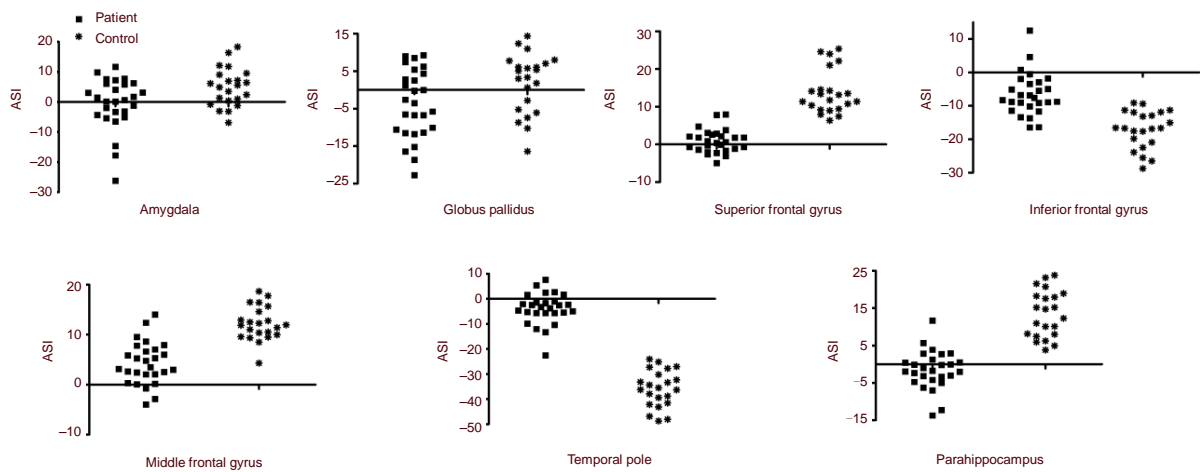
**Figure 1    Differences of asymmetric index of affected brain regions between end-stage renal disease patients and normal controls.**

The comparison of groups was performed using the Mann-Whitney test. ASI: Asymmetric index.
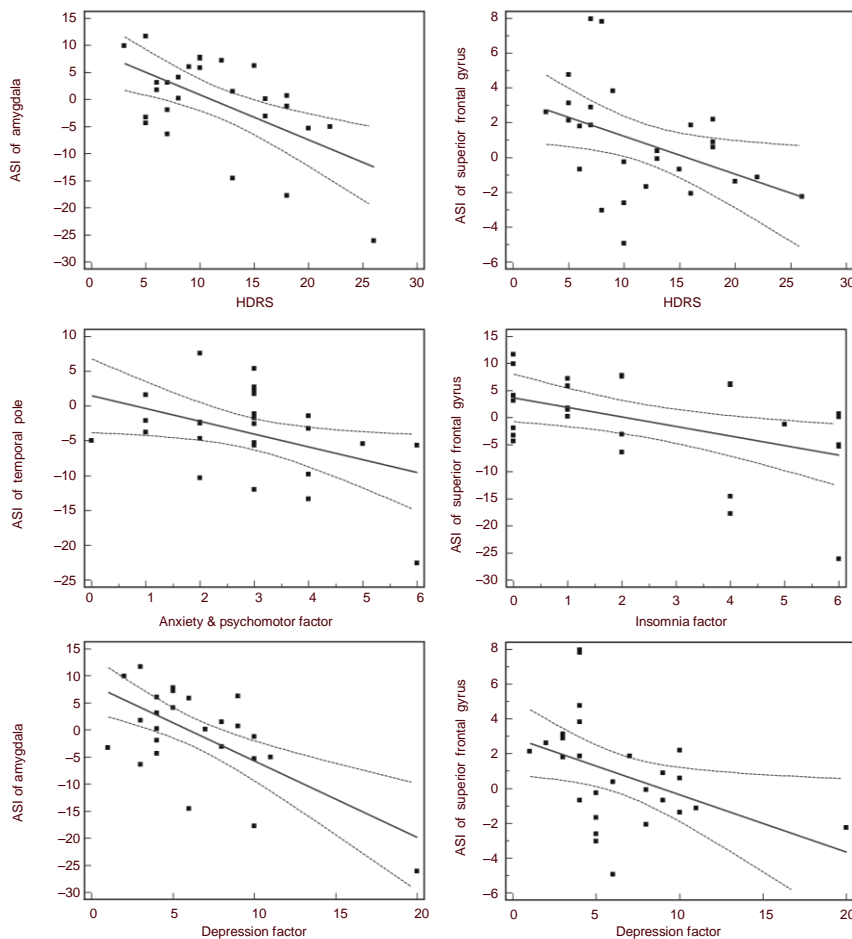


