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ORIGINAL PAPER

Hippocampus, glucocorticoids and neurocognitive functions in patients with first-episode major depressive disorders

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Abstract The aim of this study was to determine whether there was any relationship between hippocampal volume, and glucocorticoid regulation, and cognitive dysfunctions in drug-naïve major depressive disorder (MDD) patients during their first episode. Twenty drug-free female MDD patients in their first episode and 15 healthy females as control subjects were included in the study. All subjects underwent 3.0 Tesla (T) magnetic resonance imaging (MRI), comprehensive neuropsychological testing and dexamethasone suppression tests (DST). The volumes of the right and left hippocampus of the patients were found to be significantly smaller than those of the controls. Patients were found to have significantly lower scores on measures of attention, working memory, psychomotor speed, executive functions, and visual and verbal memory fields. The performance of the patients only in the recollection memory and memory of reward-associated rules were positively correlated with hippocampal volumes. The volumes of the left and right hippocampus did not correlate with basal or post-dexamethasone cortisol levels. Our findings indicate that depressed patients have smaller hippocampi even in the earlier phase of their illness. Further research efforts are needed to explain the mechanisms that are responsible for the small hippocampus in depressed patients.

Keywords Glucocorticoids · Hippocampus · Magnetic resonance imaging · Major depressive disorder · Neurocognitive dysfunction

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Introduction

Morphometric differences of the hippocampus have been detected in patients with major depressive disorders (MDD) by using magnetic resonance imaging (MRI) [5, 39]. Volumetric diverseness was shown most consistently in patients who were older [2, 19, 28, 34, 37], experienced recurrent episodes [3, 25, 39] and had more untreated days [36]. Majority of studies have shown a smaller volume in depressed patients [5, 39]. However, there are few studies investigating the volume of the hippocampus in drug-naïve MDD patients during their first episode [15, 25].

Changes in the volume of the hippocampus have been detected in experimental studies and widely attributed to excessive and long-term glucocorticoid secretion in MDD patients [10, 31, 43]. However, peripheral glucocorticoid levels and feedback mechanism were not found to be related with hippocampal volume in human studies [8, 28, 34, 35, 40]. Lack of the relationship may be due to the characteristics of the patients with depression involved in these studies. Age, number of episodes, treatment, particularly ECT, and mood status may have significant effect on glucocorticoid levels [13, 26]. Therefore, the relationship between hippocampal volume, and glucocorticoid levels,

and feedback mechanism would potentially be clearer in drug-naïve MDD patients during their first episode.

In the studies mentioned above, gender is another important conflicting variable. Gender-specific differences were detected in the prevalence and clinical course of depression [20]. Neuroendocrinologic and genetic factors, as well as psychological and sociological factors, contribute to the distinction between the genders [9, 21]. It is possible that the neurobiology of depression may be different in man and woman. HPA axis, which has the particular attention of our study, shows sex-specific differences in depressed patients [23]. The results of a recent study reflect gender differences in the pattern of cortisol rise and decline during the social challenge. Moreover, effects of genetic polymorphisms on cortisol levels vary according to the gender [23, 33] In addition, woman is at low risk in the hidden vascular compromises, which have a certain distorting effects on the hippocampal structure [1, 22]. Therefore we aimed to work on a biological parameter in a biologically homogeneous women group.

The hippocampus is known to have a role in memory-related cognitive processes and executive functions. It was stated that the structural changes of hippocampus may affect its functions. In literature, there is only one study that examines the relationship between neurocognitive tests and hippocampal volume in the first episode [25].

The aim of this study was to determine whether there was any relationship between hippocampal volume, and glucocorticoid regulation, and cognitive dysfunctions in drug-naïve MDD patients during their first episode.

