Depression-Related Variation in Brain Morphology Over 3 Years

Effects of Stress?

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Context: Results of experimental studies suggest that neuroplastic changes may occur during depressive episodes. These effects have not been confirmed in patients with depression, to our knowledge.

Objective: To examine changes in the brains of patients with major depression vs those of healthy control subjects.

Design: Prospective longitudinal 3-year study.

Setting: Inpatients with major depression were recruited from the Department of Psychiatry and Psychotherapy, Ludwig Maximilians University of Munich, Munich, Germany, and controls were recruited from the local community.

Participants: The study included 38 patients with major depression and 30 healthy controls.

Main Outcome Measures: High-resolution magnetic resonance imaging was performed at baseline and 3 years later. Voxel-based morphometric measurements were estimated from magnetic resonance images, and psychopathologic findings were assessed at baseline, weekly during the inpatient phase, and then after 1, 2, and 3 years.

Results: Compared with controls, patients showed significantly more decline in gray matter density of the hippocampus, anterior cingulum, left amygdala, and right dorsomedial prefrontal cortex. Patients who remitted during the 3-year period had less volume decline than non-remitted patients in the left hippocampus, left anterior cingulum, left dorsomedial prefrontal cortex, and bilaterally in the dorsolateral prefrontal cortex.

Conclusion: This study supports findings from animal studies of neuroplastic stress-related processes that occur in the hippocampus, amygdala, dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, and anterior cingulum during depressive episodes.

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Dysfunction of neuronal plasticity or remodeling may contribute to the pathogenesis of mood disorders. This hypothesis is supported by preclinical studies demonstrating that stress and depression lead to changes in hippocampal morphologic structure. Experimental animal studies showed that prolonged stress decreases the numbers of apical dendritic branch points and the length of apical dendrites, particularly in the laminar CA3 region of the hippocampus. This effect is glucocorticoid dependent and can emerge after 3 weeks of experimental corticosteroid treatment. In animal models, antidepressants suppress the toxic effects of stress on the hippocampus and increase hippocampal neurogenesis.

Many in vivo neuroimaging investigations have detected reduced hippocampal volumes in older and younger patients with major depression. The results for other brain regions are inconsistent. For example, enlarged amygdala volumes and reduced volumes of the anterior cingulum and the prefrontal cortex have been reported in some investigations using region of interest (ROI) analysis in structural magnetic resonance (MR) imaging, suggesting alterations in the frontolimbic network. The basal ganglia are reduced in patients with major depression, but this is more likely to occur in late-onset depression.
The first indication of a relationship between structural alterations and the course of the depression was obtained from cross-sectional investigations. Significant associations were reported between chronic depression and reduced left hippocampal gray matter density (GMD) measured by voxel-based analysis.\(^9\) Moreover, using statistical parametric mapping, a recent study\(^9\) found that the right hippocampus is reduced in older patients with depression, particularly in patients with a longer course of illness. Moreover, a relationship between hippocampal volume decline and longer cumulative illness duration has been described.\(^9\)

Voxel-based morphometry (VBM) has become an established research method in recent years.\(^11\) It enables the global assessment of brain structures without a priori identification of the ROI and is useful because it allows analysis of brain regions in which boundaries are difficult to define. Using VBM, smaller volumes of the medial part of the bilateral frontal lobes have been detected in patients with subthreshold depression,\(^12\) and smaller volumes of the right hippocampus and the bilateral middle frontal gyrus have been found in patients with major depression.\(^9\)

According to the hypothesis regarding the toxic effects of stress, hippocampal volumes may be expected to diminish during a depressive episode.\(^13\) To our knowledge, no follow-up investigations about the whole brain have been published. There is not only a lack of studies examining these changes in patients with different stages of depression (eg, remitted depressed states) but also few studies with a longitudinal prospective design. A longitudinal study\(^14\) demonstrated no significant change during 1 year in 30 patients with major depression and showed that a small hippocampal volume at the beginning of the study was related to a poor clinical outcome. Limitations of this first prospective study were that regions other than the hippocampus were not investigated, the interval (1 year) was short, and cofactors such as medication could not be accounted for because of the small number of patients participating. Furthermore, a longitudinal study\(^15\) on white matter (WM) and subcortical gray matter (GM) lesions in 164 depressed subjects and 126 healthy subjects older than 60 years found that lesion volume progression was associated not only with aging but also with the pathologic condition of late-life depression.

