# Regional Cortical Thickness and Subcortical Volume Changes Are Associated with Cognitive Impairments in the Drug-Naive Patients with Late-Onset Depression

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Previous studies have shown an association between late-onset depression (LOD) and cognitive impairment in older adults. However, the neural correlates of this relationship are not yet clear. The aim of this study was to investigate the differences in both cortical thickness and subcortical volumes between drug-naive LOD patients and healthy controls and explore the relationship between LOD and cognitive impairments. A total of 48 elderly, drug-naive patients with LOD and 47 group-matched healthy control subjects underwent 3T MRI scanning, and the cortical thickness was compared between the groups in multiple locations, across the continuous cortical surface. The subcortical volumes were also compared on a structure-by-structure basis. Subjects with LOD exhibited significantly decreased cortical thickness in the rostral anterior cingulate cortex, the medial orbitofrontal cortex, dorsolateral prefrontal cortex, the superior and middle temporal cortex, and the posterior cingulate cortex when compared with healthy subjects (all $p < 0.05$, false discovery rate corrected). Reduced volumes of the right hippocampus was also observed in LOD patients when compared with healthy controls ($p < 0.001$). There were significant correlations between memory functions and cortical thickness of medial temporal, isthmus cingulate, and precuneus ($p < 0.001$). This study was the first study to explore the relationships between the cortical thickness/subcortical volumes and cognitive impairments of drug-naive patients with LOD. These structural changes might explain the neurobiological mechanism of LOD as a risk factor of dementia.

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**Keywords:** late-onset depression; cortical thickness; subcortical volumes

## INTRODUCTION

Depression can be a significant health-care risk for older adults and a major cause of disability (Crocco et al, 2010).

In a subset of elderly depression, late-onset depression (LOD), of which the first episode occurs later in life, exhibits certain unique clinical features (Alexopoulos et al, 1988; Krishnan et al, 1995, 1997; Schweitzer et al, 2002); thus, the LOD patients are less likely to have psychiatric comorbidity or a family history of depression when compared with early-onset depression subgroups (Brown

et al, 1984; Krishnan et al, 1997). On the other hand, the LOD patients are more likely to have associated medical comorbidity (Alexopoulos et al, 1997; Emery and Oxman, 1992; Krishnan, 2002; Sheline, 2003), greater cognitive deficits, and increased risk of developing dementia (Salloway et al, 1996; Schweitzer et al, 2002). Furthermore, individuals with amnestic mild cognitive impairment (MCI) with depressive symptoms show increased propensity for Alzheimer's disease (AD), especially when they are also depressed (Apostolova and Cummings, 2008; Modrego and Ferrndez, 2004). In this regard, there might be an association between LOD and dementia, as previously shown in the literature (Schweitzer et al, 2002). However, the neural correlates of this relationship are still poorly understood.

To date, several morphometric analyses measured the gray matter volume or the density difference in the LOD using manually delineating region-of-interest (ROI) methods,

voxel-based morphometry (VBM), and the cortical pattern-matching method (Ballmaier *et al*, 2004a, 2008; Egger *et al*, 2008; Hwang *et al*, 2010; Janssen *et al*, 2007; Ries *et al*, 2009). Although they suggested that patients with LOD showed gray matter volume reductions in the frontal, temporal, and parietal regions and in the subcortical structures when compared with the healthy controls, the results were sometimes rather inconsistent. These might be attributable to the differences in the medication status, comorbid vascular diseases, small sample size, analysis methods, and illness chronicity. Moreover, most of the studies did not use the comprehensive neuropsychological battery of test; therefore, it has been hard to investigate the precise relationship between LOD and cognitive impairments.

In addition to the previous whole-brain voxel-wise analysis, other automated techniques have been developed to estimate the cortical thickness in MRI scans (Fischl and Dale, 2000; Lerch *et al*, 2005). These methods aim to identify the difference in width of the cortical gray matter on the surface of the brain, without *a priori* consumption. A previous study suggested that the cortical thickness measurement can be used to selectively investigate atrophy, whereas VBM provides a mixed measure of the cortical gray matter, including the cortical surface area or cortical folding, as well as the cortical thickness (Hutton *et al*, 2009).

To our best knowledge, there have been no studies to explore cortical thickness change in the LOD. Although only one study has tried to investigate the cortical thickness of elderly depression with early onset, the results showed no difference of cortical thickness between patients with late-life depression and the controls (Koolschijn *et al*, 2010). It has been suggested that this might be attributable to the relatively small sample size ($n = 28$ of elderly depression), moderate depressive symptoms, only female subjects, lack of information on the subjects, and medication effects. Hence, we tried to explore the cortical thickness and subcortical volumes of drug-naive LOD patients in a relatively larger sample to overcome the aforementioned problems in the cortical thickness measurement of depression. In addition, we tried to investigate the relationships between the cortical thickness and cognitive impairments of the LOD using a comprehensive neuropsychological battery. Throughout these, we sought the distinctive neural correlates of the LOD with cognitive impairments and their clinical implications. Several previous neuroimaging studies have also suggested the structural abnormalities in the fronto-striatal-limbic area of the patients with depressive disorders (Koolschijn *et al*, 2009; Savitz and Drevets, 2009). Therefore, we hypothesized that both the cortical thickness and the subcortical volumes of fronto-striatal-limbic structures might be reduced and show distinctive correlation patterns with the neuropsychological performances in LOD compared with healthy controls.

## SUBJECTS AND METHODS

### Subjects

In this study, 48 patients with a lifetime diagnosis of a major depressive disorder were included. They were recruited through the outpatient psychogeriatric clinic of St Vincent Hospital located at Suwon, South Korea, from October 2009 to October 2010.

The inclusion criteria of the patient group were as follows: (1) patients aged $>60$ years; (2) DSM-IV TR diagnosis of major depressive disorder established with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan *et al*, 1998); (3) the first episode of major depression after the age of 60 years; (4) total score of $>10$ on the 17-item Hamilton Depression Rating Scale (HAM-D$_{17}$) (Hamilton, 1967); (5) the Korean version of the Mini-Mental State Examination (MMSE) score of $>26$ (Park and Kwon, 1990); and (6) global Clinical Dementia Rating score of 0 (Morris, 1993).