**Figure 2    Correlations between statistical probabilistic anatomical map results and severity of depression and symptom clusters of end-stage renal disease patients.**

The depression severity of end-stage renal disease patients showed negative correlations with asymmetric index (ASI) of amygdala ($r$ = –0.583 9; 95% $CI$: –0.788 9 to –0.262 1, $P$ = 0.001 4) and superior frontal gyrus ($r$ = –0.427 5; 95% $CI$: –0.694 7 to –0.056 7, $P$ = 0.026 1). $Y$ axis represents %; $X$ axis is the sum of score of the symptom factors of the Hamilton Depression Rating Scale (HDRS). Correlation was assessed by Pearson correlation analysis. $CI$: Confidence interval.

The anxiety and psychomotor factor was negatively correlated with ASI of the temporal pole ($r = -0.421\ 6$; 95% *CI*: $-0.690\ 9$ to $-0.049\ 4$; $P = 0.028\ 5$). The insomnia factor was negatively correlated with ASI of the amygdala ($r = -0.474\ 4$; 95% *CI*: $-0.723\ 9$ to $-0.115\ 1$; $P = 0.012\ 4$). The depression factor exhibited statistically significant negative correlations with ASI of the amygdala ($r = -0.639\ 5$; 95% *CI*: $-0.820\ 2$ to $-0.342\ 8$; $P = 0.000\ 3$) and the superior frontal gyrus ($r = -0.417\ 5$; 95% *CI*: $-0.688\ 3$ to $-0.044\ 5$; $P = 0.030\ 3$).

## DISCUSSION

Depression has been associated with impaired recovery and increased mortality in end-stage renal disease[23]. A 2007 study by Cukor *et al* [24] investigated the prevalence of a broad range of comorbid psychiatric illnesses in an inner-city hemodialysis population and assessed the interaction of medical and psychiatric diagnoses in association with patients' perceptions of quality of life. The study authors found that a total of 7.1% of patients had either compound depression or depression coexistent with another psychiatric disorder. Their findings of both concurrent and isolated anxiety suggested that the prevalence of psychopathology in patients with end-stage renal disease might be higher than previously expected, and that the disorders may need to be treated independently.

In the current study, the HDRS items were grouped by three factors. The first factor, depressive mood, assesses depressive mood, diurnal mood variation, retardation, and social activity. In the current study, this depression factor showed a statistically significant negative correlation with cerebral blood flow in the left amygdala. However, also in the current study, positive correlation was not found between depression and cerebral blood flow in any brain areas. Similar to our results, Perico *et al* [25] reported that the severity of depressive mood was negatively correlated with cerebral blood flow in the left amygdala, lentiform nucleus, and parahippocampal gyrus, and positively correlated with cerebral blood flow in the right postero-lateral parietal cortex. Interestingly, Graff-Guerrero *et al* [26] found that in patients with unipolar depression, the depressive mood factor was positively correlated with cerebral blood flow in the right medial frontal gyrus. Milak *et al* [27] confirmed that there did not exist a significant negative correlation between the regional cerebral glucose metabolic rate in brain areas in medication-free patients with major depressive disorder and psychic depression factor. The dorsolateral prefrontal cortex has been found to be the brain structure most frequently involved in depression. However, we could not define any

correlation between cerebral blood flow and this brain area in the current study. The characteristic diversity, imaging methods, and analytic methods may be the cause of different cerebral regions studied in various studies, including our study.

Insomnia factor, the second factor, was negatively correlated with cerebral blood flow in the left amygdala, right superior frontal gyrus, right middle frontal gyrus, and left middle frontal gyrus. Similar to our findings, Graff-Guerrero *et al* [26] revealed that middle insomnia was negatively correlated with cerebral blood flow in the left amygdale significantly and in the pons non-significantly, and that delayed insomnia was negatively correlated with cerebral blood flow in the right medial frontal gyrus. However, Milak *et al* [27] showed that insomnia factor was positively correlated with the regional cerebral glucose metabolic rate in the left amygdale, left hippocampus, and basal ganglia.

