Association of the Brain-Derived Neurotrophic Factor Val66Met Polymorphism With Reduced Hippocampal Volumes in Major Depression

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Context: Brain-derived neurotrophic factor (BDNF) modulates hippocampal plasticity, which is believed to be altered in patients with major depression.

Objective: To examine the effect of the BDNF Val66Met polymorphism on hippocampal and amygdala volumes in patients with major depression and in healthy control subjects.

Design: Cross-sectional comparison between patients and controls.

Setting: Inpatients with major depression from the Department of Psychiatry and Psychotherapy and healthy controls from the community were recruited.

Participants: The study population of 120 subjects included 60 patients with major depression and 60 healthy controls.

Main Outcome Measures: Using a combined strategy, hippocampal and amygdala volumes were estimated on high-resolution magnetic resonance images, and genotyping was performed for the BDNF Val66Met polymorphism.

Results: Patients had significantly smaller hippocampal volumes compared with controls (P = .02). Significantly smaller hippocampal volumes were observed for patients and for controls carrying the Met-BDNF allele compared with subjects homozygous for the Val-BDNF allele (P = .006). With respect to amygdala volumes, no significant differences between patients and controls and no significant main effects for the BDNF Val66Met polymorphism were observed.

Conclusions: These genotype-related alterations suggest that Met-BDNF allele carriers might be at risk to develop smaller hippocampal volumes and may be susceptible to major depression. This study supports findings from animal studies that the hippocampus is involved in brain development and plasticity.

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Major depression is one of the most frequent human diseases, with a lifetime prevalence of 16% and a 12-month prevalence of 6.6%. Dysfunction of neuronal plasticity or remodeling could contribute to the pathophysiology of mood disorders. This hypothesis is supported by preclinical and clinical investigations demonstrating that stress and depression lead to reduction of the total volume of the hippocampus and to atrophy and loss of neurons in the adult hippocampus. Experimental studies found that prolonged stress decreases the number of apical dendritic branch points and the length of apical dendrites, particularly in the laminar CA3 region of the hippocampus. This effect was glucocorticoid dependent and emerged after 3 weeks of experimental corticosterone treatment. Moreover, antidepressants suppress the toxic effects of stress on the hippocampus and increase hippocampal neurogenesis. In vivo investigations detected reduced hippocampal volumes in older patients and in younger patients with major depression. Two meta-analytic studies confirmed that the hippocampus is consistently reduced in volume in patients with major depression, although there were some negative findings.

With respect to the neurotrophin hypothesis of depression, brain-derived neurotrophic factor (BDNF) is of major importance because it modulates hippocampal plasticity in physiological models and in animals. Depressive states in animal models have been shown to be associated with reduced BDNF levels in the brain, and central administration of BDNF has been demonstrated to reverse such depressive states. However, BDNF also seems to be impor-
tant for the manifestation of depressive states. In mice, BDNF function was required for the development of persistent social aversion in a social defeat paradigm. Chronic treatment then restored social functioning, and blockade of BDNF activity in the ventral tegmental area and projections to the nucleus accumbens exerted antidepressant-like effects.13

Haplotype analysis of the BDNF gene showed a robust association with major depression and with schizotypal personality disorder.24 In another study,7 no significant association was found between BDNF and unipolar depression. A common single nucleotide polymorphism consisting of a missense change (G196A) that produces a nonconservative amino acid change (valine to methionine) in the coding exon of BDNF at position 66 (Val66Met) was recently described as a functional polymorphism.18 In a large community sample of 441 subjects, the Val-BDNF allele was associated with a high neuroticism score, which is a risk factor for depression. Other investigators failed to replicate this finding in 3 large populations.15 Patients with geriatric depression in a Taiwanese veteran population showed a significant excess of the Met-BDNF allele compared with control subjects,29 whereas no significant associations were detected in a Chinese population21,22 or in a German population.19 The BDNF Val66Met polymorphism was associated with cognitive performance during the Wisconsin Card Sorting Test in patients with bipolar disorder; patients homozygous for the Val-BDNF allele had a higher percentage of correct reaction in the task.21 Recently, patients with schizophrenia carrying the Met-BDNF allele were observed to have more visuospatial impairment.24 Overall, there is great diversity in the findings regarding the association between BDNF and depression.

