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ORIGINAL PAPER

Correlation of serum BDNF levels with hippocampal volumes in first episode, medication-free depressed patients

Cagdas Eker · Omer Kitis · Fatma Taneli · Ozlem Donat Eker · Erol Ozan · Kaan Yucel · Kerry Coburn · Ali Saffet Gonul

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Abstract The hippocampus seems to be affected in MDD, and brain-derived neurotrophic factor (BDNF) has positive effects on neurogenesis within the hippocampus. Although there are inconsistencies among study results, a smaller hippocampal volume in depressed patients is thought to be related to the pathophysiology of the disease. We looked at the correlation between serum BDNF (sBDNF) levels and hippocampal volumes (HCV) of first-episode MDD patients (18 female, 7 male; mean age = 32.1 ± 9.3) and healthy controls (17 female, 5 male; mean age = 29.7 ± 6.4). Region of interest analysis was conducted on the images acquired via MRI. sBDNF levels and HCV correlated only in the MDD group (right: $r = 0.46$, $P = 0.02$; left: $r = 0.47$, $P = 0.02$); however, HCV did not differ between MDD patients and healthy controls (right: $F = 2.45$, $df = 1.46$, $P > 0.05$; left: $F = 0.05$, $df = 1.46$, $P > 0.05$). BDNF may be a factor underlying HCV differences between MDD and healthy control subjects, which become apparent as severe and multiple episodes are experienced.

Keywords BDNF · Hippocampus · Depression · MRI · Volume

C. Eker · A. S. Gonul (✉)
Department of Psychiatry, Ege University School of Medicine, Affective Disorders Unit, 35100 Bornova, Izmir, Turkey
e-mail: ali.saffet.gonul@ege.edu.tr

O. Kitis
Department of Neuroradiology, Ege University School of Medicine, Bornova, Izmir, Turkey

F. Taneli
Department of Biochemistry, Celal Bayar University School of Medicine, Manisa, Turkey

O. D. Eker
Department of Psychiatry, Izmir Ataturk Training and Research Hospital, Affective Disorders Unit, Izmir, Turkey

E. Ozan
Department of Psychiatry, Ataturk University School of Medicine, Erzurum, Turkey

K. Yucel
Mood Disorders Program, St Joseph's Healthcare Hamilton and Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

K. Coburn · A. S. Gonul
Department of Psychiatry and Behavioral Sciences, Mercer University School of Medicine, Macon, GA, USA

Introduction

A question at the forefront of neuropsychiatric research concerns changes in the hippocampal formation in patients suffering from major depressive disorder (MDD). Although obscured by interacting influences of age, chronicity, and severity, among other factors, it is becoming increasingly clear that MDD is associated with reduced hippocampal volume (HCV). A recently published major review [6] has begun to sort out the major influences on HCV in MDD. The age of the patient appears to be an important consideration. HCV reductions are unusual in patient groups below the age of 40, but are common in studies of middle age or elderly MDD patients. Such findings may be related to the age of onset [13] or the duration [3, 4] of illness. The recurrency and severity of MDD also seem to play important roles, with first-episode patients and those with less severe symptoms tending to show normal HCVs, hile

reduced HCVs are found in their more chronic and severely affected counterparts [6]. In a similar manner, comorbidity for anxiety disorders or alcohol/substance abuse or dependency appears to be associated with reduced HCV [27].

Studies of the pathophysiology underlying HCV reductions in MDD have led to the development of the neurotrophic hypothesis [19]. According to this view, chronic severe stress (including perhaps the stress of MDD itself) triggers a glucocorticoid cascade, which in turn exerts detrimental effects on hippocampal neurons through an excitotoxic mechanism (or perhaps through impaired neurogenesis), leading to neuronal loss and HCV reduction [17, 24]. The stress-induced atrophy of hippocampal neurons is mediated via disrupted secretion of brain-derived neurotrophic factor (BDNF) [18]. Serum BDNF (sBDNF) is reduced in MDD patients, the magnitude of its reduction correlates strongly with the severity of depressive symptoms, and it returns to normal levels following successful treatment [11, 12, 25].

