Antidepressant Exposure May Protect Against Decrement in Frontal Gray Matter Volumes in Geriatric Depression

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Objectives: Depressed elderly patients with and without antidepressant exposure were compared to normal controls to examine the effects of prior antidepressant exposure on regional brain gray matter volumes using magnetic resonance imaging (MRI).

Method: The study was conducted from October 1999 to January 2003. Patients and controls were closely matched by age and education. They underwent comprehensive neuropsychiatric and physical examinations. Measures of the total frontal lobe and the frontal gray and white matter volumes corrected by the intracranial volume were obtained using MRI, together with clinical measures of medical burden. Historical information about prior exposure to antidepressant drugs was collected using multiple information sources. The groups were compared using multivariate analyses of covariance, controlling for age, sex, and medical burden.

Results: The study sample comprised 41 patients who met the DSM-IV criteria for major depressive disorder (32 women; 11 antidepressant exposure and 30 drug-naive; mean age 70.5 years) and 41 controls (20 women; mean age 72.2 years). In the multivariate analysis, the depressed group had smaller corrected orbitofrontal cortex (OFC) total and gray matter volumes compared to the controls ($p < .01$). However, depressed patients with prior antidepressant exposure had larger OFC gray matter volumes compared to drug-naive depressed patients, but smaller than those in normal controls ($p = .005$). This effect was not explained by the group differences in sex ratio, age at onset of depression, or the number or duration of depressive episodes.

Conclusions: We observed larger OFC regional volumes in depressed patients exposed to antidepressants compared to the drug-naive depressed subjects, but smaller than those in age-matched controls. Antidepressant exposure may protect against gray matter loss in geriatric depression.

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As the neurobiology of mood disorders and the mechanisms of action of antidepressant drugs continue to be elucidated, neuroprotective properties of antidepressant treatment have been supported by animal and human studies.[1] Evidence from animal studies suggests that drug therapy may act on specific transcription factors and target genes that regulate processes such as neuroprotection and neuronal survival. Several clinical studies reported changes in prefrontal and orbitofrontal cortex, hippocampus, and amygdala that may be related to the course of illness and may be prevented with successful treatments.[2–6]

In geriatric depression, numerous reports[5–12] suggested structural brain changes in the gray and white matter, particularly in the frontal and orbitofrontal cortex (OFC), and the hippocampus. However, the role of cerebrovascular disease in geriatric depression has been the main focus of investigations so far. In our previous reports[7–9] of volumetric brain imaging findings in geriatric depression, we identified structural brain changes in the gray matter abnormalities detected in OFC and temporoparietal cortices, thereby providing a potentially new window into the pathophysiology of elderly depression.

In the current report, we explored the role of prior antidepressant exposure on regional gray matter volumes in the frontal and orbitofrontal regions. Depressed elderly patients with and without antidepressant exposure were compared to normal controls to examine the effects of prior antidepressant exposure on the magnetic resonance imaging (MRI) regional brain volumes.

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METHOD

Subjects were recruited through local newspapers and radio advertisements and through referrals from the geriatric psychiatry ambulatory care programs at the University of California, Los Angeles (UCLA) Medical Center. The study, conducted from October 1999 to January 2003, was performed in accordance with the UCLA policies of the Human Subject Protection Committees. After complete description of the study was provided to the subjects, written informed consent was obtained. The study protocol was approved by the UCLA Institutional Review Board. All subjects underwent comprehensive neuropsychiatric, laboratory, and physical examinations and the MRI scans. Patients and controls were closely matched by age and education. All depressed patients were assessed with the Structured Clinical Interview for DSM-III-R (SCID).[13] All met the DSM-IV criteria for major depressive disorder and had a 17-item Hamilton Rating Scale for Depression[14] score of 15 or greater. Depressed patients received comprehensive medical and neurologic examinations and laboratory testing to rule out secondary causes of depression or dementia. None of the subjects had clinical evidence of dementia, suspected dementia, or any other brain disorder based on history and mental status examination. All recruited subjects had Mini-Mental State Examination (MMSE)[15] scores of 25 or greater.