The exclusion criteria for the patient group were as follows: (1) patients with a presumptive diagnosis of dementia and other neurological or medical conditions that diminish the cognitive function (eg, hypothyroidism); (2) a history of other psychiatric disorders (eg, schizophrenia, delusional disorder, substance abuse); (3) unstable medical conditions (eg, poorly controlled hypertension, angina, or diabetes); (4) any clinically relevant abnormal electrocardiograms or laboratory findings or brain MRI findings (eg, serious deep white matter hyper intensities, lacuna infarction, or brain tumors), and (5) patients taking any psychotropic medications (eg, antidepressant, benzodiazepines, and antipsychotics).

Subjects were screened with a self-report health questionnaire that reviewed both the demographic data and the medical history. The depression duration was assessed in an interview by using the life-chart methodology. The depression severity at the time of the scan was measured with the HAM-D$_{17}$. The cognitive functions of all the subjects were assessed with the Korean version of Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K), including Verbal Fluency (VF), 15-item Boston Naming Test (BNT), MMSE, Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), Constructional Praxis (CP), and Constructional Recall (CR) (Lee *et al*, 2002). In addition, the Stroop Word-Color Interference test was administered for the measurement of executive functioning (Stroop, 1935). All clinical measurements were carried out on the day of the MRI scanning.

Through advertisement in the local newspaper, 47 healthy control participants were recruited within the community. Control subjects were matched to the patients on age, handedness, and level of education. Furthermore, control subjects were given the same self-report health questionnaire as the patients, thus enabling matching on health status. Exclusion criteria were similar to the patient group, with the addition of excluding those with any current or past Axis I psychiatric diagnosis, as established by the MINI and medication use. A clinical neuroradiologist (WSJ) examined the brain MRIs of all the subjects; no gross abnormalities were reported in any participant and showed normal-appearing white matter (Huang *et al*, 2007). All subjects were right handed and nonsmokers with no history of smoking. None of the subjects had any life-time history of taking any psychotropic medication, which was verified during an interview with each patient and members of his/her family. In addition, no subjects had any history of psychiatric or neurologic treatment, which was verified by thorough review of the medical records

of the subjects. The psychometric evaluations and the clinical diagnosis were performed by two board-certified psychiatrists (HKL and CUL).

The study was conducted in accordance with the ethical and safety guidelines set forth by the institutional review board of the Catholic University of Korea. Written consent was obtained from all subjects participating in the study.

## MRI Acquisition and Preprocessing

All participants underwent MRI scans on a 3-Tesla whole body scanner equipped with an 8-channel phased-array head coil (Verio, Siemens, Erlangen, Germany). The scanning parameters of the T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 2.5 ms; TR = 1900 ms; inversion time (TI) = 900 ms; flip angle (FA) = 9°; FOV = $250 \times 250$ mm; matrix = $256 \times 256$; voxel size = $1.0 \times 1.0 \times 1.0$ mm$^3$.

For cortical reconstruction and volumetric segmentation of the whole brain, Freesurfer image analysis suite (version 5.0, http://surfer.nmr.mgh.harvard.edu), which is documented and freely available online, was used. The technical details of these procedures have been described in previous publications (Dale et al, 1999; Fischl and Dale, 2000). Briefly, the processing stream includes a Talairach transform of each subject's native brain, removal of the nonbrain tissue, and segmentation of the gray matter/white matter (GM/WM) tissue. The cortical surface of each hemisphere was inflated to an average spherical surface to locate both the pial surface and the GM/WM boundary. The entire cortex of each subject was visually inspected, and any topological defects were corrected manually, blind to the subject's identity. The cortical thickness was computed as the shortest distance between the pial surface and the GM/WM boundary at each point across the cortical mantle. The global mean cortical thickness for each subject was computed by averaging the cortical thickness at each vertex, right and left hemispheres separately, and was used in the statistical analyses. The regional thickness value at each vertex for each subject was mapped to the surface of an average brain template allowing visualization of data across the entire cortical surface (described at http://surfer.nmr.mgh.harvard.edu/fswiki/FsAverage). In addition, the entire cerebral cortex was parcellated into 34 regions (Desikan et al, 2006; Fischl et al, 2004), and a variety of surface-based data, including maps of cortical volume and surface area as well as curvature and sulcal depth, were created. Data were resampled for all subjects onto a common spherical coordinate system (Fischl et al, 1999). The cortical map of each subject was smoothed with a Gaussian kernel of 10-mm full width at half-maximum for the entire cortex analyses. The subcortical volumes were obtained from the automated procedure for volumetric measures of the brain structures implemented in Freesurfer. In all, 27 volumetric measures were investigated and extracted seven subcortical structures (white matter, caudate, thalamus, pallidum, putamen, hippocampus, and amygdala) from each hemisphere. The reliability studies on the measuring cortical thickness and subcortical volumes reported that within-scanner variabilities of cortical thickness and subcortical volume measurements using Freesurfer were estimated to be < 0.03 mm and 4.3%, respectively (Han et al, 2006; Jovicich et al, 2009).

## Statistical Analyses

Statistical analyses for demographic data (Table 1) were performed with the Statistical Package for Social Sciences software (SPSS, version 12.0, Chicago, IL). Assumptions for normality were tested for all continuous variables. Normality was tested using the Kolmogorov–Smirnov test. All variables were normally distributed. The independent $t$-test and the $\chi^2$ test were used to assess potential differences between the LOD groups and healthy control groups for all demographic variables. All statistical analyses had a two-tailed $\alpha$ level of < 0.05 for defining statistical significance.

The general linear model (GLM) was implemented at each vertex in the whole brain to identify the brain regions in which LOD patients showed significant differences in cortical thickness relative to controls, using the FreeSurfer's mri_glmfit (described at http://surfer.nmr.mgh.harvard.edu/fswiki/mri_glmfit). The correlation analyses between regional cortical thickness/subcortical volumes and several clinical outcome measures including the HAM-D$_{17}$ scores, CERAD-K scores, Stroop Word-Color Interference test scores, and duration of illness were also conducted. In particular, vertex-wise GLM analyses were performed in the control and LOD groups independently to explore the brain regions that showed significant correlations between cortical thickness and several clinical outcome measures in both controls and LOD patients, using mri_glmfit. The interactions between diagnosis and several clinical outcomes were also examined to compare the differences in regression slopes of the clinical outcome measures between both groups. The effects of age, education, total intracranial volume (TIV), and gender were regressed out in these models. For further investigation of the effect of age on cortical thickness, we conducted regression analysis between the cortical thickness of entire cortex and age in all subjects, the LOD group and the control group, respectively. In addition, we also compared the regression patterns of age and cortical thickness between the LOD group and the control group.

