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Neuroanatomical Characteristics of Geriatric Apathy and Depression: A Magnetic Resonance Imaging Study

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Abstract

Objective—Apathy is one of the most common late-life neuropsychiatric syndromes. The objective of our study was to examine the neuroanatomical correlates of apathy in older subjects with and without geriatric major depression (MDD).

Methods—Eighty-four subjects (43 patients with MDD and 41 normal comparison subjects) underwent comprehensive neuropsychiatric examination, physical examination, and high-resolution magnetic resonance imaging (MRI) brain scans on a 1.5T GE MRI scanner. Apathy was assessed using the Apathy Evaluation Scale. MRI image analyses included cortical surface extraction, tissue segmentation, and cortical parcellation methods to measure the gray and white matter volumes in two prefrontal subregions: the anterior cingulate and orbitofrontal cortex.

Results—The depressed group had smaller orbitofrontal gray matter volumes compared to the age-matched normal comparison group. The severity of apathy was associated with the decreased gray matter volume in the right anterior cingulate gray matter volumes using partial correlation and regression analyses after controlling for age, sex, and diagnosis.

Conclusion—Apathy and depression were associated with different anatomical correlates in the prefrontal regions implicated in the regulation of cognition and emotion. Our findings offer new understanding of the neuroanatomical characteristics of apathy and depression in late life, and have broad implications for the neurobiology of behavior.

Keywords

Geriatric depression; apathy; elderly; structural MRI; orbitofrontal cortex; anterior cingulate; gray and white matter volumes

Apathy is one of the most common neuropsychiatric syndromes in the elderly that presents with decreased motivation, psychomotor retardation, and anergia.[1] Depression and apathy frequently coexist and can be misdiagnosed. Both have been linked to the function of the prefrontal and orbitofrontal cortex.[1-9] However, despite the general agreement that apathy is not a "depressive equiva-lent,"[5,9-10] its validity as a syndrome is still a matter of debate.[1,10] Apathy is defined as diminished motivation not attributable to decreased levels of consciousness, cognitive impairment, or emotional distress. Motivation denotes that aspect of behavior concerned with the initiation, direction, and intensity of goal-directed behavior.[1,7,8] Diminished motivation may affect motor (e.g., lack of initiative), cognitive

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(e.g., lack of interest), and emotional aspects of behavior (e.g., flat affect, indifference), as well as the lack of insight.[1,7,8]

Differentiating the syndromes of apathy and depression is sometimes difficult because of similarities in clinical features. For example, anhedonia, psychomotor retardation, and executive cognitive dysfunction may be a feature of both depression and apathy. During clinical interviews, however, the emotional responses of depressed patients may be more unpleasant, negative, and dysphoric, whereas apathetic patients tend to show attenuated positive and negative responses.[1] Either syndrome might require different treatment approaches. Therefore, it is important to understand the differences that underlie the pathophysiology of the two syndromes. In addition, decreased motivation may be a feature of normal aging with neurodegenerative and vascular brain changes, as well as the decline in the dopamine levels leading to decreased interest and motivation, cognitive changes, and psychomotor retardation.[11-14]

Different neuroanatomical abnormalities have been consistently identified in patients with late-life major depression. These include smaller brain volumes and larger volumes of the high-intensity lesions in the subcortical gray and white matter.[12,14] Smaller brain volumes have been reported in the prefrontal cortex[15-23] and temporal lobe structures, such as the hippocampus.[24-28] The prefrontal cortex has long been suspected to play an important role in cognitive control, regulation of mood, and motivational behavior based on neurophysiological, neurobiological, and neuroimaging as well as computational studies.[29] In the prefrontal cortex, lower volumes have been identified in the orbitofrontal cortex, anterior cingulate, and gyrus rectus subregions in patients with early-onset geriatric depression when compared with controls.[30] The clinical signs grouped under the syndrome of apathy in the context of many neuropsychiatric disorders are a common feature of prefrontal and basal ganglia lesions or dysfunctions and can therefore help to improve our understanding of the functional anatomy of the prefrontal-basal ganglia system.[31,32] Despite the growing evidence for an involvement of the prefrontal cortex in younger and older depressed patients, there have been relatively few magnetic resonance imaging (MRI) volumetric studies examining the prefrontal cortex in relation to other common neuropsychiatric syndromes, such as apathy.

