Brain-Volume Increase With Sustained Remission in Patients With Treatment-Resistant Unipolar Depression

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ABSTRACT

Objective: Previous magnetic resonance imaging (MRI) studies have demonstrated brain-volume reductions in unipolar major depressive disorder (MDD). It is not clear whether these atrophic changes can be stabilized with antidepressant treatment and/or reversed with remission. The objective of this study was to prospectively examine brain-volume changes in patients with treatment-resistant depression, comparing those who achieved sustained remission with those who did not remit.

Method: This prospective observational cohort study investigated the roles of clinical responsiveness and antidepressant treatment in lessening brain atrophy in depression. Data were collected between October 2004 and December 2008. Baseline MRI scans were obtained from 28 outpatients with treatment-resistant MDD (diagnosed according to *DSM-IV* criteria) who were recruited from the Mood Disorders Research Unit at the Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada. Twenty-seven patients underwent follow-up scanning after either 6 months of sustained remission (Montgomery-Asberg Depression Rating Scale score ≤ 12) or 12 months of failure to remit. Longitudinal whole-brain and voxel-based gray- and white-matter volume changes were estimated.

Results: Twelve patients (mean age at baseline = 47.5 years) achieved sustained 6-month remission. In contrast to nonremitters (n = 15; mean age at baseline = 44.3 years), remitted patients demonstrated a significant mean increase in whole-brain volume during follow-up ($F_{1,27} = 9.51$, $P = .005$). Within-subject voxel-based morphometry analyses identified increased gray-matter volume in remitters in the right orbitofrontal cortex ($t_{11} = 7.61$, $P = .006$) and the right inferior temporal gyrus ($t_{11} = 6.65$, $P = .004$). Nonremitters showed decreased white-matter volume in the left anterior limb of the internal capsule ($t_{13} = 3.86$, $P = .04$).

Conclusions: Given that remitters exhibited a mean increase in brain volume while nonremitters lost volume, pharmacotherapy in the absence of sustained remission is most likely insufficient to elicit brain-volume increase in MDD. The findings suggest that clinical remission rather than pharmacotherapy may be the key factor involved in driving volumetric recovery in treatment-resistant depression.

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Cross-sectional magnetic resonance imaging (MRI) studies have documented brain-volume reductions in patients with unipolar major depressive disorder (MDD) relative to healthy individuals. Such effects have been commonly localized to frontal, limbic, and striatal regions,[1] areas implicated in the emotional, cognitive, metabolic, and endocrine alterations seen in the disorder. Decreased trophic support in depression, evidenced by stress-induced reductions in levels of brain-derived neurotrophic factor,[2] is thought to contribute to these volumetric alterations.[3]

Chronic antidepressant treatment has been shown to increase brain-derived neurotrophic factor expression,[4,5] suggesting that certain pharmacotherapies may have neurotrophic effects.[6] Since neurotrophic factors are important mediators of neuronal plasticity,[7] antidepressant-induced neurotrophin increase may restore plasticity and protect against volume loss. In fact, studies have shown evidence of volume recovery with antidepressant treatment—for example, a 4.6% increase in hippocampal volume in patients with posttraumatic stress disorder treated with paroxetine.[8] The progressive nature of brain atrophy in depression[9] emphasizes the importance of capitalizing on the effects of pharmacotherapy on brain volume. Furthermore, findings of increased hippocampal volume loss with increasing duration of untreated depression[10] highlight the importance of early treatment initiation. A longitudinal study found less volume decline in the anterior cingulate, hippocampus, and prefrontal cortex of patients who remitted during 3-year follow-up relative to nonremitters.[11] Cross-sectional studies have found more gray-matter volume in the dorsolateral prefrontal cortex of remitted compared to unremitted patients[12] and increased subgenual prefrontal cortex volume with antidepressant treatment only in patients who were in remission.[13] These findings suggest that structural modifications in MDD may also be associated with treatment response. However, it is not clear whether the observed reductions in brain atrophy in such studies can be attributed to the patients' treatment or the alleviation of the depression itself.

The purpose of this prospective observational cohort study was to investigate the roles of clinical responsiveness and antidepressant treatment in lessening brain atrophy in depression. Staging methods, developed to assess resistance to antidepressant treatment,[14] were employed to provide novel information on the relationship between treatment resistance and volumetric alterations in MDD. We hypothesized that brain volume would be increased in patients who achieved sustained remission from depression and, secondly, that brain volume would be positively affected by pharmacologic intervention only if patients achieved remission with the treatment. These hypotheses were addressed in a prospective longitudinal imaging study of patients with treatment-resistant depression who were receiving intensive pharmacotherapy over a follow-up period of approximately 1 year.

Clinical Points

- Achieving sustained remission, not merely receiving medication treatment, may prevent brain-volume loss in depression.
- Using combinations of 2–3 medications is often necessary to achieve remission in depression, as in other medical illnesses.
- Remission of depression can be achieved using combinations of medications with different mechanisms of action.