All analyses were performed for the right and left hemispheres separately. The threshold was set at $p < 0.05$ (false discovery rate (FDR)) to resolve the problem of multiple comparisons (Genovese et al, 2002).

The seven subcortical structure volumes (ie, total white matter volumes, thalamus, caudate nucleus, putamen, pallidum, hippocampus, and amygdala) were imported into the SPSS 12.0 software for statistical analyses. To assess the main effects of diagnosis (LOD vs control) on the volume of subcortical structures, we used analysis of covariance (ANCOVA) with TIV, education, gender, and age as nuisance variables. In addition, regression analyses were performed to determine the contribution of clinical variables (HAM-D$_{17}$ scores, CERAD-K scores, Stroop Word-Color Interference test scores, and duration of illness) to subcortical structural volumes. For further investigation of the effect of age on subcortical volumes, we conducted the regression analysis between the subcortical volumes and age in all subjects, the LOD group and the control group,

**Table 1** Demographic and Clinical Characteristics of Study Participants

| | Control group (N = 47) | LOD group (N = 48) | P-value |
|---|---|---|---|
| Age (years ± SD) | 70.7 ± 4.37 | 71.8 ± 4.8 | NS |
| Education (years ± SD) | 9.2 ± 4.8 | 9.3 ± 4.2 | NS |
| Sex (M/F) | 9/38 | 12/36 | NS |
| Duration of illness (years ± SD) | 0 | 1.3 ± 0.5 | <0.0001 |
| HAM-D$_{17}$ total score (SD) | 1.9 ± 1.9 | 18.9 ± 6.5 | <0.0001 |
| | | | |
| *CERAD-K battery (SD)* | | | |
| VF | 13.3 ± 2.9 | 12.3 ± 3.7 | NS |
| BNT | 11.3 ± 2.1 | 9.3 ± 2.4 | <0.0001 |
| MMSE | 28.1 ± 11. | 27.1 ± 1.0 | 0.001 |
| WLM | 18.2 ± 3.5 | 14.6 ± 4.0 | <0.0001 |
| CP | 9.4 ± 1.5 | 8.1 ± 1.9 | NS |
| WLR | 6.4 ± 1.9 | 4.3 ± 1.8 | <0.0001 |
| WLRc | 9.3 ± 1.0 | 8.1 ± 1.9 | <0.0001 |
| CR | 6.7 ± 2.9 | 4.8 ± 3.0 | 0.003 |
| Stroop test reaction time (seconds ± SD) | 30.2 ± 5.7 | 42.1 ± 16.8 | 0.003 |
| Stroop test error (SD) | 1.5 ± 1.4 | 2.5 ± 2.6 | NS |
| Hypertension[a], n (%) | 5 (10.6) | 6 (12.5) | NS |
| Diabetes[b], n (%) | 3 (6.4) | 2 (4.1) | NS |
| Dyslipidemia[c], n (%) | 2 (4.1) | 1 (2.1) | NS |
| Stroke or TIA, n (%) | 0 | 0 | NS |
| History of heart disease, n (%) | 0 | 0 | NS |
| Current smokers, n (%) | 0 | 0 | NS |
| History of smoking, n (%) | 0 | 0 | NS |
| Antihypertensive agents, n (%) | 5 (10.6) | 6 (12.5) | NS |
| Hypoglycemic agents, n (%) | 3 (6.4) | 1 (2.1) | NS |
| Lipid-lowering agents, n (%) | 2 (4.1) | 1 (2.1) | NS |
| Body mass index (kg/m$^2$ ± SD) | 24.2 ± 3.9 | 23.7 ± 4.1 | NS |
| Systolic blood pressure (mm Hg ± SD) | 128.2 ± 7.3 | 127.5 ± 8.1 | NS |
| Diastolic blood pressure (mm Hg ± SD) | 83.4 ± 8.7 | 82.3 ± 7.4 | NS |
| Total cholesterol (mg/dl ± SD) | 170.8 ± 23.4 | 169.9 ± 25.1 | NS |
| High-density lipoprotein (mg/dl ± SD) | 58.5 ± 13.2 | 59.7 ± 12.5 | NS |
| Triglycerides (mg/dl ± SD) | 103.2 ± 14.9 | 104.3 ± 13.7 | NS |
| Glucose (mg/dl ± SD) | 98.9 ± 5.7 | 97.3 ± 7.4 | NS |

Abbreviations: LOD, late-onset depression; NS, statistically not significant; HAM-D$_{17}$, 17-item Hamilton Depression Rating Scale; CERAD-K, the Korean version of Consortium to Establish a Registry for Alzheimer's Disease; VF, Verbal Fluency; BNT, 15-item Boston Naming Test; MMSE, Mini Mental Status Examination; WLM, Word List Memory; CP, Constructional Praxis; WLR, Word List Recall; WLRc, Word List Recognition; CR, Constructional Recall; TIA, transient ischemic attack.
[a]Hypertension defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Chobanian et al, 2003).
[b]Diabetes mellitus defined according to International Diabetes Federation Epidemiology Task Force Consensus Group (Alberti et al, 2005).
[c]Dyslipidemia defined according to Revised The National Cholesterol Education Program Adult Treatment Panel III criteria (NCEP ATP III) (Grundy et al, 2005.

respectively. In addition, we also compared the regression patterns of age and subcortical volumes between the LOD group and the control group. An uncorrected $p < 0.001$ (two tailed) was considered a significant threshold in the statistical difference maps. This threshold, when an *a priori* hypothesis was present, was approximately equivalent to $p < 0.05$ corrected for multiple comparisons (Ashburner et al, 2003; Lyoo et al, 2006).

## RESULTS

### Baseline Demographic Data

Table 1 shows the baseline demographic data in our different subject groups. There was no significant difference in sex, age, and education between the LOD group and the healthy control group. In addition, the degree and frequencies of the vascular risk factors such as hypertension, dyslipidemia, diabetes, obesity, and stroke were not significantly different between the two groups. However, the number of female subjects was significantly larger than the male subjects in each group ($p < 0.001$). Patients with LOD showed significantly poorer performance on BNT, MMSE, WLM, WLR, WLRc, and CR on CERAD-K neuropsychological test, and Stroop Word-Color Interference test ($p < 0.05$).