The objectives of our exploratory study were to map out the relation of the frontal subregional gray and white matter volumes to apathy in older depressed patients and normal controls. Applying a locally developed MRI-based parcellation method of the prefrontal cortex, we subdivided the prefrontal cortex into the following two functionally relevant subregions: the anterior cingulate and orbitofrontal cortex.[30,33] We hypothesized that we would find a relationship between the severity of apathy and the gray and white matter volumes in the orbitofrontal and anterior cingulate cortex in subjects with major depression and age-matched controls. Our hypotheses are based on the role of these regions in inhibition and disinhibition of human behavior,[34] and reported association with apathy in patients with dementia.[35,36] Reduction in the anterior cingulate cortex volumes has been reported in association with depression in younger patients[15] and with apathy in subjects with dementia.[35,37] No studies have addressed neuroanatomical correlates of apathy in non-demented subjects with and without depression.

METHODS

Subjects

The entire sample of 84 elderly subjects (age range, 60-91 years) included: 43 patients with MDD (33 women, 34 white, mean education 14.6 ± 2.5 years, mean age 70.7 ± 7.8 years) and 41 age-matched normal controls (20 women, 32 white, mean education 15.5 ± 2.6 years,

mean age 72.2 ± 7.3 years). All patients with major depressive disorder (MDD) were recruited through local newspapers and radio advertisements and through referrals from the geriatric psychiatry ambulatory care programs at the University of California at Los Angeles (UCLA) MedicalCenter. All comparison subjects were recruited from the community through newspapers and radio advertisements.

All subjects underwent a psychiatric examination and a structured interview (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [*DSM-IV*]) to rule out current or past psychopathology. The study was performed in accordance with UCLA's policies of the Human Subject Protection Committees, and written informed consent was obtained from all subjects after the procedures had been fully explained.

All subjects underwent comprehensive neuropsychiatric, laboratory, and physical examinations, and the high-resolution MRI brain scans on a 1.5T GE MRI scanner. All depressed patients met *DSM-IV* criteria for major depressive disorder and were assessed with a structured psychiatric interview. All depressed patients had scores of 15 or greater on the 17-item Hamilton Depression Rating Scale (HAM-D; mean 17.7 ± 2.9).[38] Information on prior episodes and the age at onset, and prior treatment history was obtained from patients and family members. Depressed patients had an average of 2.6 ± 2.6 of prior episodes of depression, with mean age at onset of depression of 49.6 ± 23.1 years. Twenty depressed subjects (or 46.5%) had recurrent depression, and 26 subjects (61.9%) reported chronic course of the current episode depression lasting more than 24 months. Twenty-six (60.4%) depressed subjects were drug-naïve; other depressed subjects had a history of antidepressant treatment. All subjects were free of psychotropic drug use for at least two weeks prior to the MRI study.

Subjects received comprehensive medical and neurologic examinations and laboratory testing. None of the subjects had clinical evidence of dementia, suspected dementia, or any other brain disorder according to a review of the subjects' history and a mental status examination. The Mini-Mental Status Examination (MMSE) test was used to screen for cognitive impairment. The MMSE scores[39] were in the normal range in the major depression group as well as in the comparison group. The groups were matched by age and education. Patients were excluded if they had a history of other comorbid neuropsychiatric disorders or substance abuse.

The Apathy Evaluation Scale (AES)[8] was used to measure the overall severity of apathy (score range 18-72), as well as the estimates of several behavioral components of apathy including cognitive (i.e., level of goal—directed cognition), emotional (i.e., level of emotional responsivity), behavioral (i.e., goal-directed motor behavior), and other domains (i.e., combined insight and motivation).[1-8] The Stroke Risk Factor Prediction Chart (SRF)[40,41] of the American Heart Association was used to rate stroke risk factors including age, and systolic blood pressure, antihy-pertensive medication use, history of diabetes, smoking, previous strokes, atrial fibrillation, and left ventricular hypertrophy. The Cumulative Illness Rating Scale-Geriatric version (CIRS-G)[42] was used to rate the severity of chronic medical illness burden, including 14 organ systems.

Imaging Protocol

All subjects were studied with MRI performed on a 1.5-T Signa magnet (GE Medical Systems, Milwau-kee) that used a coronal T1-weighted spoiled gradient/recall acquisition in the steady state with the following parameters: repetition time, 20 msec; echo time, 6 msec; flip angle, 45°; 1.4-mm slice thickness without gaps; field of view, 22 cm; number of excitations, 1.5; matrix size, 256 × 192 mm; in-plane resolution, 0.859375 × 0.859375.