Patients with treatment-resistant depression were selected so as to obtain a balanced proportion of remitted and unremitted patients for comparison.

METHOD

Participants

Twenty-eight outpatients with treatment-resistant MDD were recruited from the Mood Disorders Research Unit at the Royal Ottawa Mental Health Centre, Ottawa, Ontario, Canada. Primary diagnosis of MDD was made by psychiatric consultation on the basis of *DSM-IV* criteria. *Treatment resistance* was defined as current episode duration of at least 6 months, failure to remit following treatment with at least 2 antidepressants at adequate dosage for at least 6 weeks each (determined through retrospective chart review of treatment response prior to enrollment), a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[15] score ≥ 18, and a Montgomery-Asberg Depression Rating Scale (MADRS)[16] score ≥ 22. Handedness was evaluated with the Edinburgh Handedness Inventory.[17] Exclusion criteria included history of manic, hypomanic, or mixed episode; diagnosis of posttraumatic stress disorder or any psychotic disorder, eating disorder, or substance-related disorder; presence of major medical illnesses; history of significant head trauma; exposure to oral or intravenous steroids; intelligence quotient (IQ) < 80; or any contraindications to MRI. The Royal Ottawa Mental Health Centre Research Ethics Board approved the protocol. All participants provided written informed consent.

Data were collected between October 2004 and December 2008. Twenty-eight patients underwent clinical assessment and MRI scan at baseline. Twenty-seven patients were followed longitudinally (1 patient was lost to follow-up) and assessed by administration of the MADRS (chosen for its sensitivity to change) at baseline and each subsequent visit. During the study, patients underwent intensive pharmacotherapy under the care of study investigators with the goal of attaining remission. All patients were taking medication at enrollment and received treatment throughout follow-up. At patient visits (once every 2 weeks), if an approximately 20% symptom improvement was not detected,[18] an increase in doses (if tolerated) or a medication change was implemented. Medication choices were based on the drugs' different mechanisms of action and potential synergistic effects on the serotonin, norepinephrine, and dopamine systems.[19] Follow-up scans were obtained after either a 6-month period of sustained remission (MADRS score ≤ 12 at each visit) or a 12-month period of failure to remit.

Severity of treatment resistance was measured through determination of staging scores calculated using treatment history. This method (modified from Fava[14]) considers number of failed medication trials, optimization and intensity of dosages, and use of augmentation and combination strategies (see Supplementary eTables 1–3 at PSYCHIATRIST.COM). Each patient was assigned 2 numerical scores: (1) a retrospective staging score, reflecting treatment during the 5-year period preceding study enrollment (obtained through medical-chart and pharmacy-record review for the index episode) and (2) a prospective staging score, reflecting treatment approaches used from baseline to study termination. Scores were calculated by assigning points as follows: 1 point for each antidepressant used for at least 6 weeks at an effective dosage, one-half point for treatment strategies given at or above the maximum recommended effective dosage, one-half point for medications added as augmentation or combination strategies regardless of dosage, and 3 points for each trial of electroconvulsive therapy. During follow-up, patients received individualized treatment with medications from the following drug classes: tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors, dopamine agonists, atypical antipsychotics, and others (see Supplementary eTables 1–3). No patients underwent electroconvulsive therapy during follow-up.

Brain Imaging

T1-weighted magnetic resonance images were obtained at 1.5-T (Siemens Magnetom Symphony; Siemens AG, Erlangen, Germany) using the same acquisition protocol for all images (repetition time = 1,500 milliseconds; echo time = 4.38 milliseconds; flip angle = 15°; matrix = 256 × 256 mm; slice thickness = 1 mm; voxel resolution = 1 × 1 × 1 mm). Baseline and follow-up images of most patients (n = 25) were obtained on the same scanner at St-Joseph MRI, Gatineau, Quebec, Canada. The baseline scans of 3 patients were obtained at the Ottawa Hospital, Ottawa, Ontario, Canada, with their follow-up scans acquired at St-Joseph MRI.

Images were converted to NIfTI-1.1 (Neuroimaging Informatics Technology Initiative) format using MRIConvert, version 2.0 (Lewis Center for Neuroimaging, University of Oregon, Eugene, Oregon). Images were manually reoriented and centered on the anterior commissure using the Statistical Parametric Mapping (SPM) display routine (SPM5; Wellcome Department of Imaging Neuroscience, London, United Kingdom). Estimates of whole-brain volume were obtained using Structural Image Evaluation Using Normalization of Atrophy (SIENA), version 2.6 (Oxford Centre for Functional MRI of the Brain [FMRIB],

Oxford, United Kingdom),[20] part of the FMRIB Software Library (FSL), version 4.1.1 (FMRIB, Oxford, United Kingdom).[21] For baseline scans, normalized brain volume (total brain volume normalized for head size) was estimated with SIENAX, version 2.6 (FMRIB, Oxford, United Kingdom),[20] the cross-sectional extension of SIENA.