The aim of this prospective longitudinal VBM study was to compare baseline and 3-year follow-up GMD findings in patients with major depression vs those in healthy control subjects to examine whether depression results in a further diminution of GMD. We hypothesized that, compared with healthy controls, patients with depression would show reduced GMD in the hippocampus, amygdala, anterior gyrus cinguli, and dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC), that GMD would further diminish in patients with chronic depression and relapses, and that GMD reduction would cease in patients with remission during the 3-year period.

### METHODS

#### PARTICIPANTS

Thirty-eight inpatients with major depression (mean [SD] age, 46.1 [11.3] years) were recruited from the Department of Psychiatry and psychotherapy, Ludwig Maximilians University of Munich, Munich, Germany (Table 1). Psychiatric diagnoses were made on the basis of DSM-IV criteria and the Structured Clinical Interview for DSM-IV and were determined by a consensus of at least 2 psychiatrists (T.F. and M.J.). Clinical variables were documented using the 21-item Hamilton Depression Rating Scale\(^16\) at baseline and then after 1, 2, and 3 years.

At the time of MR imaging, patients were taking the following medications: seroton reuptake inhibitors (citalopram hydrobromide by 4 patients, sertraline hydrochloride by 2 patients, and paroxetine hydrochloride by 2 patients), tricyclic antidepressants (amitriptyline hydrochloride by 5 patients, doxepin hydrochloride by 5 patients, and amitriptyline oxide by 2 patients), other new antidepressants (mirtazapine by 6 patients, venlafaxine hydrochloride by 4 patients, and reboxetine mesylate by 3 patients), maprotiline by 3 patients, lithium carbonate by 1 patient, and no antidepressant by 1 patient. Patients were also treated with supporting psychotherapy during their hospital stay.

<table>
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<th>Variable</th>
<th>Patient Group (n = 38)</th>
<th>Control Group (n = 30)</th>
<th>t Test P Value</th>
<th>Remitted Patients (n = 21)</th>
<th>Nonremitted Patients (n = 17)</th>
<th>t Test P Value</th>
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<td>43.6 (11.3)</td>
<td>.40</td>
<td>44.0 (11.2)</td>
<td>48.7 (11.3)</td>
<td>.20</td>
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<td>19:11</td>
<td>.83</td>
<td>14:7</td>
<td>11:6</td>
<td>.90</td>
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<td>.44</td>
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<td>15:2</td>
<td>.98</td>
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<td>Height, mean (SD), cm</td>
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<td>170.9 (8.6)</td>
<td>.54</td>
<td>171.9 (7.1)</td>
<td>168.1 (8.4)</td>
<td>.26</td>
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<tr>
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<td>69.8 (10.5)</td>
<td>.54</td>
<td>66.2 (14.2)</td>
<td>67.6 (14.0)</td>
<td>.76</td>
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<td>Alcohol consumption, mean (SD), g/d</td>
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<td>5.2 (6.2)</td>
<td>.80</td>
<td>5.1 (9.9)</td>
<td>4.5 (14.4)</td>
<td>.67</td>
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<tr>
<td>Age at onset, mean (SD), y</td>
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<td>38.2 (11.8)</td>
<td>42.2 (12.5)</td>
<td>.59</td>
<td></td>
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<td>22.8 (18.5)</td>
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<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>24.9 (6.8)</td>
<td>. . .</td>
<td>23.9 (6.8)</td>
<td>26.2 (6.7)</td>
<td>.30</td>
<td></td>
</tr>
<tr>
<td>After 3 y</td>
<td>6.5 (8.6)</td>
<td>. . .</td>
<td>2.0 (2.2)</td>
<td>12.1 (10.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: Ellipsis, not applicable.

\(^a\) No significant differences were found between patients and control subjects or between remitted and nonremitted patients by t test or by \(x^2\) test. Boldfaced values are the totals of remitted and nonremitted patients.
For comparison, 30 healthy controls were matched for age (mean [SD] age, 43.6 [11.3] years), sex, and handedness (Table 1). Neither the controls nor their first-degree relatives had a history of neurologic or mental illness.