The details of the image analysis including masking inhomogeneity correction and segmentations on a subset of our subjects have been previously published.[30,33,43] Total intracranial volume (ICV) including sulcal and subarachnoid cerebrospinal fluid (CSF) was calculated, excluding cerebellum and brainstem. All subregional volumes were corrected by the ICV to control for the interindividual variability in brain sizes.

Anatomical Boundaries and Parcellation Procedures

The rules applied to achieve parcellation of the prefrontal lobe into seven subregions for each hemisphere was described in our prior publications.[30,33,43] Complete details of the written anatomical protocols can be found online (http://www.loni.ucla.edu/NCRR/Protocols/index.shtml). For interrater reliability, all anatomical regions were delineated on 10 randomly chosen image data sets. Intraclass correlation coefficients for the reliability of gray matter,white matter, and CSF volumes, as well as total volumes in all subregions, ranged between 0.85 and 0.92.

To describe briefly the parcellation procedure for the subregions, the anterior cingulate gyrus was traced in both sagittal and coronal slices. The anterior cingulate was defined with boundaries encompassing the cingulate sulcus (anterior, superior, and inferior boundaries); the paracentral sulcus (posterior boundary); and the pericallosal sulcus (inferior and posterior boundaries). Tracing started on the most midsagittal image that best illustrated its course, and its most anterior point was identified on that image. Moving laterally, tracing continued in the coronal plane connecting the deepest point of the pericallosal sulcus to the deepest point of the cingulate sulcus, Tracing ended in the coronal plane where the paracentral sulcus appeared. The sagittal plane was used to identify the posterior boundary.

The orbitofrontal cortex was traced in the coronal plane. The orbitofrontal cortex included all of the orbital gyri and excluded the gyrus rectus. The orbitofrontal cortex was defined with boundaries encompassing the frontomarginal sulcus (anterior and lateral boundaries); the frontomarginal sulcus, the lateral orbital sulcus, and the circular sulcus of the insula (lateral boundary); and the olfactory sulcus (medial boundary). Before tracing began, the lateral orbital sulcus was identified in the coronal plane. In the more anterior slices, the orbitofrontal cortex was traced following the frontomarginal sulcus to its intersection with the midline. Moving posteriorly, the orbitofrontal cortex was defined as cortex between the olfactory trigone. Tracing ended on the coronal plane when the olfactory sulcus and the circular insular sulcus were no longer visible.

Statistical Analysis

Two-sided Student's *t*-tests and χ^2 analyses were used to examine differences between groups on all clinical and demographic variables of interest. The groups were also compared on the MRI variables using analyses of covariance. Gray matter and white matter, and total region volume in each of the prefrontal subregions for each hemisphere, were dependent measures in analyses of covariance with diagnosis as a between-group factor. To address potential interindividual differences in brain size that may be associated with demographic variables (i.e., sex and age), region of interest volumes as a proportion of the subject's total intracranial volume[44] were used as dependent variables. Because sex ratio of the two groups was different, sex was included as a covariate, since earlier investigations[45,46] have reported differences between male and female subjects in some of the regions. We also tested whether men and women should be analyzed separately. The linear model included terms for separate slopes as well as separate intercepts predicting the four apathy scale scores. Hierarchical F-changes indicated that separate slopes and intercepts did not significantly improve the models. Although age did not significantly differ between the groups, it was also used as a covariate. The significance level adopted was $\alpha = 0.05$ (two-tailed).

We explored the relationships between the variables (e.g., AES and HAM-D scores and regional volumes) using Pearson correlation coefficients in the depressed and the comparison group, as well as in the entire sample. Because the correlation coefficients between the AES and regional volumes were similar in the depressed and the comparison groups, we combined both study groups to identify neuroanatomical predictors of apathy using the multivariate linear regression analyses controlling for diagnosis, age, and sex, and CIRS scores (Table 1). Because multiple tests were performed, we applied a correction procedure, (i.e., the Bonferroni) to protect our results from type I error. Each table provides the unadjusted p values and a footnote for the multiple criterion value.