Longitudinal brain-volume change was estimated with SIENA, an automated technique that measures combined gray- and white-matter volume change. Patients' baseline and follow-up images were aligned to each other, resampled into the space halfway between the images, and segmented to find brain/nonbrain edge points. Perpendicular edge displacement was estimated, and mean edge displacement was converted into an estimate of percentage brain-volume change (PBVC) between the 2 time points, with positive and negative numbers representing increased and decreased brain volume, respectively.

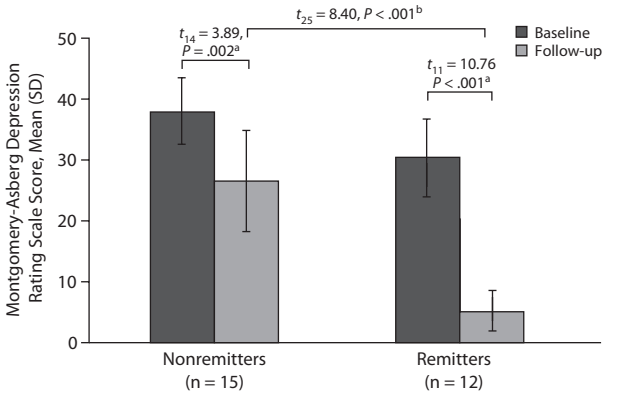
To localize regions of volume change, images were analyzed using voxel-based morphometry[22] in SPM5 running in MATLAB, version 7.3 (The MathWorks, Natick, Massachusetts). Voxel-based morphometry permits automated voxel-wise comparison of gray- and white-matter volumes. Skull-stripped images were segmented into tissue classes, and tissue segments were normalized using Diffeomorphic Anatomic Registration Through Exponential Lie Algebra (DARTEL),[23] a nonlinear iterative registration algorithm that creates and registers images to a population-specific template. Modulation was specified to ensure preservation of volumes. An affine transformation was applied to convert images to Montreal Neurological Institute space. Images were smoothed with an 8-mm Gaussian kernel.

Statistical Analyses

The demographic and clinical variables and the SIENAX-estimated baseline normalized brain volume of remitters and nonremitters were compared with 2-tailed independent-sample *t* tests or χ^2 tests using PASW Statistics, version 18.0 (SPSS Inc, Chicago, Illinois). Differences in PBVC were assessed with an analysis of covariance, adjusted for age and interscan interval. Pearson correlations were calculated to examine the relationships between PBVC and age and change in MADRS scores during follow-up. Stepwise regression analysis was performed to examine clinical predictors of PBVC, treating PBVC as a dependent variable and age, percentage of time in remission (calculated as [days in remission/interscan interval] × 100), and prospective staging scores as predictor variables. For all analyses, results were considered significant at $P < .05$.

For voxel-based morphometry analyses, the framework of the general linear model was employed to estimate within-group gray-matter volume and white-matter volume differences between baseline and follow-up with paired *t* tests (with scanner as a covariate). An absolute intensity threshold mask of 0.2 was employed in model specification. Contrasts were defined to examine gray-matter volume and white-matter volume changes in remitter and nonremitter groups. Statistical results were first thresholded at an uncorrected voxel-level *P* value < .001, and, then, to account for nonuniform smoothness in the imaging data, an SPM nonstationarity correction toolbox[24] was used to generate *t* statistic maps with cluster-size *P* values at .05 corrected for multiple comparisons. Coordinates were assigned to regions by automated labeling using the Harvard-Oxford cortical and subcortical atlases (Center for Morphometric Analysis, Charlestown, Massachusetts) and the Johns Hopkins University ICBM DTI-81 (International Consortium for Brain Mapping; diffusion tensor imaging) white-matter atlas.[25]

Figure 1. Change in Depressive Symptoms Over Follow-Up (N = 27)



[a]Paired *t* test.
[b]Independent-samples *t* test.

RESULTS

Demographic Data

During follow-up, 12 patients (44%) achieved sustained 6-month remission, while 15 patients (56%) failed to achieve sustained remission. Although remitted patients had lower MADRS scores at baseline relative to nonremitters ($t_{25} = 3.26$, $P = .003$), within-group analyses revealed significant decreases in the MADRS scores of both groups, with lower mean final MADRS scores in remitters (Figure 1). At baseline, the groups did not significantly differ on demographic variables, age at onset, number of previous episodes, $HDRS_{17}$ scores, or retrospective staging scores (Table 1), highlighting the homogeneity of the sample at enrollment. During follow-up, relative to nonremitters, remitted patients had significantly lower prospective staging scores, had a larger decrease in MADRS scores, spent more time in remission, and had shorter interscan intervals (see Table 1).

Imaging Analysis

Total normalized brain volume of remitted and nonremitted patients did not differ significantly at baseline (see Table 1). The SIENA analyses demonstrated positive mean PBVC in remitted patients (+ 0.30% [standard deviation = 0.70%]), while nonremitters showed negative mean PBVC (−0.35% [standard deviation = 1.08%]) over follow-up (Figure 2).