### Cortical Thickness Analysis

*Cortical thickness difference between LOD and control.* For the global mean cortical thickness, the LOD group ($n = 48$) showed a significant reduction in both hemispheres when compared with healthy controls ($n = 47$; Table 2). A group comparison analysis of the regional cortical thickness between the LOD and the control group showed a significant reduction in the cortical thickness of the LOD group in the left medial orbitofrontal, the dorsolateral prefrontal (DLPFC), pars triangularis, rostral anterior cingulate, superior temporal, middle temporal, precentral, postcentral, lingual, superior parietal, paracentral gyrus and right postcentral, DLPFC, pars opercularis, rostral middle frontal, precuneus, and isthmus cingulate as compared with the control group ($p < 0.05$ FDR corrected, Figure 1 and Table 3). No significant cortical thickness reduction was observed in the control group when compared with the LOD group. In addition, there have been no regional cortical thickness differences between male and female subjects in each group.

*Correlation analyses between the cortical thickness and clinical outcomes.* In the correlation analysis of the cortical thickness of the LOD group with the HAM-D$_{17}$ total scores, we found a significant negative correlation with the left rostral anterior cingulate cortex ($p < 0.05$ FDR corrected, Figure 2). There were no significant correlations between the duration of the illness and the cortical thickness of the LOD group. The WLM score in the LOD group revealed a significant positive correlation with the cortical thickness of the left superior temporal, precuneus, and insula and the right precuneus, inferior temporal, and insula ($p < 0.05$ FDR corrected and Supplementary Table S1). The WLR score in the LOD group revealed a significant positive correlation with the left fusiform, entorhinal, insula, precuneus, precentral and the right isthmus cingulate, insula, supramarginal, inferior parietal, and precuneus ($p < 0.05$ FDR corrected, Figure 2 and Supplementary Table S1). The

Stroop Word-Color Interference test score of the LOD group also displayed a significant negative correlation with the right DLPFC (pars opercularis), superior frontal, precentral, precuneus, medial orbitofrontal, rostral anterior cingulate, rostral middle frontal area, and the left insula ($p < 0.05$ FDR corrected, Figure 2 and Supplementary Table S1). There have been no significant correlations between the VF, BNT, MMSE, CP, WLRc, and CR scores and the cortical thickness of the LOD group under the FDR $< 0.05$ conditions. On the other hand, no significant correlations were observed between the neuropsychological test scores and HAM-D$_{17}$ total scores and cortical thickness in the control group. Age was not correlated significantly with the cortical thickness or cognitive functions in all subjects, the LOD group and the control group, respectively ($p < 0.05$ FDR corrected). Furthermore, age–cortical thickness regression patterns were not significantly different between

the LOD group and the control group ($p < 0.05$ FDR corrected).

### Subcortical Volume Analyses

For the mean volumes of the total white matter of both hemispheres, no significant difference between the LOD group and the control group was observed (Table 4). There were significant volume reductions in the right hippocampus in the LOD group as compared with the control group ($p = 0.001$, Table 4). In addition, there have been no total intracranial volume and subcortical volume differences between male and female subjects in each group. In the correlation analysis, the VF score of the LOD group was significantly correlated with the right putamen ($r = 0.513$, $p = 0.001$) and the hippocampus (Figure 3, $r = 0.558$, $p < 0.0001$). We could not find any significant correlations between the score of duration of the illness, HAM-D$_{17}$ BNT, MMSE, WLM, WLR, WLRc, CP, CR, and Stroop Word-Color Interference test score, and subcortical structural volumes in the LOD group. In addition, no significant correlations were observed between the neuropsychological test scores and HAM-D$_{17}$ total scores and subcortical volumes in the control group. Age was not correlated significantly with the subcortical volumes in all subjects, the LOD group and the control group, respectively. Furthermore, age–subcortical volumes regression patterns were not significantly different between the LOD group and the control group.

### DISCUSSION

To our best knowledge, this is the first study to explore the cortical thinning pattern and the subcortical volume

**Table 2** Statistics of Mean Cortical Thickness within Each Hemisphere

| | Cortical thickness (mm) | | | | | |
|---|---|---|---|---|---|---|
| | Control group (N = 47) | | LOD group (N = 48) | | Statistics | |
| | Mean | SD | Mean | SD | t | p |
| Right hemisphere | 2.50 | 0.10 | 2.40 | 0.11 | 3.44 | 0.001 |
| Left hemisphere | 2.48 | 0.10 | 2.38 | 0.11 | 3.52 | 0.001 |

Abbreviation: LOD, late-onset depression.
Uncorrected $p < 0.001$ was considered as significant.
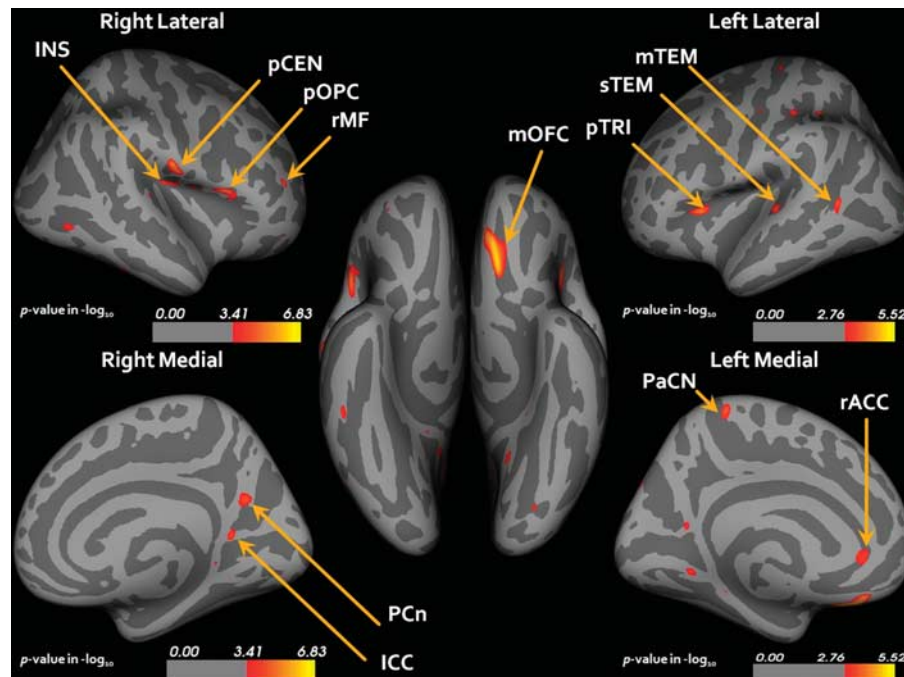


**Figure 1** Statistical maps corrected for age, education, and gender showing reduced cortical thickness in patients with LOD relative to controls ($p < 0.05$ FDR corrected). LOD, late-onset depression; FDR, false discovery rate; INS, insula; pCEN, postcentral; pOPC, pars opercularis; rMF, rostral middle frontal; mOFC, medial orbitofrontal; pTRI, pars triangularis; sTEM, superior temporal; mTEM, middle temporal; PCn, precuneus; ICC, isthmus cingulate; rACC, rostral anterior cingulate. Anatomical terms are used according to the Desikan template (Desikan et al, 2006).