If impaired BDNF secretion in MDD leads to HCV loss, which becomes increasingly apparent as the patient ages and the depressive episodes become more chronic and severe, then BDNF reduction should predate HCV reduction early in the course of this disorder. An appealing context in which to test this expectation is among young, first-episode MDD patients whose symptoms are of only moderate severity and who are free from comorbidity.

Experimental procedures

Subjects

Twenty-five depressed patients [18 female, 7 male; age (mean age ± SD): 32.1 ± 9.3 years] who were recruited from Ege University School of Medicine Department of Psychiatry Outpatient Clinic and Affective Disorders Unit were included in this study. All patients met criteria for MDD by clinical interview using DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) [1] and underwent the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P) [7]. The following patients were excluded after obtaining a detailed medical and family history and physical examination: patients with a prior depressive episode, mood congruent or incongruent psychotic features, serious or unstable medical illness, a history or a current diagnosis of seizure disorder or any other organic mental disorder, a history of head trauma associated with unconsciousness, any other axis I DSM-IV diagnosis, apparent antisocial personality disorder, alcohol or substance abuse, or clinical and laboratory evidence of hypothyroidism. We also excluded patients who had a family history of bipolar disorder and psychotic disorders to increase the homogeneity of the study group. All of the included patients were diagnosed according to DSM-IV-TR as major depressive disorder, single episode. Thirteen patients were drug-naïve, never having received any medical treatment for their disease, and the others were drug-free for 4 weeks (mean: 33 days) prior to recruitment. Several patients had a single depressive episode with a duration about 2 years without an adequate treatment and treatment compliance. Each participating patient provided written informed consent after receiving a complete description of the study, which was approved by the Institutional Review Board. Recruitment of patients was limited to 4 months because it was previously reported that sBDNF might be negatively affected by storage at −20°C and significant change might occur in samples stored more than 6 months [26].

Patients' symptoms were assessed with the 17-item Hamilton Depression Scale (HAM-D) [20] on the day of serum sampling and MRI scanning to analyze possible relationships between sBDNF levels, HCV, and concurrent symptom state as it was our primary hypothesis.

Twenty-two healthy volunteer subjects (17 female, 5 male; age (age 29.7 ± 6.4 years)) with normal neurological and psychiatric examinations were studied under identical conditions. None of the controls had a personal or family history of psychiatric or neurological diseases. All controls gave informed consent before admission to the study. All cases have been followed-up for 4 years and diagnosis of all cases remained stable.

Laboratory assay

Venous blood samples (5 ml) from the patients and normal controls were collected in anticoagulant-free tubes between 11:00 and 12:00 a.m. on the same day with MRI scan. All the samples were studied at the same time. BDNF serum concentrations were measured by the BDNF Emax Immunoassay System reagents (Promega, Madison, WI, USA) according to the manufacturer's instructions.

MRI procedure and tracing method

MRI procedure

The imaging was performed on a 1.5 Tesla MR unit (Magnetom Vision Siemens, Erlangen, Germany) with a circularly polarized head coil. The standard MRI examination included multiplanar turbo spin-echo T1-weighted (T1-W) (TR/TE: 650/14ms) and T2-weighted (T2-W) (TR/TE: 3800/90ms) images. In addition to conventional sequences, 3D MP-RAGE sequence (TR/TE: 9.70/4.00, slice thickness: 2 mm, interslice gap: 0 mm) in coronal

plane was obtained for volumetric analysis. All imaging data were transferred to a PC workstation and analyzed using the BRAINS2 software developed at the University of Iowa (http://www.psychiatry.uiowa.edu/mhcrc/IPLpages/BRAINS.htm) [2]. The 3D T1-weighted images were spatially normalized and resampled to 1.0-mm^3 voxels realigning the anterior–posterior axis of the brain parallel to the AC–PC line, as well as the interhemispheric fissure on the other two axes.