The BDNF Val66Met polymorphism in BDNF in the 5′ signal domain has been shown to affect intracellular packaging and regulation of BDNF secretion25 and human hippocampal function.26 Healthy Met-BDNF allele carriers had substantial relative decreases in hippocampal volume that are gender and age independent, suggesting that these changes may occur before adulthood.27,28 The Met-BDNF allele may be a vulnerability factor for the development of disease processes associated with dysfunction of this brain region. However, an exaggerated age-related volume reduction of the dorsolateral prefrontal cortex was found in healthy Met-BDNF allele carriers; therefore, subjects with the Met-BDNF allele might be more vulnerable to aging than individual homoyzygous for the Val-BDNF allele.29 Furthermore, stress decreases the expression of BDNF in the hippocampus.30 So far, there is no study available (to our knowledge) that has investigated the effect of the BDNF polymorphism on hippocampal volumes in patients with depression and in healthy control subjects. A possible association between the BDNF polymorphism and hippocampal reductions that in turn have an effect on the development of depression may enhance our knowledge of the neurotrophic and neurogenic hypothesis of depression.31

Herein, we used a combined strategy of neuroimaging techniques and genetic analysis to identify the effect of the BDNF polymorphism on the hippocampus and amygdala in patients with major depression and in healthy controls. In a sample of 40 patients and 40 controls, patients with major depression carrying the L/L genotype in the promoter region of the serotonin transporter gene (5-HTTLPR) were found to have reduced hippocampal volumes compared with healthy controls.32 In the present study, we sought to test the following hypotheses: (1) In this large sample, hippocampal and amygdala volumes are reduced in patients with major depression compared with healthy controls. (2) Reduced hippocampal or amygdala volumes are related to the BDNF polymorphism among the patients.

### METHODS

Sixty inpatients with major depression from the Department of Psychiatry and Psychotherapy, Ludwig-Maximilians University, Munich, Germany, were recruited (age range, 18-65 years; mean±SD age, 44.2±11.7 years) (Table 1). Psychiatric diagnoses based on DSM-IV criteria and on the Structured Clinical Interview for DSM-IV were determined by a consensus of at least 2 psychiatrists. Clinical variables were documented using the 21-item Hamilton Depression Rating Scale.33 All patients were inpatients. Thirty patients had a first depressive episode, and 30 patients had recurrent episodes. There were 8 patients with 1 earlier admission to a psychiatric hospital, 5 patients with 2 earlier admissions, 2 patients with 3 earlier admissions, and 1 patient each with 4, 12, and 15 earlier admissions. Almost all patients, except those not taking antidepressant medication, were in an outpatient service and were treated with antidepressants before the current admission. They were hospitalized because their conditions did not improve. Magnetic resonance imaging was performed in the first 2 weeks after admission to the hospital.