A structured interview was used to assess medical history, trauma, and other exclusion criteria for all subjects. Exclusion criteria for patients and controls were neurologic diseases, age older than 65 years, previous alcohol or other drug abuse, cortisone medication in the medical history, and previous head injury with loss of consciousness. Patients having comorbidity with other mental illnesses (eg, bipolar disorders) or personality disorders were also excluded. No subject had received electroconvulsive therapy before the investigation. Handedness was determined using the Edinburgh Inventory.17

Full remission during the 3-year period was defined as a score of at least 7 on the 17-item Hamilton Depression Rating Scale, calculated from the 21-item Hamilton Depression Rating Scale. Of 21 patients who fully remitted, 11 continued to take their medication during the 3 years, and, of 17 nonremitted patients, 12 continued to take their medication.

The study was described in detail to the patients and the controls, and written informed consent was obtained. The study design was approved by the local ethics committee and was prepared in accord with the ethical standards of the Declaration of Helsinki.

MR IMAGING PROCEDURES

Data Acquisition
At baseline and 3 years later, MR images were obtained (Magnetom Vision; Siemens, Erlangen, Germany) at 1.5 T. All subjects were imaged on the same scanner at baseline and at follow-up using a T1-weighted 3-dimensional MPRAGE (magnetization prepared rapid gradient echo) sequence (repetition time, 11.6 milliseconds; echo time, 4.9 milliseconds; total acquisition time, 9 minutes; number of acquisitions, 1; field of view, 230 mm; matrix, 512 x 512 pixels; and section thickness, 1.5 mm, yielding 126 contiguous axial sections with a defined voxel size of 0.45 x 0.45 x 1.5 mm). After manually reorienting and centering the images on the anterior commissure, data preprocessing was performed based on the VBM approach by Good et al18 and implemented in the VBM2 toolbox (http://dbm.neuro.uni-jena.de), a software extension (SPM2; Wellcome Department of Cognitive Neurology, London, United Kingdom), using commercially available statistical software (MATLAB 6.5; The MathWorks, Natick, Massachusetts). The VBM2 toolbox provides state-of-the-art longitudinal VBM preprocessing algorithms.

VBM Preprocessing
All data were blinded so that the staff could not distinguish between diagnosis or follow-up. Optimized longitudinal VBM was implemented as a 2-step procedure, starting with the construction of a study-specific whole-brain template and GM, WM, and cerebrospinal fluid (CSF) priors.

For the first step, the MR images were segmented into GM, WM, and CSF partitions and were reprocessed using a hidden Markov random field (HMRF) model.19 The images were then registered to the space of the Montreal Neurological Institute whole-brain template by matching the GM partitions to the Montreal Neurological Institute GM template using affine and nonlinear normalization parameters.20 The normalized T1-weighted images and the GM, WM, and CSF partitions were averaged and smoothed using an 8-mm full width at half maximum (FWHM) gaussian kernel. Therefore, a study-specific whole-brain template and tissue priors were created that accounted for the magnetic field properties of the scanner and the anatomical properties of our study cohorts.

In the second step, the custom T1-weighted template and tissue priors were used. An initial bias field correction of the baseline and follow-up images was performed. Because of differing intrasubject distributions of intensity nonuniformities caused by the time lag between baseline and follow-up MR images, an additional bias correction was performed to minimize these differences. For this purpose, an intrasubject difference bias field was approximated with the intracranial parts of the difference image smoothed using a Gaussian kernel with a large FWHM of 30 mm.

The follow-up MR images were registered to the corresponding baseline images to correct for position but not size. All baseline and follow-up images were segmented in native space and were filtered by means of the HMRF algorithm. This algorithm provides spatial constraints based on neighboring voxel intensity information within a 3 x 3 x 3-voxel cube. The procedure improves the signal to noise ratio by removing isolated voxels of a certain tissue class that are unlikely to be a member of that class and closes holes in a cluster of connected voxels of that class.