All tracings were performed by well-trained raters (O. K. and K. Y.) who were blind to the subjects' group membership and achieved an interclass correlation of 0.95 for right and 0.96 for left HCV and 0.97 for intracranial volumes.

Tracing method

Measurement of the hippocampus was done throughout its entire length from anterior to posterior (Fig. 1). The structures included in the measurement were as follows: the hippocampus proper (Ammon's horn), dentate gyrus, and the majority of the subiculum. The first slice was the slice on which the temporal horn of the lateral ventricle was first visible located lateral to the hippocampus proper, losing its slit-like appearance and also widened as described by Niemann et al. [20]. Alveus, when recognizable, and uncal recess were used as the superior border in the head [20]. The medial border was established as described by Pruessner et al. [23] to delineate the subiculum from the entorhinal cortex a 45° line passing through the most inferomedial point of the hippocampus was used. Temporal stem (fronto-temporal junction) or temporal horn was used to define the lateral border in the head of the hippocampus. The inferior border was the white matter of the parahippocampal gyrus. Superior excess of the quadrigeminal cistern was identified as the superomedial border in the body [23]. Lateral border of the hippocampal body was identified by the temporal horn, choroid plexus, or adjacent white matter. Medial and inferior borders of the hippocampal body were the same as described for the head of the hippocampus. In the tail of the hippocampus, the lateral border was defined by plexus choroideus, inferior horn of the lateral ventricle, and crus fornicis. The inferior border was the underlying white matter. The superior border was defined by the quadrigeminal cistern, fornix, pulvinar thalami, and caudate tail. We also referred to the sagittal plane to distinguish the tail of the hippocampus from pulvinar thalami and caudate tail, in addition to the coronal plane. We drew a vertical line from the medial end of the trigone of the lateral ventricle down to the down to the parahippocampal gyrus to delineate hippocampus from the Andreas-Retzius gyrus as done in the study of Pruessner et al. [23]. The last slice was the slice in which ovoid mass of hippocampal gray matter inferomedial to the trigone of the lateral ventricle was seen. The measurement on the coronal plane lasted for 40–50 min, and refining the markings on the other two planes lasted for 10–15 min. A detailed description of measurement protocol can be found at the website http://physics.stjosham.on.ca/kaan/HippoProtocol.pdf.

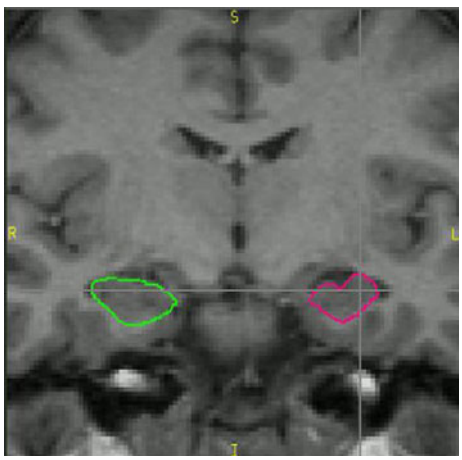

Fig. 1 Hippocampal tracing via BRAINS2 on the coronal plane

Statistical analyses

The Chi-squared test was used for the categorical variables, and Student's *t*-test or univariate analyses of variance (ANOVA) was employed for the continuous variables. Relationships between pairs of variables were examined using Pearson's correlation coefficient. The correlation between sBDNF and HCV was also investigated after HCV was normalized by intracranial volume to obtain a more precise relationship between sBDNF and HCV. Both normalized and non-normalized hippocampal results are presented in order to increase the generalizability of our findings. A P value of less than 0.05 was considered significant.

Results

The age, education, and gender distribution were similar between the patient and the control groups (Table 1). Both left and right HCV showed positive correlations with total intracranial volume (TIV) (right: $r = 0.69$, $P < 0.001$; left: $r = 0.65$, $P < 0.001$) but not with age (right: $r = 0.18$, $P > 0.05$; left: $r = 0.14$, $P > 0.05$). Univariate ANOVA with gender and TIV as cofactors revealed that HCV in each hemisphere did not differ significantly between the groups (right: $F = 2.74$, $df = 1.46$, $P > 0.05$; left: $F = 0.94$, $df = 1.46$, $P > 0.05$).