To date, the most generalized hypothesis regarding depression depends on the hyperarousal hypothesis. When falling asleep, depressed patients may experience cognitive and emotional hyperarousal states, which are presented as persistent and worrying mental activities. A functional neuroimaging study using fludeoxyglucose-18 (F-18 FDG) positron emission tomography (PET) has found that beta electroencephalographic power density during non-rapid eye movement sleep, a proposed electrophysiological marker of arousal, was negatively correlated with subjective sleep quality both in normal and depressed subjects; however, depressed patients exhibited a trend toward greater beta power than normal controls[28].

Results from the current study showed that the anxiety and psychomotor factor was positively correlated with cerebral glucose metabolism in the cerebellar vermis and negatively correlated with cerebral glucose metabolism in the left globus pallidus, right inferior frontal gyrus, both temporal poles, and left parahippocampus. Similar to the current study, a previous PET study noted a decrease in cerebral glucose metabolism in the right inferior parietal and right superior temporal regions[29]. The authors of this study assumed that their results were caused by the fact that the temporal lobe played a mediating role between affective states and behavioral responses with input from the limbic system. In addition to metabolic changes, hemodynamic alteration in panic disorder patients was also reported.

A 2006 study by Lee *et al* [30] demonstrated that there was a decreased cerebral blood flow in the temporal region of the brain in panic disorder and that this decrease may, in part, reflect the clinical severity of panic disorder. The findings of the current study suggested the hyperactivity

of two neurocircuits: afferent pathways to the amygdala and part of the startle circuit. The afferent pathways of the fear network include the nucleus of the solitary tract conveying viscerosensory information, the thalamus conveying visuospatial/auditory or cognitive information, and the hippocampus conveying fear-signifying memories[31]. A previous study has found an efferent amygdalofugal pathway to the primary startle circuit at the level of the caudal pontine reticular formation, which is relayed by the periaqueductal gray matter[32]; in addition, higher FDG uptake may have been detected in the lower dorsal pons and midbrain, which is associated with the anticipatory anxiety of panic disorder patients. A 2002 study by Sacchetti *et al* reported the relationship between cerebellar regions and panic disorder, which is a role of the cerebellum in fear-conditioning consolidation[33]. The study authors showed that interpositus nucleus functional integrity was necessary for acoustic-conditioned stimulus fear response memory formation and that vermis functional integrity was necessary for memory formation of both context- and acoustic-conditioned stimulus fear responses. Similar results were reported in a 2005 work by Sakai *et al* [34]. In that study, panic disorder patients showed appreciably high-state anxiety before scanning, and exhibited significantly higher levels of glucose uptake in the bilateral amygdala, hippocampus, and thalamus, and in the midbrain, caudal pons, medulla, and cerebellum than controls.

The overall severity of depression in the current study was negatively correlated with SPAM results from the left amygdala and right inferior frontal gyrus. According to Milak *et al* [27], overall depression severity showed a positive correlation with the regional cerebral glucose metabolic rate in part of the limbic system, the prefrontal and temporal cortices, part of the inferior parietal cortex, the thalamus, the basal ganglia, and the midbrain. However, the study authors could not find any negative correlation of the overall depression score with the regional cerebral glucose metabolic rate. The severity of depression has been found to be positively correlated with cerebral glucose metabolism and blood flow in various brain regions, including the frontal and anterior cingulated cortices, dorsolateral prefrontal cortices, temporal lobe, and hippocampus[35-39]. Other studies have reported no correlation between the severity of depression and cerebral blood flow and glucose metabolism[40-41].

A potential limitation of the current study is the relatively small sample size, thus, the results from this study may not represent the depressive condition in the overall population of chronic kidney disease patients. Moreover, the strict inclusion and exclusion criteria applied to this study hampered the collection of data during a relatively

short period. In addition, the lack of follow-up brain perfusion SPECT after renal replacement treatment was the most serious drawback of this study. Further studies concerning serial changes of cerebral perfusion pattern after renal replacement therapy and the correlation with the depressive mood of chronic kidney disease patients should be performed.

In conclusion, our results demonstrated that disease severity and the extent of cerebral blood flow quantified by a probabilistic brain atlas are related to various brain areas in terms of overall depression severity and symptom factors in end-stage renal disease patients.

## SUBJECTS AND METHODS

### Design
A non-randomized, concurrent, controlled trial.

### Time and setting
This study was conducted at the Department of Internal Medicine, Pusan National University Hospital, Republic of Korea, from June 2007 to April 2008.