### Table 1. Demographic and Clinical Characteristics of Study Subjects*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 60)</th>
<th>Healthy Control Subjects (n = 60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.2 ± 11.8</td>
<td>41.6 ± 12.3</td>
<td>.23</td>
</tr>
<tr>
<td>Female-male ratio</td>
<td>29.31</td>
<td>29.31</td>
<td>&gt;.99†</td>
</tr>
<tr>
<td>Handedness (right/left), No. of patients</td>
<td>56/4</td>
<td>56/4</td>
<td>&gt;.99†</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.2 ± 8.5</td>
<td>175.7 ± 9.3</td>
<td>.006</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.8 ± 15.4</td>
<td>72.6 ± 13.8</td>
<td>.49</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>9.7 ± 15.9</td>
<td>10.1 ± 10.5</td>
<td>.87</td>
</tr>
<tr>
<td>Age at onset of depression, y</td>
<td>37.7 ± 11.7</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Illness duration, y</td>
<td>6.7 ± 8.7</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale score</td>
<td>23.0 ± 6.3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>BDNF frequency, No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
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<tr>
<td>Val/Val</td>
<td>37</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Val/Met</td>
<td>21</td>
<td>19</td>
<td>.76†</td>
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<tr>
<td>Allele</td>
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<tr>
<td>Val/Val</td>
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</tr>
<tr>
<td>Met carriers</td>
<td>23</td>
<td>20</td>
<td>.57†</td>
</tr>
</tbody>
</table>

Abbreviation: BDNF, brain-derived neurotrophic factor.  
*Data are given as mean ± SD unless otherwise indicated. 
†Student t Test. All other P values are by t test.
On the day of magnetic resonance imaging, patients were taking the following medications: 17 patients were taking serotonin reuptake inhibitors (sertraline [n=7], citalopram hydrobromide [n=7], paroxetine hydrochloride [n=2], and fluvoxamine maleate [n=1]), 11 patients were taking tricyclic antidepressants (amitriptyline hydrochloride [n=4], doxepin hydrochloride [n=5], maprotiline hydrochloride [n=1], and trimipramine maleate [n=1]), and 23 patients were taking other antidepressants (venlafaxine hydrochloride [n=7], reboxetine [n=9], and mirtazapine [n=7]). Nine patients were not taking antidepressant medication at the time of magnetic resonance imaging. Patients taking antidepressants had a mean±SD duration of treatment of 15.2±12.9 days.

For comparison, 60 healthy controls were matched with respect to gender, handedness, and age (age range, 22-64 years; mean±SD age, 41.6±12.3 years) (Table 1). A structured interview was used to assess medical history, trauma, and other exclusion criteria. Neither the control subjects nor their first-degree relatives had a history of neurological or mental illness. Exclusion criteria for patients and controls were previous head injury with loss of consciousness, cortisol medication in the medical history, previous alcohol or other substance abuse. Other mental illnesses including personality disorders as well as neurological diseases were also exclusion criteria. No subject had received electroconvulsive therapy. Handedness was determined using the Edinburgh Inventory.34

After an extensive description of the study to the patients, informed consent was obtained. The study design was approved by the local ethics committee and was prepared in accord with the ethical standards laid down in the Declaration of Helsinki.

**MAGNETIC RESONANCE IMAGING PROCEDURES**

Magnetic resonance images were obtained (1.5-T Magnetom Vision; Siemens, Erlangen, Germany) using a coronal T2-weighted and proton density–weighted dual-echo sequence (repetition time, 3710 milliseconds; echo times, 22 milliseconds [first echo] and 90 milliseconds [second echo]; total acquisition time, 9 minutes; number of acquisitions, 1; field of view, 230 mm; matrix, 240×236 pixels; and section thickness, 3 mm) and a 3-dimensional magnetization prepared rapid acquisition 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, 512×512 pixels; and section thickness, 1.5 mm). A commercial software package was used for further image processing (Analyze; Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn), with size reduction from 16 to 8 bits and transformation to a uniform matrix of 256×256 pixels on 192 sections of 1.0-mm thickness. All data sets were realigned and resampled 3-dimensionally for the anterior commissure to posterior commissure line according to Talairach coordinates using a software program (BRAINS; Brain Research: Analysis of Images, Networks and Systems; developed by Andreassen et al35). This program allowed control of the regions of interest for the sagittal and transverse sections simultaneously, as well as control of the segmentation for calculating intracranial content and gray and white matter volumes (in cubic centimeters) within the defined region of interest.