**Table 3** Mean Cortical Thickness for Clusters Where a Significant Cortical Thinning Was Observed in LOD Patients Relative to Healthy Controls (FDR Corrected, $p < 0.05$)

| Region | No. of vertexes in cluster | Cluster size, (mm²) | Cortical thickness (mm, SD) | | Effect size (Cohen's d) | p |
|---|---|---|---|---|---|---|
| | | | Control group (N = 47) | LOD group (N = 48) | | |
| *Left* | | | | | | |
| Medial orbitofrontal | 445 | 196.28 | 2.64 (0.15) | 2.51 (0.17) | −0.81 | <0.00001 |
| Pars triangularis | 188 | 59.05 | 2.59 (0.16) | 2.48 (0.17) | −0.66 | <0.0001 |
| Superior temporal | 136 | 64.46 | 2.32 (0.23) | 2.17 (0.28) | −0.58 | <0.0001 |
| Lateral occipital | 96 | 84.27 | 2.20 (0.17) | 2.08 (0.20) | −0.64 | <0.0001 |
| Middle temporal | 85 | 58.16 | 3.10 (0.18) | 2.96 (0.21) | −0.72 | <0.0001 |
| Paracentral | 112 | 50.31 | 2.36 (0.17) | 2.24 (0.20) | −0.64 | <0.0001 |
| Supra marginal | 64 | 22.38 | 2.75 (0.15) | 2.68 (0.20) | −0.40 | <0.001 |
| Postcentral | 107 | 34.22 | 2.14 (0.16) | 2.05 (0.19) | −0.51 | <0.001 |
| Lingual | 67 | 29.02 | 2.86 (0.15) | 2.78 (0.20) | −0.45 | <0.001 |
| Precentral | 55 | 16.24 | 2.84 (0.20) | 2.74 (0.20) | −0.50 | <0.001 |
| Superior parietal | 76 | 42.25 | 2.40 (0.18) | 2.31 (0.20) | −0.47 | <0.001 |
| Rostral anterior cingulate | 83 | 42.72 | 2.58 (0.16) | 2.49 (0.16) | −0.56 | <0.001 |
| Precuneus | 38 | 16.30 | 2.56 (0.20) | 2.45 (0.22) | −0.52 | <0.001 |
| | | | | | | |
| *Right* | | | | | | |
| Postcentral | 265 | 107.62 | 2.61 (0.18) | 2.47 (0.16) | −0.82 | <0.0001 |
| Pars opercularis | 264 | 154.40 | 2.73 (0.14) | 2.59 (0.20) | −0.81 | <0.0001 |
| Rostral middle frontal | 42 | 29.12 | 2.66 (0.14) | 2.57 (0.15) | −0.62 | <0.001 |
| Precuneus | 134 | 72.32 | 2.46 (0.23) | 2.36 (0.18) | −0.48 | <0.001 |
| Isthmus cingulate | 71 | 35.15 | 2.67 (0.21) | 2.53 (0.27) | −0.57 | <0.001 |
| Insula | 202 | 56.99 | 2.92 (0.16) | 2.77 (0.21) | −0.80 | <0.0001 |
| Inferior temporal | 40 | 25.63 | 3.12 (0.22) | 3.00 (0.25) | −0.51 | <0.001 |

Abbreviations: LOD, late-onset depression; FDR, false discovery rate.

reduction in the drug-naive patients with LOD, relative to group-matched healthy controls. The strength of this study lies on the recruitment of relatively larger samples and drug-naive LOD patients compared with the other neuroimaging studies on LOD. Hence, we could investigate more on the subtle differences of cortical thickness/subcortical volumes between the LOD and controls, as well as the relationships between the cortical thickness/subcortical volumes and the various clinical/neuropsychological measurements, without interference of the medication effects. Indeed, there have been some suggestions that antidepressants may exert a neurotrophic effect on particular regions of the brain (Duman and Monteggia, 2006; Rocher *et al*, 2004; Stewart and Reid, 2000). Furthermore, in geriatric patients with depression, antidepressant exposure was associated with larger orbitofrontal gray matter volume as compared with medication-naive patients (Lavretsky *et al*, 2005).

## Cortical Thickness and Subcortical Volume Difference Between LOD and Control

In this study, we have found the cortical thinning and subcortical volume reduction of the fronto-striatal-limbic structures in LOD patients as compared with healthy