In accordance with patients' mean normalized brain volume at baseline (see Table 1), these changes represent an approximate 4.5-mL brain-volume increase in remitters and an approximate 5.1-mL volume loss in nonremitters. Analysis of covariance adjusted for age and interscan interval revealed a significant main effect of outcome group (remission status) on PBVC ($F_{1,27} = 9.51$, $P = .005$), with age contributing significant variance ($F_{1,27} = 16.53$, $P < .001$). A post hoc t test revealed significant between-group differences in PBVC ($P = .005$, Bonferroni corrected). Further, Pearson correlation analyses demonstrated significant negative correlations between patients' baseline age and PBVC ($r = -0.52$, $P = .003$) and between change in MADRS scores and PBVC ($r = -0.37$, $P = .03$). These results indicate associations between aging and volume loss and between symptom improvement and volume increase.

Patients' PBVC was regressed on age, percentage of time in remission, and prospective staging scores using stepwise linear regression. The first variable, age, resulted in a significant increase in explained variance in PBVC ($\Delta R^2 = 0.27$, $F_{1,25} = 9.07$, $P = .006$), as did the second variable, percentage of time in remission ($\Delta R^2 = 0.12$, $F_{1,24} = 4.47$, $P = .04$). Together, age ($\beta = -0.53$, $t = -3.32$, $P = .003$) and percentage of time in remission ($\beta = 0.34$, $t = 2.12$, $P = .04$) were the best predictors of PBVC (adjusted $R^2 = 0.33$, $F_{2,24} = 7.40$, $P = .003$). Prospective staging score was not a significant predictor variable ($\beta = -0.06$, $t = -0.26$, $P = .80$).

In longitudinal voxel-based morphometry analyses, paired t tests in the remitted group revealed significant clusters of increased gray-matter volume in the right orbitofrontal cortex and the right inferior temporal gyrus, while a cluster of decreased gray-matter volume was found in the right superior parietal lobule (Figure 3). No significant changes in gray-matter volume were detected in nonremitters.

Voxel-based morphometry analyses revealed no changes in white-matter volume in remitters. Within nonremitters, while there were no significant regions of white-matter volume increase, there was a significant cluster of decreased white-matter volume detected in the left anterior limb of the internal capsule (Figure 4).

DISCUSSION

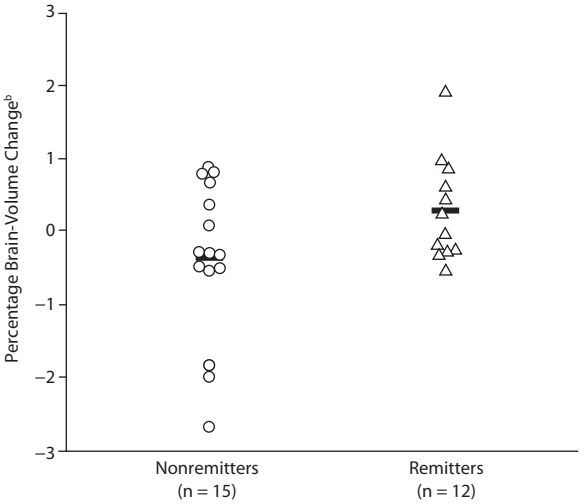
The main finding of this study was that, although both remitted and nonremitted patients received intensive pharmacologic treatment and showed some degree of clinical improvement during the study, mean whole-brain volume increase was seen in the group of patients who achieved sustained remission, while mean brain-volume loss was evident in nonremitters. Forty-four percent of patients achieved sustained remission, a remarkable number considering the severity of treatment resistance demonstrated. Although the inclusionary definition of treatment resistance was consistent with

Table 1. Demographic and Clinical Data of Remitted and Nonremitted Patient Groups

Variable	Remitted Patients (N = 12), n	Nonremitted Patients (N = 15), n	Analysis		
			χ^2	*df*	*P*
Gender, male/female	5/7	4/11	0.68	1	.41
Handedness, right/left	9/3	14/1	1.78	1	.18
No. of depressive episodes, A/B/C[a]	4/3/5	7/3/5	0.49	1	.78
	Mean (SD)	Mean (SD)	*t*		
Age at baseline, y	47.5 (10.6)	44.3 (10.2)	0.80	25	.43
Age at follow-up, y	48.5 (10.7)	45.4 (10.3)	0.77	25	.45
Interval between scans, d	331 (107)	417 (38)	2.93	25	.007
Age at illness onset, y[b]	31.3 (14.2)	29.7 (14.0)	0.29	24	.78
Baseline $HDRS_{17}$ score	22.5 (4.2)	24.9 (4.7)	1.33	25	.20
Change in MADRS score[c]	−25.0 (8.1)	−11.1 (11.1)	3.63	25	.001
Retrospective staging score[d]	5.1 (2.7)	5.5 (3.1)	0.37	25	.72
Prospective staging score[e]	4.4 (2.1)	7 (2.4)	2.92	25	.007
Follow-up spent in remission, %[f]	62 (14)	7 (16)	9.49	25	< .001
Normalized brain volume, mL[g]	1,482 (65)	1,464 (68)	0.72	25	.48