**DEFINITION OF THE HIPPOCAMPAL AND AMYGDALA FORMATION**

We used the definition of the hippocampus according to Niemann et al16 and the detection of the hippocampal–amygdala border from the description of Convit et al.37 The evaluation staff (T.F.) was blinded to each subject's study group status. The amygdala was outlined manually using a mouse-driven cursor. The definition of the amygdala according to the criteria established by Convit et al17 was applied. To obtain the most anterior boundary, the definition in accord with Alshuler et al35 was used (for a detailed description, see Frodl et al.38).

The hippocampus and amygdala are illustrated in Figure 1. For determination of interrater reliability, 10 brains were randomly chosen, and regions of interest were determined by 2 raters independently. The intraclass correlations for the interrater reliability and the intrarater reliability in randomly chosen brains were high.9,39

**LABORATORY ANALYSIS**

DNA was extracted from a 5-ml blood sample using a kit (QiAamp Blood Isolation Kit; QiAGEN GmbH, Hilden, Germany) following the instructions of the supplier. All genotypes were performed by the fluorescence resonance energy transfer method using a commercially available system (Light Cycler System; Roche Diagnostics, Mannheim, Germany). For the G196A polymorphism in BDNF, the following conditions were applied: forward primer, 5'-TCA TAC TTT GGT TGC ATG AAG G-3'; reverse primer, 5'-AGA AGA GGA GGC TCA AAA GG-3'; and acceptor hybridization probe, 5'-LCRed604-TGT TGG ATG AAG ACC AGA AAC TTC GGC-p-3'. Polymerase chain reaction was performed using 50 ng of DNA in a total volume of 20 µL containing 2 µL of reaction mix (0.4µM each primer, 0.2µM each hybridization probe, and 2µM magnesium chloride) according to the manufacturer's instructions for 40 cycles of denaturation (95°C for 0 seconds), annealing (64°C for 10 seconds), and extension (72°C for 10 seconds), with ramp rates of 20°C/s. After amplification, a melting curve was generated by holding the reaction at 40°C for 20 seconds and then by heating slowly to 95°C with a ramp rate of 0.2°C/s. The fluorescence signal was plotted against temperature to give melting curves of each sample. Peaks were obtained at 52°C for the A allele and at 57°C for the G allele.

**STATISTICAL ANALYSIS**

All statistical tests were considered significant at P<.05. Morphometric measurements in both study groups were tested for normal distribution and for homogeneity of variance. Depar-
Patients and controls did not differ with regard to demographic variables (Table 1). The BDNF Val66Met genotype distributions for the patients and controls were in Hardy-Weinberg equilibrium. Age and weight were not different between patients and controls for each BDNF allele group (Met carriers or Val/Val). Illness duration (F1,115=3.3, P=.07), age at onset (F1,58=1.7, P=.20), and depression severity (Hamilton Depression Rating Scale, F1,58=0.01, P=.91) were not significantly different between patients who were Met-BDNF allele carriers and patients who were homozygous for the Val-BDNF allele.

Furthermore, the antidepressant medications taken (none, serotonin reuptake inhibitors, tricyclic antidepressants, or other antidepressants) were not significantly different among patients with the various BDNF genotypes (x2=3.1, P=.50). The BDNF genotype frequencies are given in Table 1. They did not differ between patients and controls.

HIPPOCAMPUS

The analysis of covariance results for the gray matter and the white matter of the hippocampus are given in Table 2. A significant main diagnosis effect was found indicating smaller hippocampal gray and white matter volumes in patients with major depression compared with healthy controls. Moreover, there was a significant effect of BDNF allele on the hippocampal gray matter volume (Figure 2).

In an exploratory analysis, the factor of first depressive episode vs recurrent episodes did not reveal significant interactions for hippocampal gray matter volume.