controls. These results were in line with the previous structural neuroimaging studies on depressive disorders, including LOD. The rostral anterior cingulate cortex is thought to be involved in assessing both emotional and motivational information and in the regulation of the emotional response (Bush *et al*, 2000). The orbitofrontal cortex dysfunction may yield the characteristic state of of depression, which shows impaired ability to interrupt perseverative melancholic thoughts and anxious responses to ordinarily nonthreatening stimuli (Ballmaier *et al*, 2004b; Ongr and Price, 2000). Deficit in the top-down inhibitory control of the DLPFC over the amygdala and sundry limbic tissue may result in chronic limbic overactivity and negative emotions (Davidson, 2002; Savitz and Drevets, 2009). Many studies reported smaller hippocampal volumes in patients with major depressive disorder as compared with healthy control subjects, which may stem from the dysfunctional hypothalamic–pituitary–adrenal (HPA) axis (MacQueen and Frodl, 2011; Vreeburg *et al*, 2009). The hippocampus plays an inhibitive role in regulating the HPA axis (Jacobson and Sapolsky, 1991), and chronic exposure to glucocorticoids with repeated depressive episodes could lead to cell death and hippocampal atrophy (Knoops *et al*, 2010; Sapolsky *et al*, 1986).
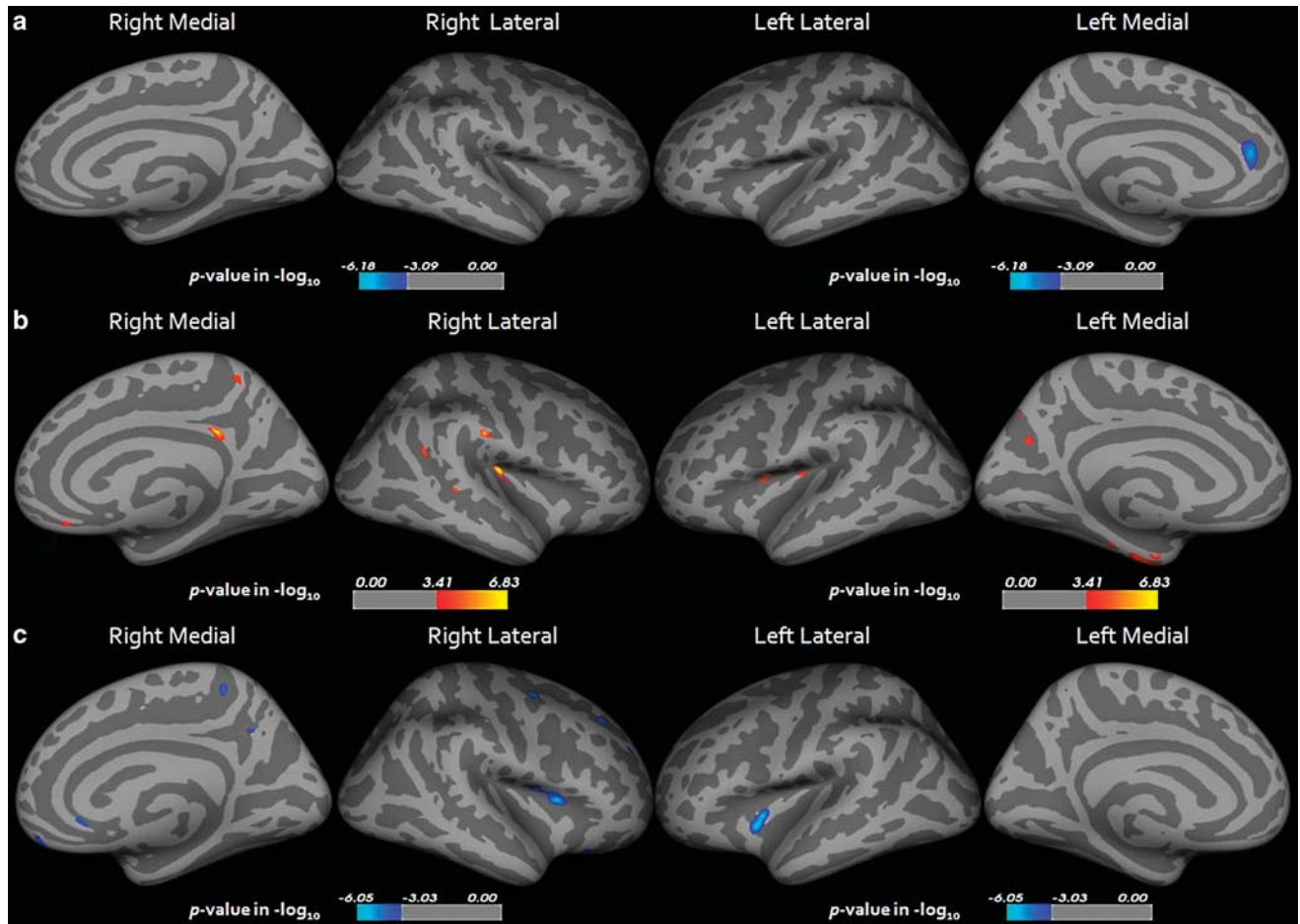
**Figure 2** Statistical maps showing the regions of cortical thickness correlated with HAM-D$_{17}$ total score (a), CERAD-K word list recall score (b), and Stroop Word-Color Interference test score (c) in the LOD group ($p < 0.05$ FDR corrected). Maps are shown for right and left hemispheres in lateral and medial views respectively, and significant regions are shown in blue (negative correlation) and red (positive correlation). LOD, late-onset depression; CERAD-K, Korean version of Consortium to Establish a Registry for Alzheimer's Disease; HAM-D$_{17}$, Hamilton Depression Rating Scale; FDR, false discovery rate.

In addition to the fronto-striatal-limbic structural abnormalities, we also found the cortical thinning of the temporo-parietal-limbic structures in LOD patients as compared with controls. Previous voxel-wise whole-brain structural neuroimaging studies have revealed reduced gray matter volumes in the temporo-parietal cortex in LOD patients, and suggested that these structural abnormalities might be the distinctive pattern of the LOD (Ballmaier *et al*, 2004a; Egger *et al*, 2008). More specifically, in this study, we found the reduced cortical thinning of the bilateral precuneus and the right posterior cingulate cortex in patients with LOD. The bulk of the previous structural neuroimaging studies have shown the precuneus and posterior cingulate structural and functional abnormalities in early AD and MCI (Fennema Notestine *et al*, 2009; McDonald *et al*, 2009; McEvoy *et al*, 2009; Mosconi, 2005). Moreover, the gray matter reductions in both the precuneus and the posterior cingulate cortex in patients with MCI were considered a predictor of the conversion to AD (Misra *et al*, 2009). Therefore, we suggest that the structural abnormalities found in these areas might explain the neurobiological mechanisms of LOD as a risk factor of dementia.