Materials and methods

Subjects

Twenty consecutive adult patients from the Department of Psychiatry, Hacettepe University currently with first-episode MDD participated in the study. Fifteen healthy subjects were recruited as control group by local advertisements. All participants were female. None of them had ever used any psychotropic drugs before. All subjects were assessed with a structured psychiatric interview (the Structured Clinical Interview for Diagnosis for DSM-IV disorders; SCID) by a senior psychiatrist [14]. SCID, which also assesses previous psychiatric symptoms, and history taken from the family were used to confirm that the index episode of illness was the first episode for the patients. Patients and comparison subjects underwent comprehensive medical and neurological examinations. Subjects were excluded if they had: (1) a history of DSM-IV Axis I disorder (except major depression for the patients); (2) a history of the use of any psychotropic or corticosteroid medication; (3) scores lower than 17 on the 17-item Hamilton Depression Rating Scale (HDR-S) [17]; (4) any neurological disease, (5) any physical illness demonstrated by personal history, or clinical or laboratory examinations; (6) pregnancy or lactation within a year; (7) left-handedness as assessed by Chapman and Chapman Handedness Inventory [7, 27]; (8) contraindications to magnetic scans; (9) being under 18 years or over 50 years; (10) first-degree relatives having a history of neurological or mental illness. During neurocognitive assessment, MRI scanning and DST evaluations, all participants were not in the menstruation phase of the cycle.

The study, which conforms to the code of ethics set out in the Declaration of Helsinki, was approved by the local ethical committee (FON0331-8/2003). Written informed consent was obtained from all subjects after the study was fully explained.

Neurocognitive assessment

The neuropsychological assessment was carried out on the same day as the MRI examinations. Digit Span, Logical Memory and Visual Reproduction subtests of the Wechsler Memory Scale Revised Version [41], the Wisconsin Card Sorting Test [18], the Trail Making Test [29] and the Verbal Fluency Test [43] were included in the neurocognitive assessment battery.

MRI scanning and analysis protocol

None of the patients were taking medication at the time of MRI scanning. The MRI (3T, Allegra, Siemens, Erlangen, Germany) images were acquired using the three-dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) data sets with the following parameters: TR, 2250.0 ms; TE, 4.4 ms; TI, 1100 ms; flip angle, 8°; FOV, 261; FOVP, 68.8; resolution, 256; P resolution, 75; matrix, 132 × 256; TS, 4.59; voxel size, 1.4 × 1.0 × 1.0; slice thickness, 1 mm. The sequences were chosen to give good gray–white matter contrast. Transverse T2-weighted FLAIR images were obtained to exclude the presence of cranial abnormalities (Fig. 1). The parameters were as follows: TR, 7,000 ms; TE, 84 ms; flip angle, 180°; FOV, 240; FOVP, 71.9; resolution, 256; P resolution, 91; matrix, 132 × 256; TS, 3.12; voxel size, 1.0 × 0.9 × 6.0; slice thickness, 4 mm. The scanner alignment tool and immobilizing head helped to ensure standardized positioning. DICOM images were transferred to a computer workstation (Macintosh, Apple Computer). Volume rendering was performed using OSIRIX, version 3.2, image processing software for medical research. Images were reoriented to the anterior posterior commissure line before volume rendering.

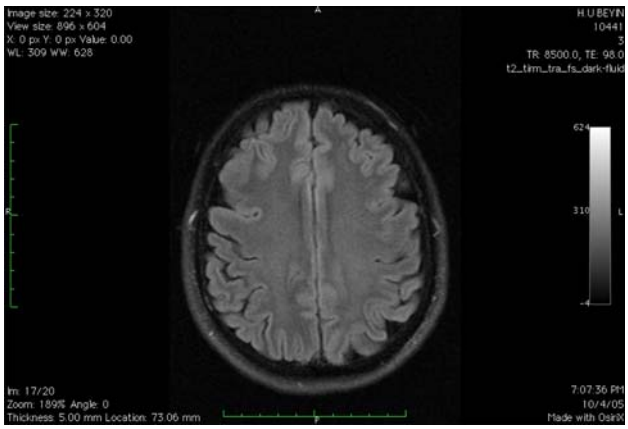

Fig. 1 Transverse T2-weighted FLAIR images were obtained to exclude the presence of cranial abnormalities

The definition of the anatomy and the boundaries of the hippocampus were based on the protocol of O'Brien et al. [28]. Sagittal and coronal views of the hippocampus are shown in Fig. 2. The fimbria, alveus, dentate gyrus, subiculum and the cornu ammonis were included in the measurements. The fornix and CSF spaces around and within the hippocampus were excluded. The hippocampus was measured beginning from the most caudal slice where