RESULTS

Tables 2 and 3 summarize the results of the group comparison on clinical, demographic, and MRI variables. The groups did not differ by age, education, or racial composition. As expected in a clinical sample, a greater proportion of women were included in the depressed group compared to the comparison group (77 versus 49%, respectively). However, we did not find any sex effects on regional volumes in relation to apathy or depression in the multivariate or in the principle component analyses, as explained above. The depressed patients had greater severity of non-vascular medical burden (CIRS), but not cerbrovascular risk factors (CVRF), compared to the comparison groups (Table 2). The MMSE scores were in the normal range in the major depression group with a mean score of 28.7 ± 1.47 as well as in the comparison group with a mean score of 29.5 ± 0.81 (Table 2). The depressed patients had lower total and subscale AES scores signifying greater severity of apathy compared to the comparison group (Table 2). Differences of ≥8 points for total AES and ≥4 points for AES subtests were clinically significant. However, the correlation between the AES and HAM-D scores was less than 0.3 among the depressed subjects. The correlation coefficients between the AES scores and regional MRI volume did not differ between the depressed patients and controls.

We observed significantly smaller gray matter volumes in the orbitofrontal cortex in the depressed group compared to the normal comparison group (Table 3) that is consistent with our prior reports.[30] Although we found significantly decreased white matter volumes in the depressed group in the left orbitofrontal volume compared to the comparison group, the level of significance was more marginal compared to the significance of the gray matter findings and became nonsignificant after adjustment for multiple comparisons (Table 3).

Table 1 shows the results from several multivariate regression analyses. For each AES subscale, eight models were run. Each of these models included diagnosis, age, and sex (coefficients not reported). In the multivariate linear regression analyses, subregional volumes predicted the total and subscale AES scores after controlling for diagnosis, age, and sex. The AES behavioral subscale scores were predicted by the right anterior cingulate gray matter volume (Table 1). We repeated the analyses controlling for the CIRS scores, but it did not appreciably change our results.

DISCUSSION

To our knowledge, this is the first study to use a volumetric MRI-based parcellation method of the prefrontal cortex to examine the patterns of neuroanatomical changes associated with apathy in older patients with major depression and age-matchednormal comparison group. We found an association between depression and gray matter volumes in the right and left orbitofrontal cortex. However, the severity of apathy was associated with reduced gray matter volumes in the anterior cingulate.

Overall, our findings are consistent with the expected alteration in the anterior cingulate and prefrontal cortex implicated in the pathophysiology of apathy[9,16,18,35] in older adults. Unfortunately, prior reports included only subjects with Alzheimer disease and related dementias,[35-37,47] which complicates the comparison of our results to other studies.

Interestingly, we did not find an association between the AES scores and orbitofrontal volume. This suggests that the orbitofrontal cortex is involved in the mediation of depressed mood but not apathy, and the anterior cingulate cortices involvement in the mediation of apathy.[34] We doubt that this result can be attributed to the interaction between the apathy and depression because we combined the two study groups and controlled for the diagnosis. It is possible that having decreased anterior cingulate volumes can predispose one to the development of apathy in the context of a depressive syndrome.

In our prior study of a subset of depressed elderly subjects with early-onset depression, we reported significant bilateral reduction in the gray matter volumes in the anterior cingulate and the orbitofrontal cortex.[30] However, the overlap in the clinical features of depression and apathy was not addressed in the previous reports.[30,43] Our current findings are consistent with our previous reports in smaller samples implicating dorsolateral prefrontal and orbital fron-tal cortex (OFC) in the pathophysiology of depression.[15,48,49] However, we did not find group differences in the anterior cingulate volumes that could be due to combining subjects with early- and late-onset depression, or those with a single episode and recurrent depression in the current sample.

In geriatric depression, marked volumetric reductions in the prefrontal cortex and OFC were observed in MRI data.[50] Moreover, two studies demonstrated a reduction in whole prefrontal cortical volume in elderly minor and major depression,[51,52] with volumes of prefrontal lobe decreasing with increasing severity of illness. Using voxel-based morphometry, another study in geriatric depression found smaller gray matter volumes bilaterally in the middle frontal gyrus.[53] Studies focused on elderly depressed patients have repeatedly suggested a potential involvement of the OFC in the disorder. Reduced OFC volume,[54] a significant association between smaller OFC gray matter and functional impairment,[55] as well as increased lesion density in orbitofrontal white matter, have been specifically reported in elderly depression.[56]