However, there was a significant 3-way interaction between diagnosis, BDNF allele, and the factor episode for hippocampal white matter volume (F1,115=5.1, P=.03). Post hoc testing revealed a significant effect among the patients with a first depressive episode that demonstrated smaller hippocampal white matter volume in patients carrying the Met-BDNF allele (F1,37=11.2, P=.003), without a significant effect in matched controls (F1,37=0.08, P=.78). In patients with recurrent episodes, no significant effect was found for BDNF allele (F1,37=0.81, P=.38). An effect between diagnosis and the factor of first depressive episode vs recurrent episodes was not detected.

AMYGDALA

Left and right amygdala volumes did not show a significant effect for diagnosis (F1,115=1.9, P=.20) or for BDNF allele (F1,115=1.1, P=.31). Nor did they show a significant interaction between BDNF allele and diagnosis (F1,115=1.1, P=.31).

In an exploratory analysis, gender had a significant effect on these results. There was a significant 3-way interaction between diagnosis, BDNF allele, and gender for amygdala volumes (F1,115=3.8, P=.05). Post hoc analy-
sis detected that women had a significant interaction between diagnosis and BDNF allele (F_{1,35} = 6.4, P = .01), whereas men did not show such an effect (F_{1,32} = 0.19, P = .66). Female patients with the Val/Val genotype had significantly larger amygdala volumes compared with female controls with the same genotype (F_{1,27} = 8.9, P = .006), whereas this was not the case for female patients with the Met allele compared with female controls with the same allele (F_{1,25} = 0.3, P = .62). The exploratory analysis that included the factor of first depressive episode vs recurrent episodes did not show any significant interactions for amygdala volumes.

**CORRELATIONS TO CLINICAL VARIABLES**

There were no significant correlations between hippocampal or amygdala volume and illness duration. Furthermore, there was no significant correlation between hippocampal or amygdala volume and severity of depression as measured by the Hamilton Depression Rating Scale.

### COMMENT

**HIPPOCAMPUS**

Our study identified for the first time (to our knowledge) an effect of the functional variation in the Val66Met locus in the 5′ prodomain of BDNF on hippocampal morphologic structure in patients with major depression. The observed decreases in hippocampal volumes were independent of whether subjects were depressed or not and may occur during development of the hippocampus. This view is supported by the finding that the reduction of hippocampal volumes in healthy Met-BDNF allele carriers is age and gender independent.27 The BDNF Val66Met polymorphism seems to be associated with altered hippocampal morphologic structure, which might have an effect on the susceptibility to or the expression of illnesses such as major depression that involve hippocampal neuronal integrity. Indeed, reduced hippocampal volumes affect the course of depressive illnesses,40 they are related to executive dysfunctioning,41 and changes in hippocampal neuronal integrity are associated with poor episodic memory.25

Patients with a first depressive episode did not differ from patients with recurrent episodes for hippocampal gray matter volumes and for the association between the BDNF Val66Met polymorphism and hippocampal gray matter volumes. However, hippocampal white matter volumes were smaller in patients with a first depressive episode who were Met carriers compared with those with the Val/Val genotype, whereas no such difference was detected in patients with recurrent episodes. The number of subjects may have been too small for a subgroup analysis, so this result should be interpreted with caution. In patients with recurrent episodes, other depression-related effects on hippocampal volumes may be present,6 whereas this may not be the case at the beginning of the disease. Therefore, patients with a first depressive episode may show a greater effect of the BDNF polymorphism on hippocampal volumes.

It can be theorized that synaptic and cellular plasticity changes in the hippocampus might result in cognitive deficits. Brain-derived neurotrophic factor seems to play an important role in the early and late phases of long-term potentiation.13 In the late phase, cyclic adenosine monophosphate– and the cyclic adenosine monophosphate–responsive element binding protein signaling pathway are recruited to direct protein synthesis–dependent changes in structure and function of the hippocampal synapsis.42 In vitro investigations demonstrated that depolarization-induced secretion was reduced in Met-BDNF–transfected neurons compared with Val-BDNF analogues, leading to decreased BDNF activity in subjects with the Met-BDNF allele compared with those with the Val-BDNF allele.25 Therefore, Met-BDNF allele carriers might manifest decreased synaptic and cellular plasticity during development and may have reduced hippocampal volumes.