A neuropsychiatric examination and the structured clinical diagnostic interview (SCID) were administered to all control subjects to rule out current or past psychopathology as well. Other measures of comorbid medical conditions included the Stroke Risk Factor Prediction Chart[16] of the American Heart Association, which was used to rate stroke risk factors including age, systolic blood pressure, antihypertensive medication use, history of diabetes, smoking, previous strokes, atrial fibrillation, and left ventricular hypertrophy. The Cumulative Illness Rating Scale-geriatric version (CIRS-G)[17] was used to rate the severity of chronic medical illness burden including 14 organ-systems. Thorough information about prior exposure to antidepressant drugs was collected using multiple sources. All subjects with prolonged (i.e., greater than 1 month) or repeated exposure to antidepressants were identified (N = 11). Thirty depressed subjects were drug-naive with no history of antidepressant exposure. All patients were free of psychotropic medications for at least 2 weeks before imaging. The groups were compared using univariate and multivariate analyses of covariance, controlling for age, sex, and medical burden.

Imaging Protocol

All subjects were studied with MRI performed on a 1.5-T Signa magnet (GE Medical Systems, Milwaukee, Wis.) using a coronal T_1-weighted spoiled gradient/recall acquisition in the steady state (spoiled GRASS) sequence of 42/5/1, 43/6/1, or 43/7/1 (TR/TE/excitations). All image data sets had a slice thickness of 1.4 mm without gaps, a flip angle of 35°, and a matrix size of 256 × 192 mm; on-plane resolution = 0.859375 × 0.859375.[7–9]

Image Analysis

All image data sets were processed with a series of steps in preparation for manual delineation of prefrontal subregions. First, images were subjected to brain masking with removal of non-brain tissue (i.e., scalp and orbits). Brain volumes were corrected for signal intensity inhomogeneities, aligned, and placed into stereotaxic coordinates, without scaling. This procedure was used to correct for differences in head position and to place data in a common space that was specifically used for group comparisons.

Fully automated tissue segmentation was then applied to the brain volumes, where voxels were automatically classified as most representative of gray matter, white matter, or cerebrospinal fluid. The fully automated protocol was used in the previous reports.[7–9]

Finally, a high-resolution shape representation of the cortex was extracted for each subject using automated software. By using a 3-dimensional active surface algorithm, a spherical mesh surface was created that was continuously transformed to fit a cortical surface tissue threshold intensity value from individual brain volumes. Total intracranial brain volume (ICV) was calculated and did not include the cerebellum or brain stem. Regional volumes were adjusted to ICV to account for interindividual variability in head and brain sizes.

All anatomical delineations were reconciled using each individual's 3-dimensional surface model and all 3 planes to corroborate sulcal and subregion identity. The details of delineations of the regions are described in detail on the Web site of the UCLA Laboratory of Neuro Imaging (http://www.loni.ucla.edu/).

Although a single rater performed all tracings, we established interrater reliability among several raters performing delineation of the anatomical regions on 10 randomly chosen image data sets. Intraclass correlation coefficients for the reliability of the total volumes in the regions of interest ranged between .85 and .92.[7–9]

Statistical Analysis

Clinical and the MRI variables of gray matter and white matter regional volumes were analyzed using 2 separate multivariate models. Three groups were compared controlling for age and sex. We used multivariate analysis of variance to partially control for type I errors, but the results of the univariate analyses were not adjusted. The level of significance was set at $p < .05$ (2-tailed).