After HMRF filtering, the segmented baseline data were normalized to the customized whole-brain template by affine and nonlinear normalization of GM partitions to the customized GM template. The normalization estimates derived from this procedure were applied on the corresponding follow-up images. Therefore, spatial normalization removed interindividual anatomical differences, while preserving intraindividual longitudinal changes. All normalized whole-brain volumes were resegmented, which further removed nonbrain voxels from the brain tissue. This segmentation step was finished by reapplying the HMRF model to the GMD maps (GMD refers to the probability of finding GM in a certain voxel, not to absolute GM volume). Before statistical analysis, normalized GMD maps of baseline and follow-up images were smoothed using a 10-mm FWHM gaussian kernel.

STATISTICAL ANALYSIS
The framework of the general linear model was used for the longitudinal VBM analysis of patients and controls. Group and time interactions for GMD changes during the follow-up period were tested using a longitudinal repeated-measures analysis of variance. After parameter estimation, contrasts were defined for GMD increases and decreases over time within and between groups. Longitudinal GMD reductions occurring in both groups were assessed at P < .05 (corrected for familywise error) after exclusion of GMD changes in the control group from the statistical maps of interest at a height threshold of uncorrected P < .05 (mask height threshold).

To test our hypothesis of different longitudinal GMD changes in patients and controls at P < .001, small-volume-corrected VBM analyses were performed for the following 5 ROIs: the hippocampus, amygdala, anterior cingulum, DMPFC, and DLPC. The chosen threshold of P < .001 was difficult to achieve because Bonferroni correction would have required P < .01.

The small-volume-corrected patient subgroup analyses were performed for the 5 ROIs. We tested the longitudinal GMD differences in stable remitted patients vs nonremitted patients. With Bonferroni correction, the statistical threshold was reduced from P < .05 to P < .01. Coordinates of peak significant voxels were assigned to anatomic regions by means of automated anatomic labeling.20
RESULTS

DEMOGRAPHIC DATA

Age, sex, height, weight, handedness, and alcohol consumption were similar in patients and controls. These variables, as well as age at onset, cumulative illness duration, and Hamilton Depression Rating Scale score at baseline, were also similar in stable remitted patients and nonremitted patients after 3 years (Table 1). Patients with stable remission did not discontinue their antidepressants more often than nonremitted patients ($t_{35} = 1.3, P = .25$).

LONGITUDINAL GMD

Whole-Brain Analysis

The most significant longitudinal GMD reductions were found within the DMPFC, anterior cingulum, hippocampus, DLPFC, and orbitofrontal cortex, as well as in some other areas of the frontal, temporal, parietal, and occipital cortices and the cerebellum; these reductions were found in patients with major depression but not in controls (Figure 1 and Table 2). Within the frontal cortex, significant volume decline was detected in the superior and medial frontal cortices and in the superior and medial orbitofrontal cortices in patients with major depression but not in controls. The temporal cortices showed GMD reductions with right-pronounced localizations in the temporal pole and superotemporal lobe and with left-pronounced localizations in the fusiform gyrus and in the left hippocampus and parahippocampal gyrus. The cerebellum also showed GMD decline (which was more pronounced on the left side) in patients with major depression but not in controls. Additional bilateral structural alterations were found within the cuneus, lingual gyrus, and left precuneus. Bilaterally, the superior and middle occipital cortex showed reductions in GMD at the 3-year follow-up in patients but not in controls. No significant GMD losses were observed in the head and body of the basal ganglia and the thalamus.

No significant GMD increases were found at the 3-year follow-up in patients compared with controls. Some regions showed GMD decline from baseline to follow-up in the controls that was not seen in the patients. This decline was found bilaterally within the superior and inferior orbitofrontal cortices, the gyrus rectus, and some regions of the cerebellum.

ROIs Analysis

In patients compared with controls, small-volume corrections for our ROIs revealed significantly greater GMD decline in the hippocampus (bilaterally left pronounced), as well as in the anterior cingulum and the left amygdala. The right DMPFC also diminished during the 3-year follow-up to a greater extent in patients than in controls. The DLPFC, right amygdala, and left DMPFC did not show more volume decline in patients than in controls at the follow-up (Figure 2).