**Neurobiological Mechanisms of Brain Structural Changes in LOD**

To date, the glucocorticoid-induced fronto-striatal-limbic area dysfunction was considered the central neurobiological model of depression (Jacobson and Sapolsky, 1991; MacQueen and Frodl, 2011; Savitz and Drevets, 2009; Vreeburg *et al*, 2009). Additionally, cerebrovascular risk factors, such as hypertension, diabetes, and subcortical white matter hyperintensities, were known to play a crucial role in the physiopathology of LOD (Alexopoulos *et al*, 1988, 1997; Krishnan, 2002). In this study, we could minimize the significant effects of subcortical white matter hyperintensities in the LOD by exclusion of subjects with significant white matter hyperintensities and inclusion of subjects with normal-appearing white matter. In this regard, we might raise the possibilities of other putative mechanisms of the LOD, such as the $\beta$-amyloid- or tau protein-induced fronto-striatal-limbic disruption. A recent positron emission tomography study by Butters *et al* (2008a) demonstrated the Pittsburgh Compound B (PiB) retention in approximately one-half of 9 nondemented subjects with

**Table 4** Subcortical Volumes of Control Group and LOD Group

| Region | Subcortical volume (mm³, SD) | | Effect size (Cohen's *d*) | Percent difference | *p* |
|---|---|---|---|---|---|
| | Control group (*N* = 47) | LOD group (*N* = 48) | | | |
| *Left* | | | | | |
| White matter | 219 060.6 (21 135.9) | 215 750.2 (24 193.5) | −0.14 | 1.5% | NS |
| Caudate | 3105.1 (577.5) | 3070.1 (494.1) | −0.07 | 1.1% | NS |
| Thalamus | 6096.9 (577.5) | 5890.3 (895.9) | −0.27 | 3.4% | NS |
| Pallidum | 1616.8 (202.6) | 1530.5 (242.0) | −0.39 | 5.3% | NS |
| Putamen | 4730.7 (537.9) | 4380.7 (792.5) | −0.52 | 7.4% | NS |
| Hippocampus | 3738.2 (393.1) | 3456.4 (476.6) | −0.65 | 7.5% | NS |
| Amygdala | 1489.2 (189.2) | 1327.5 (270.8) | −0.69 | 10.8% | NS |
| *Right* | | | | | |
| White matter | 221 073.4 (21 358.1) | 217 153.3 (25 059.1) | −0.17 | 1.7% | NS |
| Caudate | 3109.5 (336.7) | 3027.8 (445.4) | −0.21 | 2.6% | NS |
| Thalamus | 6146.4 (544.5) | 5915.4 (858.9) | −0.32 | 3.7% | NS |
| Pallidum | 1462.2 (132.6) | 1385.6 (233.7) | −0.40 | 5.2% | NS |
| Putamen | 4451.5 (523.1) | 4185.0 (584.6) | −0.48 | 5.9% | NS |
| Hippocampus | 3995.4 (380.9) | 3656.3 (497.3) | −0.77 | 8.5% | 0.001 |
| Amygdala | 1583.4 (238.9) | 1433.1 (264.0) | −0.60 | 9.5% | NS |

Abbreviations: LOD, late-onset depression; NS, statistically not significant.
Uncorrected *p* < 0.001 was considered as significant.

treated depression and variable cognitive impairment, indicative of brain *β*-amyloid accumulation in cortical areas in a pattern characteristic of early AD. In addition, a postmortem study by Sweet *et al*, (2004) has confirmed the predominance of AD neuropathology among well-characterized LOD patients with varying cognitive impairment, who were followed longitudinally.

## Correlation Analyses with Clinical Outcomes and Neuropsychological Performance

In this study, the depression severity in LOD measured by the HAM-D$_{17}$ total score was significantly correlated with the rostral anterior cingulate cortex, which was in line with the result from other study (Chen *et al*, 2007). In addition, a previous volumetric study on geriatric depression revealed that patients who failed to remit following escitalopram treatment had smaller dorsal and rostral anterior cingulate gray matter volumes than patients who remitted (Gunning *et al*, 2009). However, the neural substrates associated with the severity of depression have been rather inconsistent (Savitz and Drevets, 2009); this might be attributable to the difference in the subjects, depression scales, and chronic episodes. In our study, the Stroop Color-Word Interference test score, which was measuring executive function, of LOD patients showed significant inverse correlation with the rostral anterior cingulate, orbitofrontal cortex, and DLPFC. It has been demonstrated that the executive dysfunction is characteristic of the clinical presentation of most patients with LOD (Herrmann *et al*, 2007; Murphy and Alexopoulos, 2006), it remains present even after amelioration of depressive symptoms (Alexopoulos *et al*, 2005), and may

predict the treatment response (Alexopoulos *et al*, 2005). The previous studies suggested that disruption in white matter integrity might be closely related to the executive dysfunction of LOD (Murphy and Alexopoulos, 2006). Although we showed the associations between the frontal cortical thinning and the executive functions, it is still unclear whether these associations are related to further clinical courses such as treatment response of LOD with the lack of white matter changes. Further longitudinal studies will be needed for clarification of these relationships. Through these, we will also be able to find the predictors of various clinical courses including treatment response.

In this study, we observed the VF deficits and significant positive correlations with the volumes of the putamen and the hippocampus in the LOD. A fundamental component of the CERAD VF task is the retrieval of semantically associated words from long-term memory storage (semantic fluency task). It has been recognized previously as one of the reflections of the frontal and the temporal lobe function (Baldo *et al*, 2006; Phelps *et al*, 1997). A previous study using single photon emission computed tomography (SPECT) showed the prefrontal and the hippocampal activations in depressed patients under the semantic fluency test conditions, compared with the phonemic fluency conditions (Audenaert *et al*, 2002). They suggested that depression patients might compensate for their dysfunctional prefrontal 'search' mechanisms by using more direct strategies to obtain entrance to their verbal hippocampal memory systems. In addition, significant correlations between the hippocampal volumes and semantic fluency task were observed in the patients with MCI and AD (Dos Santos *et al*, 2011; Gleissner and Elger, 2001). A previous
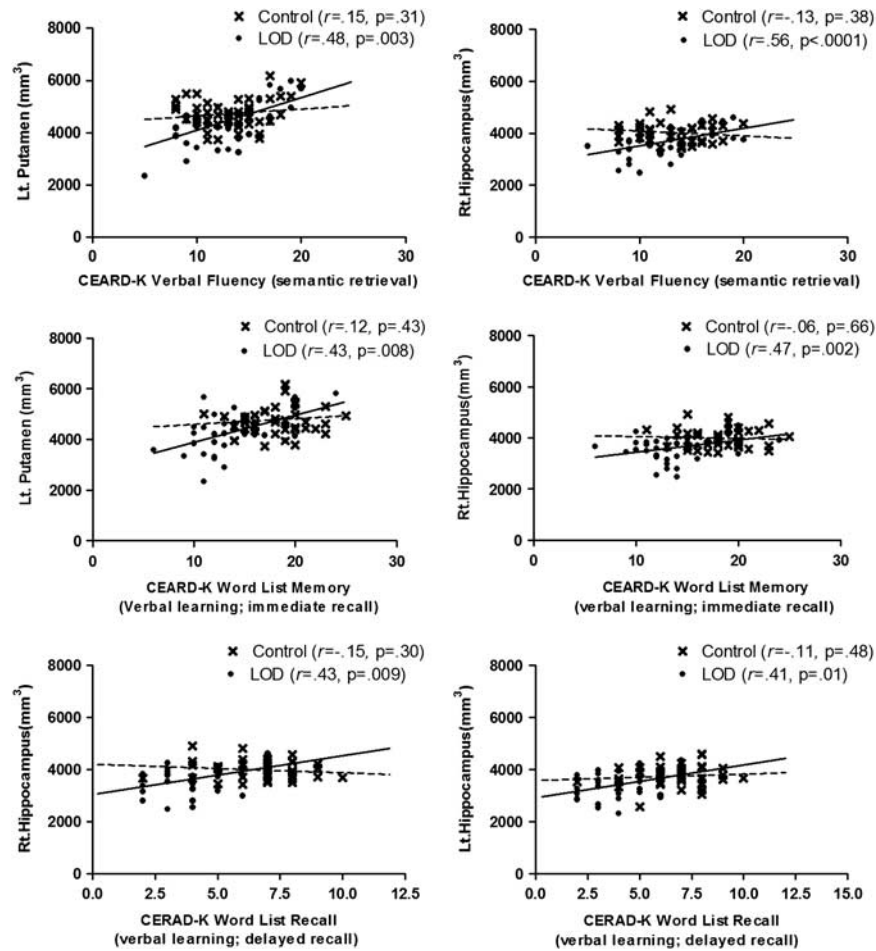
**Figure 3** Relationships between CERAD-K VF, WLM, and WLR scores, and subcortical volumes. CERAD-K, Korean version of Consortium to Establish a Registry for Alzheimer's Disease; VF, Verbal Fluency; WLM, Word List Memory; WLR, Word List Recall.