[a]Number of episodes prior to study enrollment expressed as categories: A = 1–2 episodes, B = 3–4 episodes, C = 5+ episodes.
[b]Data not available for 1 subject.
[c]Change in MADRS score was calculated as [follow-up MADRS – baseline MADRS].
[d]Treatment history of the index episode from 5 years prior to study enrollment to baseline, calculated according to the modified Massachusetts General Hospital staging method for treatment resistance,[14] with 1 point assigned for each drug used for the treatment of depression for at least 6 weeks at an effective dosage, plus one-half point for treatment strategies given at or above the maximum recommended dosage, plus one-half point for medications added as augmentation or combination strategies, plus 3 points for each adequate trial of electroconvulsive therapy.
[e]Treatment history from baseline to study termination, calculated as above.
[f]Percentage of time in remission was calculated as [(consecutive days in remission between baseline and final assessment/days between images) × 100].
[g]Baseline total brain-tissue volume (gray matter plus white matter), normalized for participant head size, was calculated with SIENAX, version 2.6 (Oxford Centre for Functional MRI of the Brain, Oxford, United Kingdom).
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MRI = magnetic resonance imaging.

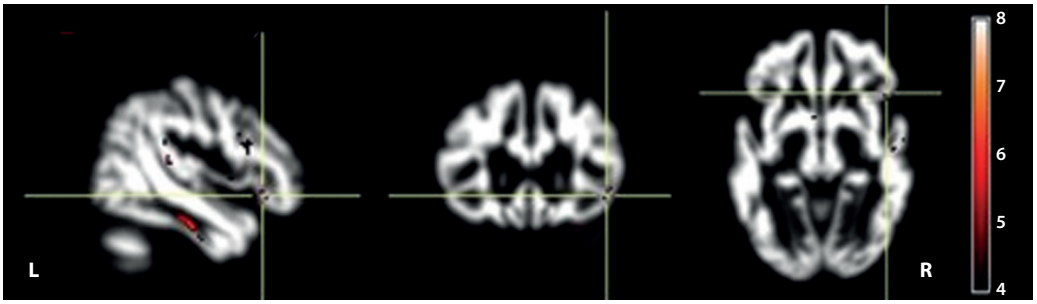
Figure 2. Percentage Brain-Volume Change Over Follow-Up (N = 27)[a]



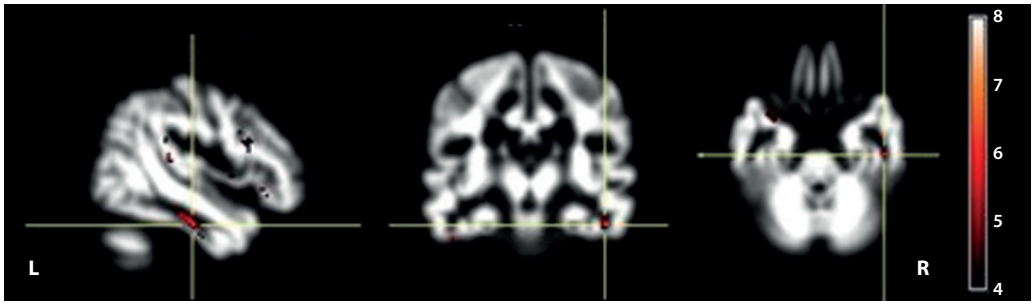
[a]Each circle or triangle represents a patient; horizontal bars indicate group means.
[b]Analysis of covariance (adjusted for age and interscan interval); significant main effect of outcome group: $F_{1,27} = 9.51$, $P = .005$.

Figure 3. Regions of Gray-Matter Volume Change Over Follow-Up in Remitted Patients (N = 12)[a]

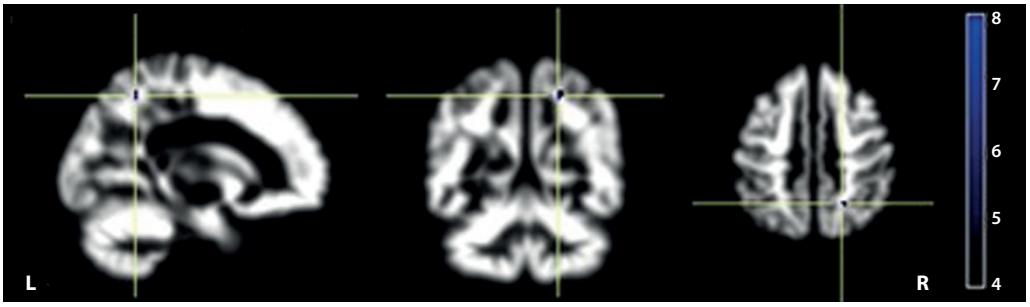
A. Right Orbitofrontal Cortex (increased gray-matter volume)