Table 1. Clinical, Demographic, and MRI Characteristics of Depressed Subjects With and Without Antidepressant Exposure and Normal Controls

Clinical and Demographic Variables	Depressed × AD[a] (N = 11)	Depressed × NAD[b] (N = 30)	Normal Control (N = 41)	F (df = 2,73)	p
Age, mean (SD), y	67.4 (6.1)	71.7 (7.8)	72.2 (7.3)	1.4	.3
Sex, women, N (%)*	7 (63)	25 (83)	20 (49)	4.8	.01
Education, mean (SD), y	13.9 (2.5)	14.8 (2.6)	15.5 (2.6)	1.6	.2
Family history of depression, N (%)*	8 (73)	10 (33)	5 (12)	9.9	.0001
CIRS-G score, mean (SD)*	5.2 (3.8)	4.4 (2.7)	2.7 (2.2)	5.7	.005
CVRF score, mean (SD)	14.3 (17.5)	11.3 (4.8)	11.1 (6.6)	0.9	.4
MMSE score, mean (SD)*	28.6 (1.5)	28.8 (1.5)	29.5 (0.9)	3.4	.04
HAM-D score, mean (SD)	17.7 (3.0)	17.7 (3.0)	NA	0.001	.9
Age at depression onset, mean (SD), y	36.4 (21.5)	52.5 (22.5)	NA	3.8	.06
No. of depressive episodes, mean (SD)	3.3 (2.6)	2.5 (2.7)	NA	3.5	.07
Duration of current depressive episode, mean (SD), mo	92.2 (205.8)	103.2 (191.3)	NA	0.008	.9
MRI Variables				F (df = 2,77)	p
ICV, mean (SD), cc	1297.555 (147.140)	1292.646 (129.436)	1314.923 (150.237)	0.9	.4
Regional volume adjusted by ICV					
Total frontal	0.236 (0.019)	0.233 (0.017)	0.236 (0.016)	1.8	.2
Total frontal gray matter[c]	0.135 (0.013)	0.130 (0.010)	0.131 (.0072)	0.7	.5
Total right frontal	0.118 (0.008)	0.117 (0.008)	0.118 (0.006)	1.8	.2
Right frontal gray matter[c]	0.067 (0.004)	0.065 (0.005)	0.065 (0.006)	0.4	.7
Total left frontal	0.118 (0.006)	0.116 (0.010)	0.117 (0.008)	1.8	.2
Left frontal gray matter[c]	0.068 (0.004)	0.065 (0.005)	0.066 (0.006)	1.7	.2
Total orbitofrontal*	0.027 (0.003)	0.026 (0.005)	0.029 (0.003)	7.7	.001
Total OFC gray matter[c]*	0.018 (0.002)	0.017 (0.003)	0.019 (0.002)	8.3	.001
Total right orbitofrontal*	0.0134 (0.0017)	0.0130 (0.0026)	0.0144 (0.0015)	5.3	.007
Right OFC gray matter[c]*	0.0091 (0.0010)	0.0085 (0.0017)	0.0095 (0.0001)	7.2	.001
Total left orbitofrontal*	0.0135 (0.0011)	0.0129 (0.0027)	0.0146 (0.0013)	8.8	.0001
Left OFC gray matter[c]*	0.0090 (0.0011)	0.0085 (0.0017)	0.0096 (0.0009)	9.7	.0001

[a]Depressed patients with antidepressant exposure.
[b]Depressed patients with no antidepressant exposure.
[c]Gray matter volume = ratio to ICV.
*$p < .05$.
Abbreviations: CIRS-G = Cumulative Illness Rating Scale-geriatric version, CVRF = Cerebrovascular Risk Factor scale, HAM-D = Hamilton Rating Scale for Depression, ICV = total intracranial volume (brain stem and cerebellum are excluded), MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, NA = not applicable, OFC = orbitofrontal cortex.

RESULTS

The study sample comprised 41 patients with major depressive disorder (32 women; 11 patients with prior antidepressant exposure [7 women] and 30 drug-naive patients [25 women]; mean age 70.5 [SD = 7.6] years) and 41 controls (20 women; mean age 72.2 [SD = 7.3] years). Depressed patients had a mean of 2.7 (SD = 2.7) prior episodes of depression with mean age at onset of depression of 48.5 (SD = 23.5) years. Information on prior episodes and age at onset was obtained from patients and caregivers.