We report a reduction in the white matter volume in the orbitofrontal regions in depressed subjects compared to the normal comparison group (Table 3), which lost its statistical significance after correction for multiple comparisons. This could be supported by postmortem findings indicating glial density reduction in distinct areas of the OFC in major depression.[48,49] Possible mechanisms for tissue loss include neuronal loss and decreased neuronal density through exposure to repeated episodes of hypercortisolemia; glial cell loss, resulting in increased vulnerability to glutamate neurotoxicity; stress-induced reduction in neurotrophic factors; and stress-induced reduction in neurogenesis.[57]

Despite the lack of the neuroimaging studies to identify neuroanatomical substrates of the late-life neuropsychiatric syndromes in older subjects without dementia, a similar conceptual approach has been used in the neuroimaging studies of behavioral manifestations of dementia, including apathy and depression. Sultzer[47] summarized disparate findings from the existing structural and functional neuroimaging studies in identifying behavioral substrates expressed in regional cerebral pathology in dementia. Depressed mood, apathy, and blunted affect were associated with structural lesions in subcortical nuclei and resulting frontal cortical dysfunction. Paul et al.[58] studied MRI correlates of apathy and depression in patients with human immunodeficiency virus. Apathy, but not depression, was correlated with lower volume of the nucleus accumbens. Several recent positron emission tomography

studies identified correlates of depression and apathy in Alzheimer disease. Holthoff and colleagues[36] reported significant decreases in left orbitofrontal regions in subjects with apathy in the context of early Alzheimer disease when compared with patients free of apathy, whereas clinical depression was associated with hypometabolism in dorsolateral prefrontal regions. Mega and colleagues[37] used the same approach in evaluating correlates of response to galantamine in behavioral subgroups of patients with Alzheimer disease. Right cingulate metabolic change significantly correlated with improvement in depression and right ventral putamen metabolic change with improvement in apathy. Rosen et al.[35] reported an association of apathy with tissue loss in the ventral portion of the right anterior cingulate cortex and adjacent ventromedial superior frontal gyrus in subjects with dementia. None of these findings are identical to ours, which can be explained by the difference in the clinical populations with underlying neurodegenerative changes and comorbid cognitive symptoms in dementia.

The limitations of our study were the exploratory nature, the lack of matching by sex, and unavailability of the analyses of lacunar and deep white matter lesions, which are typically prevalent in this age group. However, we examined sex differences directly and found no group differences. Despite all subjects being free of psychotropic medications at the time of the study, we did not control for the prior medication exposure. Although we controlled for the severity of medical burden in the analyses, we did not address the potential contribution of psychomotor retardation or executive cognitive dysfunction to mediate the relationship between the AES scores and the regional MRI volumes. We combined the depressed and nondepressed subjects under the assumption that the all subjects will have the same neuroanatomical correlates of apathy controlling for diagnosis, which was supported by the similar correlation coefficients between the brain regions and the apathy scores in both group. Only postmortem studies, however, may elucidate the biological mean-ing of brain tissue changes in elderly depressed patients. Finally, our depressed outpatients suffered from moderate major depression, thus the results may not generalize to a more severely depressed population. With this caveat in mind, our findings offer the first important insights into the neuroanatomical correlates of apathy in an elderly clinical sample.

In summary, this is the first study to examine neuroanatomical correlates of apathy in older adults with and without major depression, which yielded intriguing results warranting replication in the future studies. We examined neuroanatomical features of apathy and depression using the MRI parcellation analyses of the frontal lobes in depressed elderly patients and age-matched controls. We observed different patterns of neuroanatomical substrates of depression and apathy, supporting the role of these regions in the mediation of late-life depression and apathy.

Neuroimaging can serve as a tool for redefining the endophenotypes of late-life neuropsychiatric disorders. Further development of neuroimaging techniques, more focused neuroimaging study designs, and corroboration with neuropathologic studies will help clarify the pathophysiologic mechanisms involved in neuropsychiatric and cognitive symptoms and will suggest opportunities for therapeutic intervention.