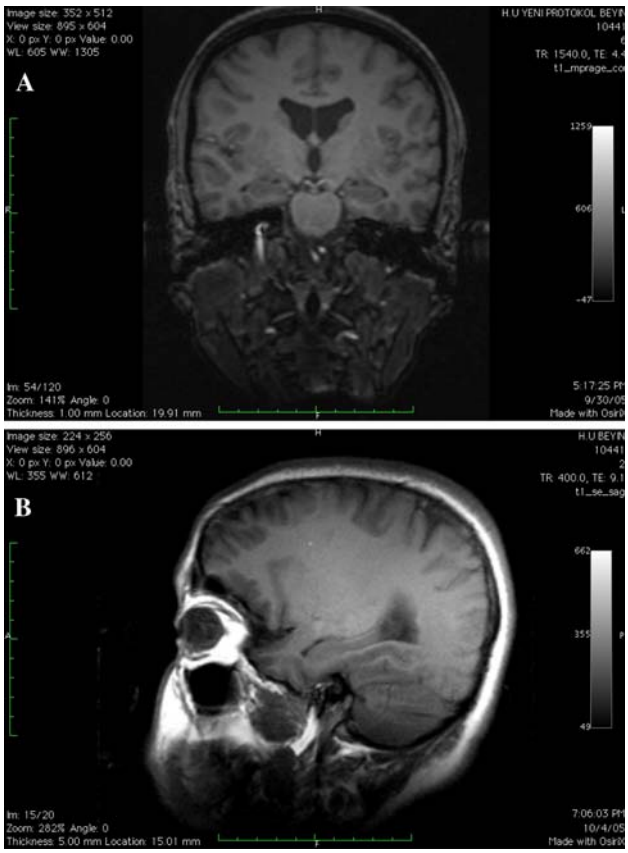

Fig. 2 Sagittal (**a**) and coronal (**b**) views of the hippocampus

the hippocampus was clearly visible, on which the fornix was visible at its longest length, to the rostral where the head of the hippocampus was not clearly visible. To briefly summarize, the boundaries of the hippocampus were defined as follows: the choroid fissure in the superior boundary, the medial subarachnoid structures of various cisterns (for example, ambient cistern), the white matter of the parahippocampal gyrus in the inferior boundary and the temporal horn of the lateral ventricule on the lateral side. The amygdala–hippocampal boundaries were defined in the sagittal plane and then projected to the coronal plane. To separate the anterior side of the hippocampus from the amygdala alveus, a white matter structure, was used as a demarcation line.

To outline the region of interest (ROI), manual tracing with a mouse-driven cursor was used. Boundaries were traced in the following order: lateral, inferior, medial and superior, so as to be certain of the consistency and comparability of techniques between both hemispheres. One rater, trained in MRI and blinded to the diagnosis of the data sets, measured the ROI. Intra-class correlation coefficients were counted as a measure of reliability. On ten brain scans, which were randomly selected to determine inter- and intra-rater reliability, the intra-class correlations of hippocampal volume were 0.92 and 0.93, respectively. All brain tissue superior to the pons was included in the measurement of the whole brain volumes. To determine inter- and intra-rater reliability, ten brain scans were randomly selected and the intra-class correlations of the whole brain volumes were 0.94 and 0.92, respectively.

Dexamethasone suppression test (DST)

DST was used to evaluate the levels and feedback mechanism of glucocorticoids. The commercially available solid faze, chemiluminescence enzyme *immunoassay kits* (*Immulite 2000, Biermann, Germany*) were used for cortisol measurements with a detection limit of 0.20 μg/dl and intra- and inter-assay coefficients of variation of 6.1 and 8.2%, respectively.

On the first day, blood samples were collected twice (at 08:00 and 16:00 hours) to measure baseline cortisol concentrations, and on that night (at 23:00 hours) 1 mg of dexamethasone was administered orally. The following day, blood samples were again taken twice at the same intervals. At least one cortisol level after dexamethasone administration of 5 μg/dl or above was defined as non-suppression [6].

Statistical analysis

Student's *t* test was performed to compare sociodemographic features, MRI measurements, neurocognitive test

scores and blood cortisol levels. Pearson's correlation coefficient was used to correlate sociodemographic features, clinical variables, neurocognitive test scores and blood cortisol levels with MRI measurements. Bonferroni correction was used to adjust for multiple testing. Two-tailed significance level was set at $P < 0.05$.

Results

Demographic and clinical characteristics

Demographic variables of the subjects can be seen in Table 1. Two groups were similar in terms of age, years of education, height and weight. The mean duration of the patients' illnesses and the standard deviations derived from it was 4.65 ± 3.55 months. Means and the standard deviations of the HDRS scores, which show the severity of the illness was 23.10 ± 4.20.