B. Right Inferior Temporal Gyrus (increased gray-matter volume)



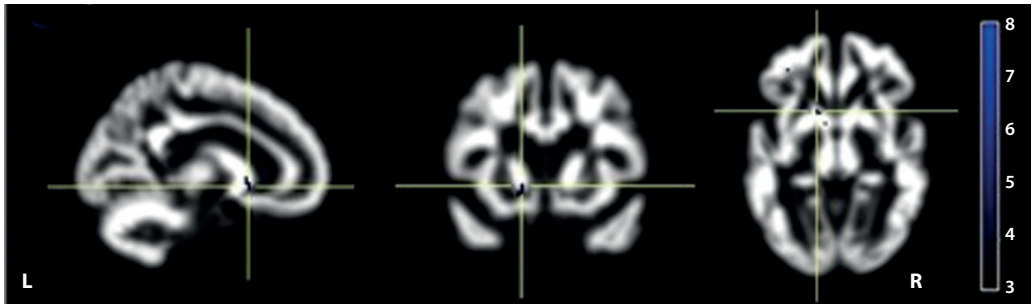
C. Right Superior Parietal Lobule (decreased gray-matter volume)



[a]Clusters of increased gray-matter volume from baseline to follow-up (in red) were detected in (A) the right orbitofrontal cortex ($t_{11} = 7.61$, $P = .006$; MNI coordinates: 50, 28, −6) and (B) the right inferior temporal gyrus ($t_{11} = 6.65$, $P = .004$; MNI coordinates: 50, −18, −26). Decreased gray-matter volume (in blue) was detected in (C) the right superior parietal lobule ($t_{11} = 6.28$, $P = .03$; MNI coordinates: 22, −54, 54). Statistical parametric maps were thresholded at cluster-size P value of .05, nonstationarity corrected for multiple comparisons and overlaid on the DARTEL-registered population-specific template. Crosshairs are centered on coordinates of local maxima.

Abbreviations: DARTEL = Diffeomorphic Anatomic Registration Through Exponential Lie Algebra, L = left, MNI = Montreal Neurological Institute, R = right.

Figure 4. White-Matter Volume Decrease Over Follow-Up in the Left Anterior Limb of the Internal Capsule in Nonremitted Patients (N = 15)[a]



[a]A cluster of decreased white-matter volume from baseline to follow-up (in blue) was detected in the left anterior limb of the internal capsule ($t_{13} = 3.86$, $P = .04$; MNI coordinates: −14, 16, −4). A statistical parametric map was thresholded at cluster-size P value of .05, nonstationarity corrected for multiple comparisons and overlaid on the DARTEL-registered population-specific template. Crosshairs are centered on coordinates of local maxima.

Abbreviations: DARTEL = Diffeomorphic Anatomic Registration Through Exponential Lie Algebra, L = left, MNI = Montreal Neurological Institute, R = right.

traditional descriptions, most patients were significantly more resistant than these criteria suggest. Many patients had previously experienced failure of up to 5 antidepressant trials, 3 had experienced failure of electroconvulsive therapy, and most had experienced chronic depressive episodes since their illness onset. Of the remitted patients, all remitted while receiving SSRIs or SNRIs given in combination with other medications, while no patients remitted while receiving SSRI treatment in monotherapy. Studies have shown combination therapy to be superior to SSRI monotherapy from treatment initiation,[26,27] and augmentation and combination strategies are now commonly thought to represent an important means to enhance response among pharmacotherapy-resistant patients.[28] The effects of such treatment strategies on brain volume, however, have yet to be determined. Previous studies have shown increases in whole-brain gray-matter volume in psychiatric patients following short-term treatment with various medications. These findings include a 4% gray-matter volume increase in bipolar patients following 4-week treatment with lithium[29,30] and a 3% gray-matter volume increase in schizophrenia patients treated with atypical antipsychotics.[31] While antidepressants have been shown to increase brain volume regionally, in the hippocampus in posttraumatic stress disorder[8] and in the anterior cingulate in MDD,[13] for example, to our knowledge, this study is the first to demonstrate whole-brain volume increase in unipolar MDD patients undergoing pharmacotherapy.

Volume changes were expected in the fronto-limbic areas implicated in depression, especially the hippocampus, anterior cingulate, and prefrontal cortices.[1,11] In remitted patients, gray-matter volume increases were localized to the right orbitofrontal cortex and inferior temporal gyrus. Studies have found decreased gray-matter volume and abnormal glucose metabolism and cerebral blood flow in the orbitofrontal cortex in MDD patients relative to controls.[32] Conversely, nonremitted patients demonstrated white-matter volume reduction in the left anterior limb of the internal capsule. Diffusion tensor imaging studies have shown reduced fractional anisotropy (a measure of white-matter integrity) in this region in MDD and have shown an association between decreased fractional anisotropy values and symptom severity.[33] Further, diffusion tensor imaging–based tractography has revealed structural projections between the anterior limb of the internal capsule and several brain regions commonly implicated in depression and antidepressant response.[34]

Voxel-based morphometry revealed no hippocampal volume increases in remitters. Although a recent longitudinal study found modest increases in hippocampal volume in MDD patients following 3-year antidepressant treatment,[35] no hippocampal modifications were observed at 1-year follow-up.[36] Hippocampal volume changes were not detected in another MDD sample following 7 months of SSRI treatment.[37] Antidepressant-mediated changes in hippocampal volume may not have been detected in this study because these changes may require a longer time period to become apparent.