Table 1 presents the results of the univariate analyses of the clinical, demographic, and MRI variables in the 3 comparison groups. In the univariate analysis, the depressed group had lower MMSE scores ($p < .05$) and greater severity of medical comorbidity (CIRS scores; $p < .01$) compared to the controls (Table 1). In the univariate analyses, the drug-naive subjects had the smallest OFC total ($p = .001$) and gray matter ($p = .001$) volumes, followed by the antidepressant-exposed group and the controls (Table 1). We did not include MRI variables of white matter volumes in the table for conciseness because they did not reach the level of statistical significance.

In the multivariate analysis, controlling for age and sex, depressed patients with prior antidepressant exposure had larger OFC total and gray matter volumes compared to drug-naive depressed patients, but smaller than the corresponding volumes in normal controls ($F = 2.0$; df = 36,122; $p = .005$). Our results did not change after we controlled for medical burden (CIRS) ($F = 1.8$; df = 36,120; $p = .008$).

In addition, we have also explored the potential sources of bias in prior antidepressant exposure that could potentially explain the effect of antidepressant exposure on brain volumes. We found differences in the group composition by sex, presence of family history, and age at onset of depression in depressed subjects, as presented in Table 1. The drug-naive or antidepressant-exposed depressed patients did not differ on the prior number of depressive episodes or the current duration of the episode. None of the other variables, such as having a family history of depression, age at depression onset, duration of the current episode, or number of episodes explained the observed differences in the OFC gray matter volumes. After controlling for sex in the analyses, its main effect in the model was not statistically significant ($F = 1.9$; df = 36,122; $p = .1$).

DISCUSSION

We have observed group differences in frontal regional brain volumes with depressed elderly patients having smaller OFC gray matter volumes than normal controls, which is consistent with our previous reports,[7–9] as well as reports from other research groups.[10–12] However, depressed patients with prior history of antidepressant exposure had larger gray matter volumes in the regions of interest than those without such exposure. Our findings are consistent with the recent reports of neuroprotective qualities of antidepressants, mood stabilizers, and electroconvulsive therapy[1–6] associated with larger regional volumes of brain structures, which are attributed to the induced neurogenesis and neuroplasticity. This suggests that antidepressant exposure may be neuroprotective against gray matter loss in geriatric depression. In fact, as suggested by Santarelli and colleagues,[6] increase in neurogenesis may be necessary for the expression of antidepressant action.

Our findings may be limited by a relatively small number of depressed patients exposed to antidepressants. Another limitation includes the lack of quantification of white or gray matter lesions,[10] which might contribute to the observed volumetric changes in the regions of interest. The finding of significantly lower MMSE scores in the depressed sample may signify prodromal stages of a neurodegenerative dementia, which may also be responsible for smaller regional volumes in depressed men but will need to be confirmed in a longitudinal follow-up study. We have identified differences in the group composition by sex, presence of family history, and age at onset of depression in depressed subjects. Despite the differences in the sex ratio among the 3 groups, the drug-naive group had a greater proportion of women than the 2 other groups, which should have resulted in the greater adjusted OFC gray matter volumes, as has been reported in our recent publication and by other investigators.[9,18] Instead, the drug-naive group had the smallest OFC gray matter volumes, followed by the antidepressant-exposed group, and by normal controls. Those subjects with antidepressant exposure had earlier age at onset of depression, greater proportion of family history of depression, and greater medical burden expressed in the CIRS scores compared to the drug-naive subjects, which might indicate a greater vulnerability to depression in this group. Later age at onset has been shown to be associated with greater structural changes on brain MRI,[19,20] and might be responsible for the smaller OFC total and gray matter volumes in the drug-naive group. However, these variables did not contribute to the observed differences in the OFC volumes among the antidepressant-exposed drug-naive depressed subjects in the statistical analyses.

Despite these limitations, we find our results intriguing, potentially shedding light on underlying pathophysiology of geriatric depression and antidepressant response, which warrants further investigations. Future prospective longitudinal treatment studies with repeated MRI scans are needed to support this observation. Such neurobiological markers, if proven accurate, can ultimately help identify patients who respond and remit to treatment and help in decisions about specific treatments for an individual patient.

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