Volumetric results

The whole brain volumes of the two groups were similar. The normalized values of the right and left hippocampus of the patients were found to be significantly lower than those of the controls (Table 2).

Hippocampal volumes of patients and controls did not show any significant correlations to the age, length of education, or severity and duration of the illness.

Table 1 Demographic characteristics of first-episode MDD patients and healthy subjects

	MDD patients Mean (SD)	Healthy controls Mean (SD)	*t*	*P*	*df*
Age (years)	32 (8.52)	29.3 (5.8)	1.05	0.302	33
Education (years)	11.8 (2.44)	13.2 (2.6)	−1.63	0.112	33
Height (cm)	163.1 (4.44)	165.8 (4.1)	−1.86	0.071	33
Weight (kg)	61.2 (7.48)	62.2 (4.4)	−0.48	0.633	33

MDD major depressive disorder

Neurocognitive performance

As can be seen in Table 3, patients exhibited poorer performance in many subsets of the battery as compared to the healthy subjects. On examining the correlation, left hippocampal volume was significantly correlated with the Logical Memory-I ($r = 0.50$, $P = 0.024$) and right hippocampal volume was significantly correlated with the percentage conceptual level response in the WCST ($r = 0.46$, $P = 0.05$) in the patients. The other analyses did not show any significant correlation in patients. None of the subsets of the battery was correlated with hippocampal volumes.

Hormonal evaluation

The only difference of cortisol level between the patients and the control group was found to be in the post-dexamethasone evening measurement (Table 4).

DST non-suppression was observed in five patients (25%) of the patient group and two subjects (13%) of the control group ($P > 0.05$). Hippocampal volumes correlated with neither baseline nor post-dexamethasone cortisol levels in patients and controls.

Discussion

In this study, we found that decreased hippocampal volume exists in female patients with major depression in the first episode. Moreover, it was related to poor performances in some cognitive skills. However, no significant correlation was detected between the duration of illness and hippocampal volume. In addition to these findings, peripheral glucocorticoid levels and feedback mechanism were not found to be related to the volume of the hippocampus.

Few studies have evaluated the hippocampal volume of patients in their first episode. The first study reported lower volumetric measurements in male, but not female, patients [15]. In a further study, hippocampal volume was investigated in patients with recurrent episodes and in the first-episode patients. Patients having recurrent episodes only revealed statistically significant decreased volume of

Table 2 MRI data for first-episode MDD patients versus healthy subjects

	MDD patients Mean (SD)	Healthy controls Mean (SD)	*t*	*P*	*df*
Whole brain volume (cm^3)	877.32 (54.54)	889.26 (45.51)	−0.69	0.497	33
N-HV left	2.85 (0.33)	3.52 (0.33)	−6.01	0.000	33
N-HV right	2.72 (0.32)	3.40 (0.25)	−6.72	0.000	33

MDD major depressive disorder, N-HV, normalized value of the hippocampal volume = volume of the hippocampus/volume of the whole brain × 100

Table 3 Neurocognitive test performances in patients and controls

	MDD patients Mean (SD)	Healty controls Mean (SD)	*t*	*P*
Digits forward	5.80 (2.44)	7.47 (1.85)	−2.21	0.034
Digits backward	5.60 (1.43)	6.80 (1.82)	−2.18	0.036
Logical memory-I	21.45 (6.65)	34.40 (10.83)	−4.37	0.000
Logical memory-II	20.50 (7.58)	32.20 (11.74)	−3.58	0.001
Visual reproduction-I	29.95 (5.28)	36.13 (3.60)	−3.90	0.000
Visual reproduction-II	27.85 (6.36)	36.53 (3.13)	−4.85	0.000
Trail making-A	52.25 (17.91)	31.87 (9.37)	4.01	0.000
Trail making-B	116.60 (50.73)	70.47 (24.40)	3.24	0.003
Verbal fluency-word	26.60 (11.07)	34.00 (13.42)	−1.73	0.094
Verbal fluency-category	41.90 (12.82)	55.00 (10.12)	−3.37	0.002
Verbal fluency-alternation	11.15 (5.55)	12.13 (2.48)	−0.64	0.500
WCST subscores				
Errors	29.05 (10.92)	14.67 (5.49)	4.67	0.000
Preservative errors	14.95 (5.94)	8.13 (3.02)	4.04	0.000
Trials complete, first category	13.68 (6.41)	12.27 (3.22)	0.78	0.441
Percentage of conceptual level responses	64.84 (10.46)	78.13 (6.00)	−4.38	0.000