### Subjects
Twenty-seven patients with stages 4 and 5 end-stage renal disease were enrolled in the current study. Exclusion criteria were as follows: history of psychologic disease, neurologic disease, previous stroke or transient ischemic attack, cognitive impairment, head trauma, atypical headache, substance abuse, alcoholism, malnutrition, or electrolyte imbalance. Twenty-five healthy volunteers for routine health examination were enrolled as control subjects. Healthy volunteers were screened for neuropsychiatric and medical illnesses. Depressive mood was assessed by psychiatric interview using the HDRS[42]. Each patient was assessed for depressive mood on the enrollment date, and the assessing psychiatrist was blinded to the medical status of the patients and healthy volunteers. All end-stage renal disease patients were in an antidepressant drug-naïve state. Tc-99m ethyl cysteinate dimer (ECD) brain perfusion SPECT was performed prior to and on the same day as the self-assessment and psychiatric interview.

All end-stage renal disease and healthy controls voluntarily agreed to participate in this study, and written informed consent was obtained from all participants.

### Methods
#### *Assessment of clinical parameters*
To assess clinical status, we measured patients' blood urea nitrogen, creatinine, and glomerular filtration rate by the Modification of Diet in Renal Disease Study as

clinical parameters[43].

### Neuropsychiatric assessments

In short, the HDRS[42] is a 17-item scale that evaluates depressive mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. HDRS items were grouped by three factors. Higher scores signify more severe symptoms. The first factor, depressive mood (the sum of scores on items 1, 2, 7, 8, and 10 from HDRS), assesses depressive mood, diurnal mood variation, retardation, and social activity. The second factor, insomnia (items 4–6), assesses difficulties in falling asleep, sleep continuity disturbances, and early morning awakening. The third factor, anxiety and psychomotor aspects (items 11, 13, and 15), assesses agitation and psychotic and somatic anxiety[22, 42]. Although investigating the symptom clusters instead of individual symptoms poses the advantage of minimizing the number of correlations examined, this clustering consequently has the risk of committing a type I error.

### Tc-99m ECD brain SPECT

All subjects, including normal healthy volunteers, lay in the supine position, with their eyes closed, in a quiet room with dimmed lights. Brain SPECT imaging was performed with a commercially available two-head gamma camera (Vertex™, Philips, Milpitas, CA, USA) with a lower energy high resolution collimator. The SPECT image was obtained 45 minutes after injection of 750 MBq of Tc-99m ECD. The energy window was set at 140 keV with a symmetrical 10% window width. A total of 128 frames were acquired in a step-and-shoot mode with intervals of 3° for 15 seconds per step. The images (matrix 128 × 128) were reconstructed with the filtered back-projection method using a Butterworth filter. All images were corrected for attenuation using Chang's method[44].

### SPAM analysis

SPAM images of the Montreal Neurological Institute were used to objectively calculate the brain SPECT counts. SPAM images consist of 98 VOIs including bilateral cortical gyri, and each image consists of the probability from 0 to 1, which belongs to a specific region. Tc-99m ECD brain SPECT images were counted and spatially normalized by a 12-parameter affine (linear) transformation to the ICBM SPECT template provided in statistical parametric mapping (SPM2 software). The counts from normalized SPECT images were multiplied by the probability from 98 VOIs of SPAM using a program developed with Matlab (Mathworks Inc., Natick, MA, USA). The SPAM probability-weighted mean counts were calculated by dividing the probability-weighted sum of all voxels in the VOI by the sum of the probability sum

of the VOI and the number of voxels. With this multiplication of normalized SPECT and SPAM, the probability-weighted counts were obtained for all VOIs. As a result, 98 VOIs, including bilateral cortical gyri segmented by SPAM, were overlaid on the patient's spatially normalized SPECT. ASI of the specific brain regions was acquired using the following equation: ASI (%) = $(SPAM_A - SPAM_{NA}) \times 200/(SPAM_A + SPAM_{NA})$, where $SPAM_A$ indicates SPAM probability-weighted mean counts of affected VOIs; $SPAM_{NA}$ indicates SPAM probability-weighted mean counts of contralateral non-affected VOIs.

If bilateral hemispheric brain cortical structures were affected, the right hemispheric structure was considered as $SPAM_A$ for the calculation of ASI.

### Statistical analysis

All continuous variables were expressed as mean ± SD. Comparison of groups was performed using the Mann-Whitney test, and Fisher's exact test (MedCalc® version 8.1, Mariakerke, Belgium), as appropriate. Correlation between SPAM results and HDRS score and symptom factors was assessed by Pearson correlation analysis.

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