Table 1 Sociodemographic and clinical variables of patients and controls

	Depressed patients ($N = 25$)	Healthy controls ($N = 22$)	Comparison
Gender (male/female)	7/18	5/17	$X^2 = 0.17$, $df = 1$, $P > 0.05$
Age	32.1 ± 9.3	29.7 ± 6.4	$T = 1.01$, $df = 45$, $P > 0.05$
Education (years)	11.0 ± 3	12 ± 2.6	$T = 0.9$, $df = 45$, $P > 0.05$
Duration of the depressive episode (weeks)	30.8 ± 30.3	–	
HAM-D	24.4 ± 4.8	–	
Serum BDNF	21.7 ± 6.6	27 ± 5.7	$T = 2.95$, $df = 45$, $P = 0.005$*
HCV (cc)			
Right	3.31 ± 0.42	3.11 ± 0.26	$F = 2.74$, $df = 1.46$, $P > 0.05$
Left	3.38 ± 0.35	3.33 ± 0.30	$F = 0.94$, $df = 1.46$, $P > 0.05$
nHCV (cc)			
Right	2.2 ± 0.2	2.2 ± 0.2	$F = 2.45$, $df = 1.46$, $P > 0.05$
Left	2.2 ± 0.1	2.32 ± 0.2	$F = 0.05$, $df = 1.46$, $P > 0.05$
Total intracranial volume (cc)	1482 ± 183.5	1443 ± 110.6	$T = 0.87$, $df = 45$, $P > 0.05$

BDNF brain-derived neurotrophic factor, *HAM-D* Hamilton depression rating scale, *HCV* hippocampal volume, *nHCV* normalized hippocampal volume

* Significant

When the analyses were repeated for normalized hippocampal volumes (nHCV), similar results were found (Table 1).

MDD patients (mean: 21.7 ± 6.6 ng/ml) had lower sBDNF levels than did healthy controls (mean: 27.0 ± 5.7 ng/ml; $T = 2.95$, $df = 45$, $P = 0.005$). Gender and age did not have any effects on the difference of sBDNF levels between groups (gender: $F = 0.2$, $df = 1.46$, $P > 0.05$; age: $F = 0.5$, $df = 1.46$, $P > 0.05$). There was no significant correlation between sBNDF levels and HAM-D scores ($r = 0.04$, $P > 0.05$).

When we correlated the sBDNF values with HCV, we found a positive correlation between nHCV and sBDNF (right: $r = 0.46$, $P = 0.02$; left: $r = 0.47$, $P = 0.02$) in the MDD group (Fig. 2). However, we could not observe any relationship between sBDNF and HCV in the healthy control group (right: $r = 0.21$, $P > 0.05$; left: $r = 0.29$, $P > 0.05$) (Fig. 2). These findings did not change when the correlations were controlled for the gender (MDD patients, right: $r = 0.51$, $P = 0.01$; left: $r = 0.52$, $P = 0.01$; control group, right: $r = -0.16$, $P > 0.05$; left: $r = -0.21$, $P > 0.05$). When we did partial correlation with controlling possible confounding factors; previous antidepressant use, HAM-D score, and duration of episode; the results did not change for MDD patients (right: $r = 0.45$, $P = 0.03$; left: $r = 0.42$, $P = 0.05$).

Duration of illness did not have any effect on nHCV in either hemisphere (for right nHCV $r = 0.059$, $P > 0.05$; for left nHCV $r = 0.062$, $P > 0.05$) nor the age at onset (for right nHCV $r = 0.06$, $P > 0.05$; for left nHCV $r = 0.05$, $P > 0.05$) and medication (for right nHCV $F = 3.3$, $df = 1.22$, $P > 0.05$; for left nHCV $F = 0.07$, $df = 1.22$, $P > 0.05$) had any effect on nHCV.