voxel-based lesion symptom mapping study on the stroke patients showed that the scores of semantic fluency task were correlated with the putamen and the insula (Baldo *et al*, 2006). Our results indicate that both the hippocampus and the putamen were also engaged in the retrieval process during the semantic fluency task in LOD. To our best knowledge, there have been no previous structural neuroimaging studies on the semantic fluency task in depression. Therefore, it is not clear whether these relationships were distinct process in LOD or not. Further replication and longitudinal studies will be needed to clarify the relationships between the VF and the striatal-limbic structures in LOD.

### Clinical Implications of Cognitive Impairments in LOD

In this study, several cognitive functions were significantly reduced in LOD patients compared with control group. Although the mean scores of several cognitive functions were within the normal range and did not reach the degree of MCI, these cognitive impairments, especially memory function impairment, might be meaningful in terms of the risk of dementia. The WLM (verbal learning; immediate recall) and WLR (verbal learning; delayed recall) scores were significantly correlated with the cortical thickness of the entorhinal cortex, the precuneus, and the isthmus

cingulate in the LOD group but not in the control group, which were in line with the previous study on the MCI (Schmidt Wilcke *et al*, 2009). A hippocampal shape analysis by Ballmaier *et al* (2008) revealed that delayed recall scores were correlated significantly with the hippocampal volumes of LOD but not in early-onset elderly depression. In this study, we extended this previous result to the structural abnormalities of the other medial temporal and posterior parietal structures, which might be a distinctive feature of LOD as compared with early-onset elderly depression. A previous VBM study by Avila *et al* (2011) suggesting direct correlation between delayed visual–verbal memory recall scores with left parahippocampal volumes in elderly depressed individuals provided support to the view that depression in elderly populations may be a risk factor for dementia. As our results showed that depression severity was not correlated with the medial temporal and posterior parietal structures, these cognitive impairments might be an independent and co-occurring process in LOD (Butters *et al*, 2008b). However, previous researchers have also proposed that fronto-striatal dysfunction might exert a significant effect on cognitive impairments of LOD (Butters *et al*, 2008b). They suggested that the amyloid burden, vascular insults, and glucocorticoid insults to the fronto-striatal circuits might be added to the total brain injury burden, lowering reserve and vulnerability to express

cognitive impairments. Further longitudinal neuroimaging studies will be needed to prove these causal relationships of cognitive impairments and depressive symptoms. Taken together, these structural abnormalities of the medial temporal, the precuneus, and the posterior cingulate in LOD might explain the neurobiological mechanisms of LOD as a risk factor of dementia. Furthermore, longitudinal studies will be needed for investigation of the effectiveness of early intervention of LOD for the prevention of dementia.

## LIMITATIONS AND CONCLUSIONS

The limitations of our study were as follows. First, the mean duration of LOD was relatively shorter in this study. Thus, we could not observe the relationship of cortical thinning/subcortical volumes with disease duration. In this regard, the results of this study might be interpreted cautiously and should not be generalized to the chronic LOD patients; a longitudinal study is needed. Second, the number of female subjects was larger than male subjects in each group. Although the total brain volumes and cortical thickness were not significantly different between the male and female subjects, further investigation of the gender effect on the cortical thickness and subcortical volumes will be needed. Finally, although we suggested the possibility of LOD with cognitive impairment as a risk factor of dementia, we should bear in mind that cognitive impairments and structural changes in LOD could be temporary and improved after effective treatments such as antidepressants and cognitive training. Indeed, previous studies showed that antidepressants increased neurogenesis in adult hippocampal neurons (Anacker *et al*, 2011; Boldrini *et al*, 2009). Although no data are available for elderly depression, antidepressant treatment is known to increase hippocampal volume in posttraumatic stress disorder (Bossini *et al*, 2007). In addition, there were also evidences suggesting increase in cortical thickness of the healthy elderly by cognitive training (Engvig *et al*, 2010). Therefore, further longitudinal structural neuroimaging studies, thorough observations of clinical courses, and precise patient stratification throughout the molecular imaging (ie, PiB), and analysis of CSF $\beta$-amyloid and tau protein will be needed for clarification of our hypothesis.

In conclusion, we showed cortical thickness and subcortical volume reductions in multiple fronto-striatal-limbic structures and various temporo-parietal-limbic structures in LOD. In addition, we also showed significant correlations between the cortical thickness of the medial temporal, the posterior cingulate, and the precuneus and the episodic memory functions in LOD. These structural changes might explain the neurobiological mechanisms of LOD as a risk factor of dementia. Cortical thinning observed in this study may be related to impairment of emotional and cognitive processing in LOD, but longitudinal studies will be necessary to confirm this hypothesis.

## DISCLOSURE

The authors declare no conflict of interest.

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