This study is one of the first to examine morphological changes in a well-defined sample of patients with treatment-resistant MDD. Moreover, this study is among the first to investigate longitudinal brain-volume changes associated with remission status in depression. Despite these strengths, the study has certain limitations that warrant consideration. The first is the relatively small sample size. Although the longitudinal design of the study permitted powerful within-subject analyses, these results must be replicated in larger samples. Second, due to the naturalistic treatment approach used, it is not possible to perform in-depth analyses of the effects of any individual medication or combination/augmentation strategy on brain volume. Such analyses would require longitudinal imaging studies combined with randomized medication trials. Third, region-of-interest approaches in structural imaging studies provide more power to detect changes compared to voxel-based morphometry. Given the subtlety of the magnitude of volume changes in this study, region-of-interest analyses may be required to detect changes in small structures such as the hippocampus. The use of voxel-based morphometry, however, provides an unbiased volumetric assessment across the entire brain and is thus valuable, as it may have identified regions that respond to treatment and/or remission that have not been previously reported and/or investigated.

Antidepressants, mood stabilizers, and atypical antipsychotics are each thought to contribute to brain-volume increase through their neurotrophic and neuroprotective effects.[38] While all patients were treated with drugs from pharmacologic classes shown to protect against brain-volume loss, as a group, nonremitters had significantly higher prospective staging scores than remitters (indicating exposure to more intensive treatment due to pharmacologic nonresponse). Despite this fact, nonremitters on average still showed evidence of brain atrophy, suggesting that pharmacotherapy in the absence of sustained remission might be insufficient to elicit brain-volume increase in MDD. This finding is supported by the results of the regression and correlation analyses. Overall, brain atrophy was shown to increase with increasing patient age, consistent with findings in healthy individuals.[39] Further, while clinical improvement was associated with increased brain volume and time in remission was a significant predictor of volume change, treatment intensity was not a significant predictor variable. In other words, the amount of time a patient spent in remission was a better predictor of his or her brain-volume change than was the intensity of pharmacotherapy he or she received. Collectively, these results suggest that, in treatment-resistant depression, remission rather than pharmacologic treatment is most likely the key factor involved in halting atrophy and driving volumetric recovery. This finding is an important one since the restoration of brain volume in patients with treatment-resistant depression may have positive implications for their future prognosis.

Drug names: lithium (Lithobid and others), paroxetine (Paxil, Pexeva, and others).

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Previous presentations: Presented in part at the 64th Annual Scientific Convention and Meeting of the Society of Biological Psychiatry, May 14–16, 2009, Vancouver, British Columbia, Canada; the 15th Annual Meeting of the Organization for Human Brain Mapping, June 18–23, 2009, San Francisco, California; the 48th Annual Meeting of the American College of Neuropsychopharmacology–Hot Topics, December 6–10, 2009, Hollywood, Florida; and the 27th Biennial Congress of the International College of Neuropsychopharmacology, June 6–10, 2010, Hong Kong, China.
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Supplementary material: Supplementary eTables 1–3 are available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Brain-Volume Increase With Sustained Remission in Patients With Treatment-Resistant Unipolar Depression

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Supplementary eTable 1. Staging Score Methodology

Staging Method to Classify Retrospective[a] and Prospective[b] Degree of Treatment Resistance in Major Depressive Disorder

(1) For each adequate trial of an antidepressant medication (6 weeks at or above minimum recommended dose), 1 point was assigned per trial.

(2) For each optimization of dosage (treatment given at or above maximum recommended dose), an additional 0.5 points were assigned per trial.

(3) For each medication added to a primary antidepressant as an augmentation or combination strategy (treatment given for at least 6 weeks regardless of the dosage), an additional 0.5 points were assigned per trial.

(4) For each adequate trial of electroconvulsive therapy (at least nine sessions), an additional 3 points were assigned per trial.

[a] Retrospective staging scores reflect treatment approaches taken during the five-year period preceding study enrollment. No points were assigned in retrospective chart reviews if trial dosage, time frame, or strategy was unclear.

[b] Prospective staging scores were calculated from baseline visit to first remission visit. No points were assigned if drugs were discontinued due to side effects or noncompliance. Medication changes made during sustained remission were not included in calculations.