Discussion

Consistent with the predominant findings in the literature, our young, first-episode MDD patients whose symptoms were of only moderate severity and who were free from comorbidity exhibited no evidence of HCV reduction compared to healthy controls. Among the controls, sBDNF levels were not correlated with HCV. Among the patients, however, sBDNF levels were found to be both significantly reduced below normal levels and significantly correlated with HCV. To our knowledge, this is the first study, which has reported such a relationship.

Psychological stress is well known to reduce the level of BDNF, which further leads to decrease in neuronal plasticity and neurogenesis in the hippocampus [5]. Studies that measured functions of the hippocampus have shown that functions deteriorate before the detectable HCV changes even in the first episode of the MDD [17]. Together with the findings of shape analysis, which did not detect volumetric differences though finding morphological differences [22] in accordance with functional deterioration of the hippocampus, one may argue that the reduction of BDNF may be related to functional and morphological changes predating and presaging HCV reduction. Through the course of MDD, BDNF reductions may lead to hippocampal volume loss, consistent with the neurotrophic hypothesis of depression [5].

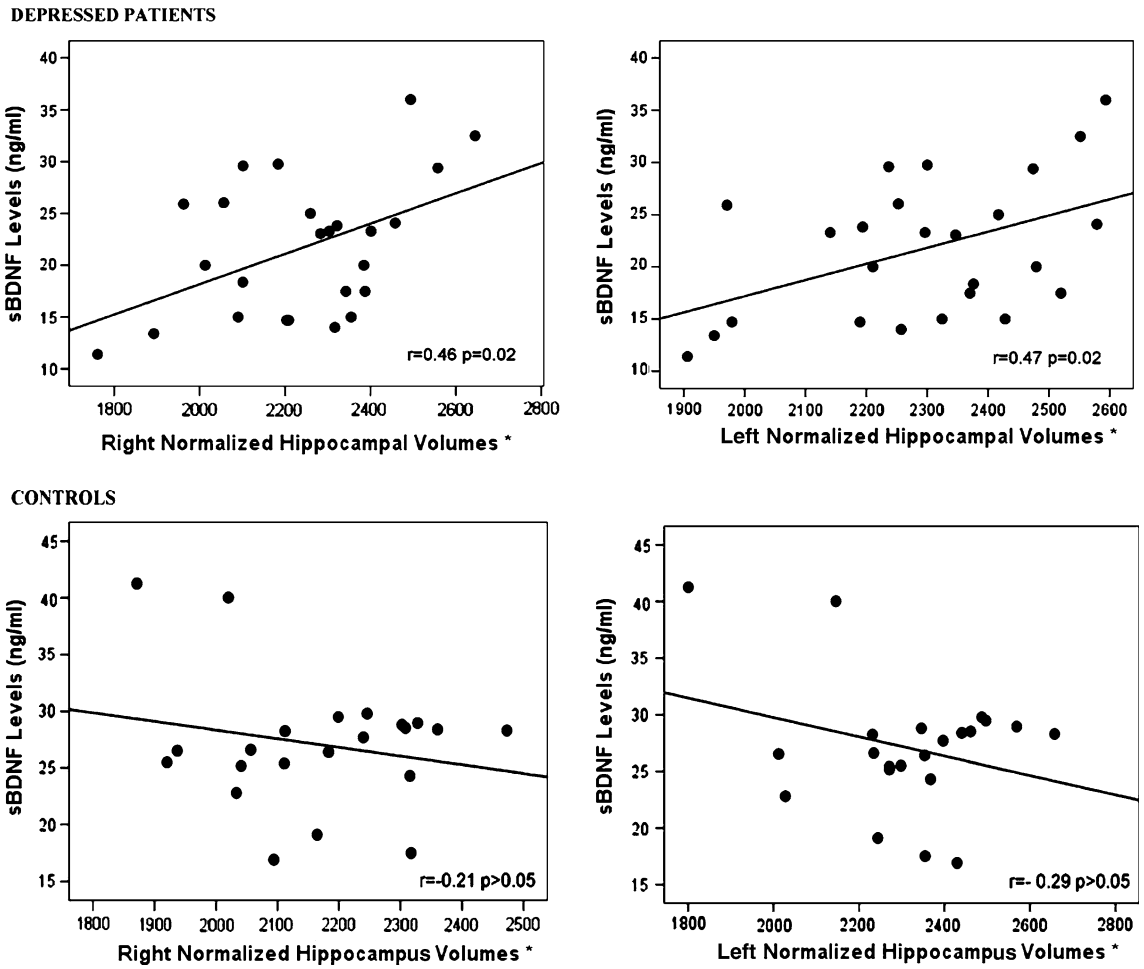

Fig. 2 The correlations between the normalized hippocampal volumes and the sBDNF values of depressed patients and healthy controls (* = 10^{-3} cc^3)

Our results do not support the point of view that already smaller HCV leads to depressive illness. Pitman et al. [21] proposed that small HCV could be a pre-existing risk factor, increasing the vulnerability to develop PTSD after a traumatic event, and this proposition has its evidence in the elegant twin study of Gilbertson et al. [10]. The hypothesis that "smaller hippocampal volumes may predispose the individual to psychiatric disorders" also finds some support in non-human primate studies [16]. However, the correspondence of PTSD to MDD and the relevance of animal studies to MDD are unclear. Recently, Kronmüller et al. [14] also postulated that smaller HCV may predispose an MDD patient (esp. male) to the recurrence of the illness. Moreover, Frodl et al. [8] suggested that "reduced hippocampal volumes may predispose to a poor clinical outcome" in MDD. Our present results are silent on these issues of chronicity and treatment resistance, though these important issues need further investigation.

Duration of illness and age at onset were found in our study to be unrelated to nHCV. Another study that included only first-episode patients also did not find any relation of HCV to the duration of illness or age at onset [9]. The longest duration of illness was 2 years in our study, and this time period may not be sufficient to cause volume decline necessary to detect volumetric changes of the hippocampus.