The L/L genotype of the serotonin transporter polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) was associated with reduced hippocampal volumes in patients with major depression but not in control subjects.32 Moreover, patients with late-onset geriatric depression who were homozygous for the L allele of 5-HTTLPR exhibited smaller hippocampal volumes than other subject groups, whereas a significant association between the S allele of 5-HTTLPR and smaller hippocampal volumes was observed in patients with early onset.43 Disease-specific effects other than a genetic susceptibility might contribute to this effect of 5-HTTLPR. Stress may be a prominent factor that can result in neuroplastic changes in the hippocampus.4

The presence of the Met-BDNF allele may independently reduce hippocampal volumes and increase the susceptibility to develop depression via altered hippocampal functioning. However, this is weakened by a study18 among a community sample demonstrating that the Val-BDNF allele was associated with a high neuroticism score (which may be a risk factor for depression), by another study19 that showed no association between the BDNF Val66Met polymorphism and neuroticism. In line with our hypothesis, another study20 found an association between the Met-BDNF allele and geriatric depression. Moreover, among patients with bipolar disorder, the Met-BDNF allele was associated with executive dysfunctioning.23 However, in another population, no significant relationship between the BDNF polymorphism and depression was found.21,22 Our investigation supports the view that the Met-BDNF allele results in reduced hippocampal volumes (eg, via neuroplastic effects), which, in turn, increases the risk for depression. This indirect relationship may explain the inconsistent findings among previous BDNF studies.

### AMYGDALA

We found no significant differences between patients and controls with respect to amygdala volumes in this largest sample of patients and controls to date (to our knowledge). Two other studies failed to find altered total amygdala volumes. The first study26 did not show significantly smaller total amygdala volumes in 20 patients with depression compared with 20 healthy controls, whereas
amygdala core volumes were found to be significantly smaller in the patients. In the second study, among 34 drug-resistant patients with major depression, no significant differences in amygdala volumes were observed compared with 17 age-matched healthy controls. In an earlier investigation, no significant differences in amygdala volumes in patients with recurrent depression compared with healthy controls were observed.45

However, larger amygdala volumes have been detected in patients with a first episode of major depression, in patients with bipolar disorder,46 and in patients with borderline personality disorder.47 An explanation for differences between patients with a first depressive episode and those with recurrent episodes may be an increased amygdala volume at the beginning of the disease and a reduction to normal size during the course of the disease.45 In the present study, we focused on the genetic effects among patients and on the differences between patients with a first depressive episode and those with recurrent episodes.

There was no significant main effect of the BDNF polymorphism in patients or in controls. In an exploratory analysis, there was a significant 3-way interaction between diagnosis, BDNF allele, and gender. However, this result should be interpreted with caution because a statistical correction for a post hoc analysis would result in nonsignificant post hoc effects. This finding must be replicated before it can be interpreted.

The primary limitation of this study is its case-control design, which is sensitive to population stratification. This is unlikely to be problematic herein because the patients and controls with each BDNF allele did not differ for age, gender, origin, illness duration, age at onset, or medication use. There was a small number of subjects with the Met-BDNF allele. It could be argued that equal numbers of individuals with the genetic subtype should have been sampled. This would have required a very large number of subjects.

Our findings suggest that Met-BDNF allele carriers may be at risk of developing smaller hippocampal volumes and might be susceptible to developing major depression. The association between hippocampal volumes and the BDNF Val66Met polymorphism underlie the hippocampal involvement in brain development and plasticity. This in vivo study confirms in vitro findings that BDNF is required for neuroplastic changes and brain development and further supports the neurotrophic and neurogenic hypothesis of depression.32

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