Supplementary eTable 2. Minimum and Maximum Doses of Antidepressants and Other Medications Used in the Calculation of Staging Scores for Treatment Resistance

Drug Class **Generic Name**	**Minimum Recommended Dose (mg/day)**	**Maximum Recommended Dose (mg/day)**
Tricyclic Antidepressants		
clomipramine	150	250
amoxapine	150	250
amitriptyline	150	250
maprotiline	100	250
desipramine	150	250
nortriptyline	75	125
doxepin	150	250
trimipramine	150	250
imipramine	150	250
protriptyline	30	60
Monoamine Oxidase Inhibitors (MAOIs)		
isocarboxazid	30	60
phenelzine	45	90
tranylcypromine	30	60
maclobemide	300	900
Selective Serotonin Reuptake Inhibitors (SSRIs)		
fluvoxamine	50	300
paroxetine	20	60
fluoxetine	10	60
sertraline	50	150
citalopram	20	60
escitalopram	10	30
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)		
venlafaxine	125	250
duloxetine	60	100
Norepinephrine Reuptake Inhibitor		
atomoxetine	40	100

Supplementary eTable 2 (cont.)

Drug Class **Generic Name**	**Minimum Recommended Dose (mg/day)**	**Maximum Recommended Dose (mg/day)**
Other Antidepressants		
trazodone	300	600
nefazodone	300	600
bupropion	300	450
mirtazapine	15	45
pinodolol	7.5	15
topiramate	300	600
Atypical Antipsychotics		
quetiapine	50	600
clozapine	25	100
olanzapine	5	20
ziprasidone	40	100
aripiprazole	5	30
paliperidone	1.5	9
risperidone	0.25	4
Other Medications		
lithium	600	1200
triiodothyronine	0.025	0.05
buspirone	20	60
Dopamine agonists		
pramipexole	1	5
bromocriptine	2.5	5

Supplementary eTable 3. Treatment Approaches Used by Patients at Baseline and Follow-Up Imaging and Remission Status at Follow-Up

Patient	Baseline Treatment, Dosage (mg/day)	Follow-Up Treatment, Dosage (mg/day)	Status
1	citalopram 10, venlafaxine 225, quetiapine 50, trazodone 100	fluoxetine 40, quetiapine 300, trazodone 150	NR
2	venlafaxine 300, quetiapine 50, dextroamphetamine 20	tranylcypromine 20, atomoxetine 60	NR
3	venlafaxine 150	venlafaxine 150, bupropion 300	NR
4	escitalopram 10, atomoxetine 60, trazodone 100	bupropion 450, atomoxetine 60, trazodone 75	R
5	doxepin 300, flurazepam 30	venlafaxine 225, mirtazapine 30	NR
6	paroxetine 50	tranylcypromine 20, quetiapine 300	NR
7	fluoxetine 40, bupropion 300	fluoxetine 40, atomoxetine 25, trazodone 150	R
8	venlafaxine 300	moclobemide 900, bupropion 300	NR
9	venlafaxine 150, risperidone 0.5	venlafaxine 300, mirtazapine 45, pindolol 15, lamotrigine 100	R
10	bupropion 150	venlafaxine 300, bupropion 450	R
11	escitalopram 15, bupropion 150	escitalopram 30, buspirone 30, lithium 900, quetiapine 25	NR
12	paroxetine 50, trazodone 100	escitalopram 40, risperidone 2, lamotrigine 175	NR
13	venlafaxine 150, bupropion 150, trazodone 100	escitalopram 15, bupropion 150, mirtazapine 30	R
14	venlafaxine 300, amitriptyline 50, zopiclone 10	venlafaxine 300, amitriptyline 50, risperidone 2	NR
15	fluoxetine 40, clomipramine 50	escitalopram 10, bupropion 150, trazodone 100	R
16	venlafaxine 225, bupropion 300, risperidone 1	venlafaxine 300, nortriptyline 50, paliperidone 6	NR
17	moclobemide 750	escitalopram 40, pramipexole 3, bupropion 300	NR
18	paroxetine 20, bupropion 100, trazodone 50	paroxetine 20, bupropion 100, risperidone 1	R
19	paroxetine 20, amitriptyline 20, trazodone 150	paroxetine 40, pindolol 10, trazodone 150	R
20	paroxetine 60, mirtazapine 45, olanzapine 10, lithium 900	escitalopram 40, mirtazapine 60, buspirone 30, zopiclone 7.5	R
21	venlafaxine 225	venlafaxine 225, pindolol 10, trazodone 100	R
22	venlafaxine 225, olanzapine 10, trimipramine 100, temazepam 60, clonazepam 1, eltroxin 0.1	venlafaxine 150, ziprasidone 40, trimipramine 20 diazepam 20, levothyroxine 0.075	NR
23	citalopram 40, bupropion 150	escitalopram 20, atomoxetine 80, pramipexole 4, quetiapine 50	NR
24	venlafaxine 300, bupropion 150	venlafaxine 375	NR
25	escitalopram 20, bupropion 150, topiramate 100, temazepam 15	escitalopram 40, ziprasidone 40, pindolol 5, trazodone 100	NR
26	venlafaxine 187.5	venlafaxine 225, bupropion 450, trazodone 200	R
27	paroxetine 40, bupropion 150, trazodone 50	paroxetine 40, atomoxetine 40, modafinil 100, trazodone 150	R

Abbreviations: NR = nonremitter; R = Remitter