Effects of Clinical Outcome

The investigation of whether patients with stable remission during the 3-year follow-up period differ from the nonremitted patients revealed significant GMD decline in the left hippocampus, left anterior cingulum, left DMPFC, and bilaterally in the DLPFC in nonremitted patients (Figure 3). Compared with controls, nonremitted and stable remitted patients had greater GMD decline in these regions.

COMMENT

To our knowledge, this study demonstrates for the first time the progression of changes in GMD during 3 years in individuals with major depression compared with healthy controls. In this first longitudinal study, patients showed higher volume decline in the anterior cingulum, left amygdala, and right DMPFC and bilaterally in the hippocampus, compared with controls. The GMD of the superior and medial frontal cortices and the superior and medial orbitofrontal cortices and cerebellum also diminished significantly.

A growing amount of scientific data suggests that the cerebellum and its relevant neural connections to prefrontal areas should be integrated in models of depression. Because the vermis has the highest density of glucocorticoid receptors during development, exceeding that of the hippocampus, it may be particularly vulnerable to the effects of stress hormones. An early MR imaging study showed reduced cerebellar vermis size in patients with unipolar depression, compared with healthy controls, whereas a more recent quantitative MR imaging study failed to demonstrate any statistically significant differences.

Most of our patients remitted after the inpatient treatment phase, but about 17 patients (45%) relapsed during the follow-up period. These were patients with the worst outcomes. The remaining 21 patients (55%) were stable over 3 years. Patients with incomplete remission and relapses to depression during the 3-year follow-up had a larger volume decline in the hippocampus, anterior cingulum, DLPFC, and DMPFC compared with stable remitted patients. The GMD decline in the amygdala did not differ between stable remitted patients and nonremitted patients. Therefore, GMD decline in the hippocampus, anterior cingulum, and prefrontal cortices seems to depend on depression-related factors such as stress, whereas GMD decline in the amygdala seems to be independent of the depressive state. In line with this, a cross-sectional study reported an association between days of untreated depressive episodes and hippocampal volume reduction.

These results support changes in the structural integrity of neuronal cells in these specific important brain regions constituting a fronto-limbic-cerebellar network during depressive episodes and in particular during the course of depression. These data suggest that neuroplastic changes occur as a result of stress- and depression-related factors. Therefore, our results support transla-
Figure 1. Overall brain gray matter density decline during 3 years in patients with major depression. Shown are regions in which gray matter density significantly diminishes from baseline to the follow-up investigations in patients with major depression, masked for the decline in healthy control subjects to determine a major depression–specific pattern. Numbers below sections represent the vertical distance in millimeters to the anterior commissure. Significant longitudinal gray matter density reductions within the dorsomedial prefrontal cortex, anterior cingulum, hippocampus, dorsolateral prefrontal cortex, and orbitofrontal, temporal, parietal, and occipital cortices are shown for patients with major depression compared with controls. Color of bar scales indicate the amount of significance. A difference between patients and controls is shown.
Table 2. Progression of Gray Matter Density Decline in Whole-Brain Baseline and Follow-up Magnetic Resonance Images of Patients With Major Depression, Compared and Masked for the Decline in Healthy Control Subjects to Determine a Major Depression–Specific Pattern

<table>
<thead>
<tr>
<th>Variable</th>
<th>Left MNI Coordinates</th>
<th>Right MNI Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>k</td>
<td>k %</td>
</tr>
<tr>
<td>Frontal superior</td>
<td>1535</td>
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<td>Frontal superior orbital</td>
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<td>2.6</td>
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<tr>
<td>Frontal mid</td>
<td>440</td>
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<tr>
<td>Frontal inferior</td>
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<td>Frontal medial orbital</td>
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<td>Limbic</td>
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<td>Cingulum anterior</td>
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<td>Vermis_6</td>
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<td>13.5</td>
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</table>

Abbreviations: FEW, familywise error; k, number of significant voxels; k %, percentage of significant voxels in the anatomical region; L, left, MNI, Montreal Neurological Institute; R, right, ellipsis, not applicable.

a Corrected for multiple comparisons.
tion of the hypothesis regarding toxic effects of stress in depression to humans and are in agreement with cross-sectional findings on the relationship between illness duration and hippocampal volumes.