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TABLE 1

The Relationship Between the MRI Subregional Volumes and the Apathy Evaluation Scales Scores, Controlling for Diagnosis, Age, and Sex

Subregions	Total AES			AES Cognitive			AES Behavioral			AES Emotional		
	β	Standard error	p value	β	Standard error	p value	β	Standard error	p value	β	Standard error	p value
Right OFC gray	−725.23	753.52	0.34	−484.30	429.18	0.26	−404.75	245.26	0.10	4.38	155.96	0.98
Right CG gray	2066.76	912.29	0.03	336.15	519.61	0.52	1004.53	296.94	0.001[a]	262.04	188.83	0.17
Left OFC gray	−520.09	790.08	0.51	−698.53	437.76	0.12	13.34	268.86	0.96	−19.87	161.16	0.90
Left CG gray	963.36	862.82	0.27	58.32	478.06	0.90	578.88	293.61	0.05	−64.23	175.99	0.72
Right OFC white	−134.19	1170.13	0.91	−424.37	643.00	0.51	−154.23	406.59	0.71	192.51	234.55	0.42
Right CG white	459.38	2320.49	0.84	−415.57	1275.14	0.75	387.47	806.32	0.63	21.58	465.14	0.96
Left OFC white	216.44	1001.07	0.83	−103.51	527.75	0.85	110.98	342.02	0.75	59.88	197.79	0.76
Left CG white	762.23	1712.13	0.66	−173.15	902.61	0.85	516.18	584.95	0.38	138.95	338.28	0.68

Notes: The criterion value for multiple comparisons for all of coefficients is p <0.002, for an overall p value of 0.05.

OFC: orbital frontal cortex; CG: cingulate gyrus; gray: gray matter volume; white: white matter volume; AES: Apathy Evaluation Scale.

[a]The p values are from Student's *t*-tests of the regression coefficients using multivariate models with df = 61.

TABLE 2

Demographic and Clinical Characteristics of Older Subjects With Major Depression and Normal Comparison Group

	Depressed Patients	Normal Comparison Group	*t*-Test	p Value
N	43	41		
Women	33 (77%)	20 (49%)	7.05[a]	0.007
White	34 (79%)	32 (78%)	3.4a	0.5
Age	70.67 (7.76)	72.19 (7.27)	0.926	0.36
Education	14.56 (2.52)	15.48 (2.64)	1.649	0.10
CIRS[b]	4.60 (2.94)	2.71 (2.25)	− 3.306	0.001
CVRF	12.12 (9.24)	11.05 (6.62)	−0.582	0.56
MMSE[b]	28.71 (1.47)	29.51 (0.81)	3.053	0.003
AES total[b]	30.63 (10.57)	46.94 (4.13)	8.791	0.0001
AES cognitive[b]	14.67 (5.21)	20.78 (3.04)	6.219	0.0001
AES behavior[b]	3.72 (2.64)	8.19 (2.66)	7.379	0.0001
AES emotional[b]	5.23 (1.78)	6.95 (1.41)	4.681	0.0001
AES other[b]	8.05 (5.13)	11.05 (1.15)	3.481	0.001

MMSE: Mini-Mental State Examination Scale score; CIRS-G: Cumulative Illness Rating Scale-Geriatric version; CVRF: Cerebrovascular Risk Factor Scale; AES: Apathy Evaluation Scale.

[a] χ^2 test.

[b] The criterion value for multiple comparisons among the five AES scores is p <0.01 for an overall p value of 0.05.

TABLE 3

Comparison of the MRI Regional Volumes in Older Depressed and Control Subjects Controlling for Age and Sex

	Depressed Patients	Normal Comparison Group	F Value	p Value
ICV	1297.555 (147.140)	1314.923 (150.237)	0.9	0.41
MRI regional volumes adjusted by ICV				
Right OFC gray[a]	0.0086 (0.0016)	0.0096 (0.0010)	13.0	0.001
Right OFC white	0.0045 (0.0011)	0.0049 (0.0008)	2.5	0.12
Left OFC graya	0.0086 (0.0016)	0.0097 (0.0009)	17.9	0.0001
Left OFC white	0.0045 (0.0010)	0.0050 (0.0008)	5.6	0.02
Right CG gray	0.0043 (0.0014)	0.0044 (0.0007)	0.03	0.88
Right CG white	0.0014 (0.0005)	0.0013 (0.0005)	0.002	0.96
Left CG gray	0.0044 (0.0016)	0.0043 (0.0010)	0.2	0.64
Left CG white	0.0014 (0.0008)	0.0012 (0.0006)	0.5	0.48

OFC: orbital frontal cortex; CG: cingulate gyrus; gray: gray matter volume; white: white matter volume; AES: Apathy Evaluation Scale.

[a]The criterion value for multiple comparisons among these eight regions is $p < 0.006$ for an overall p value of 0.05.