Our study has several limitations. First, the lack of the glucocorticoid data precludes strong arguments about the glucocorticoid cascade hypothesis [24]. Second, childhood abuse history was not questioned in our study. None of our patients mentioned childhood trauma during the diagnostic process, though this factor was not specifically assessed. Patients with a history of childhood trauma may represent a unique group, because early childhood trauma itself may cause reduced HCV, leading to vulnerability to developing psychiatric disorders such as MDD [27]. However, MDD patients who had suffered childhood abuse have very high rates of comorbidity, especially with anxiety disorders and alcohol misuse [27], and these were specifically excluded from our patient sample. It is also a possibility that we

might have excluded abused patients because diagnosis of any other Axis I disorder is an exclusion criterion. Moreover, Lenze et al. [15] found that abuse history did not have any effect on the smaller HCV of MDD subjects. Third, we did not separately analyze volumes of gray matter and white matter of the hippocampus. However, when the small proportion (3%) of the white matter in overall hippocampal formation is considered [9], we may argue that our measurement of hippocampal volume is mainly the equivalent of the gray matter.

Despite these limitations, however, a coherent overall picture is emerging: among healthy individuals, sBDNF levels and HCV are uncorrelated. This may represent a threshold phenomenon in which some requisite level of BDNF is necessary for normal HCV, but fluctuations above that level have no further effect. In first episode, MDD sBDNF levels are reduced and become correlated with HCV as their levels approach the threshold required for normal HCV maintenance. Over time, further BDNF reductions lead to smaller HCV, producing chronic, severe MDD symptoms that are refractory to treatment. BDNF may be a cause of the HCV loss detected in severe and multi-episode MDD patients. If this overall picture is correct, future studies may be expected to find further progressive reductions in BDNF levels and significant correlations between BDNF levels and HCV throughout the course of the illness. Longitudinal studies of individuals at high risk for MDD, and of first-episode MDD patients, should be conducted to test this general idea.

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Conflict of interest statement None of the authors have any conflict of interest regarding this article.

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