A recent study found no significant volume decline in the hippocampus during 1 or 3 years using manual tracing methods (ROI). We have analyzed the data using VBM and found different results from those of the ROIs analysis. The strength of VBM is that altered parts of anatomical regions can be detected and the whole brain can be analyzed. However, a limitation of VBM is that the normalization procedure...
reduces the power to identify alterations in anatomically complex regions.

Mayberg\textsuperscript{25} suggests a model of depression in which a dorsal compartment (including the DLPFC, DMPFC, and anterior cingulum) that is involved in the cognitive symptoms of depression is hypoactive and in which a ventral compartment (consisting of the hippocampus, amygdala, subgenual cingulum, insula, brainstem, and hypothalamus) is hyperactive. Our results indicate GMD decline in the DLPFC, DMPFC, and anterior cingulum,
particularly in patients with ongoing depression; the hypoa
citivity in these regions during depressive episodes may
be related in part to GMD decline. However, the hippo-
campus, which is supposed to be hyperactive in May-
berg’s model, also shows GMD decline, which may be in
line with experimental findings on the toxic effects of
stress.13

Because GMD diminishes during the course of the dis-
ease, probably due to effects of depression, and because
this decline has consequences for the clinical course,
therapy with antidepressants or psychotherapy should
be started as early as possible. Therefore, early diagnos-
sis of depression is just as important as early diagnosis
of dementia and schizophrenia.

The findings of the study are new and deserve discus-
sion, particularly with respect to some limitations. Pa-
tients were taking medication at baseline and at follow-
up. We did not detect any differences between patients
taking their medication over the 3-year period vs those
who stopped taking medication because they remitted.
In 20 patients with posttraumatic stress disorder, the mean
hippocampal volume was increased by about 4.6% after
a 36- to 48-week antidepressant trial with paroxetine.20
However, in patients with major depression, no signifi-
cant change in the hippocampal volume was found after
a mean (SD) of 7 (3) months of successful treatment with
serotonin reuptake inhibitors (in particular, fluoxetine)
compared with the pretreatment investigation.27 A pre-
liminary investigation in 10 pediatric patients with ob-
ssive-compulsive disorder showed enlarged thalamic
volumes before treatment and a decrease of thalamic vol-
umes after 12 weeks of treatment with paroxetine, but it
is unclear whether this effect was due to the medication
or to symptom changes during treatment.28 It may be that
morphologic changes are more likely to be seen after a
longer period, as in our study, than after a few months
of treatment.

Patients who during the entire 3-year period were re-
mitted had less volume decline in the left hippocampus,
left anterior cingulum, and left DMPFC and bilaterally
in the DLPFC compared with nonremitted patients. We
are aware of no evidence that antidepressants act unilat-
erally on neurogenesis or neuropsychic processes, so we
have to regard this finding with caution. The lack of
changes in the right hippocampus and anterior cingu-
ulum could be a result of too small sample size and power.

The sample was insufficient to allow the clinical out-
come to be assessed for all relevant treatment factors (eg,
different pharmacotherapy or psychotherapy), so only the
overall clinical outcome can be considered for VBM anal-
ysis. Studies in larger samples are necessary to investi-
gate this question.

Our patients were treated according to current clini-
cal practice in German hospitals for moderate to severe
major depression after outpatient treatment has failed or
when an episode is too severe. Therefore, the disease in
this population may be more severe than that in an out-
patient sample, which should be considered when com-
paring our results with those future studies.

Patients in our study have a somewhat older age at
onset than the mean age at onset in the general popula-
tion. The reason for this is unclear but may be because
our sample had more treatment resistance than an out-
patient sample.

In summary, our findings indicate that during depres-
sive episodes GMD diminishes in limbic and frontal cor-
tical brain regions, indicating neuropsychic changes due
to the effect of depression. More severe neuropsychic
abnormalities in the hippocampus, DLPFC, and an-
terior cingulum, particularly during the course of de-
pression, seem to be clinically associated with a more
severe outcome of depression. It is likely that an early
start of treatment with antidepressants and psycho-
therapy may prevent neuropsychic changes that, in turn,
worsen the clinical course. Moreover, much more effort
is needed to explore the nature of these changes (eg, by
translational research approaches), and further studies
are necessary to address these aims.

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