df: 33. *MDD* major depressive disorder

Table 4 Cortisol measurements in patients and controls

Cortisol levels (μg/dl)	MMD patient Mean (SD)	Healty controls Mean (SD)	*t*	*P*	*df*
Baseline					
08.00 a.m.	19.09 (5.06)	17.66 (7.33)	0.68	0.500	33
16.00 p.m.	9.48 (3.78)	7.15 (3.26)	1.91	0.055	33
Post-dexamethasone					
08.00 a.m.	2.71 (3.04)	2.47 (4.43)	0.19	0.800	33
16.00 p.m.	2.92 (2.55)	1.43 (1.17)	2.10	0.020	33

MDD major depressive disorder

hippocampus [25]. Lack of volumetric differences in the first-episode patients was attributed to the younger age of the participants. Moreover, they speculated that older age of onset may be associated with greater exposure of subthreshold depression or to depression associated with vascular or other neurological disease [22, 25]. In contrast to these studies, we found significant differences in hippocampal volume between the female patients with first-episode depression and the controls.

Although severity of the illness, duration of illness and days without treatment were found to be related to hippocampal volume in patients with recurrent episodes [4, 32, 35, 39], in our study, parallel to the findings of other first-episode studies [15, 25], these variables did not correlate with the hippocampal volume.

There are powerful experimental evidences for the hypothesis of glucocorticoid toxicity in hippocampal damage [10, 11, 30]. However, the relationship between the volume of the hippocampus and peripheral glucocorticoid system has not been clearly demonstrated by volumetric studies in human beings [8, 28, 34, 35, 40]. In previous studies, correlation was only evaluated in patients with recurrent depression. It is well known that not only recurrent depression, but also age, treatment, particularly ECT, and mood status may have significant effect on glucocorticoid levels [26]. To eradicate these confounding factors, we assessed the relationship between hippocampal volume and glucocorticoid levels in early phases of the illness. However, we did not detect any correlation between the volume of the hippocampus and the peripheral glucocorticoid system. One of the possible reasons behind that may be the use of DST, which is probably not the best approach for identifying HPA abnormalities. Presumably, hypercortisolemia may exert effects on hippocampus in the presence of some other factors. Among these other possible determinants of hippocampal damage are apolipoprotein genotype [28], serotonin transporter promoter polymorphism [16, 38] and brain-derived neurotrophic factor Val66Met polymorphism [24].

Depressed patients show differential impairment on recollection memory tasks that are dependent on the hippocampus [5]. It has been reported that hippocampal changes may precede neurocognitive functional deterioration in depression patients [28]. However, MacQueen et al. [25] detected poor performance in several hippocampus-related neurocognitive tests in first-episode depressed patients, despite hippocampal volumes of these patients not being significantly different from the controls. In our study, patients exhibited a poorer performance in many of the

subtests of neurocognitive battery. Patients were found to have significantly lower scores on measures of attention, working memory, psychomotor speed, executive functions, and visual and verbal memory fields. Moreover, hippocampal function-related tests (Logical Memory tests and percentage conceptual level) were found to be associated with the hippocampal volume. The Logical Memory test gives us some insight into recollection memory. Percentage conceptual level response in the WCST is related with not only executive functions, but also memorizing reward-associated rules [12]. These results indicate that hippocampal pathology has functional importance in the presentation of the neurocognitive dimension of depression symptomatology.

There are some limitations in this study. Low sample size is the main limitation of this study. Also, we recruited only female patients in the study; therefore, our results cannot be generalized to both genders. SCID, including questions regarding previous psychiatric symptoms and history taken from family members, are important in highlighting the sub-syndromal symptoms of the past. Therefore, in this study, we used SCID and comprehensive psychiatric history to confirm that the index episode of illness was the first episode. However, sub-syndromal symptoms seen in the past cannot be completely ruled out with the subjective narrative of patients or their family members.

Conclusion

Our findings indicate that depressed patients have smaller hippocampi even in the earlier phase of their illness. Poor performances in some cognitive skills seem to be related with the volume of the hippocampus. However, peripheral glucocorticoid levels and feedback mechanism were not found to be associated with the hippocampal volume. Further research efforts are needed to explain the mechanisms that are responsible for the smaller hippocampus in depressed patients. Moreover, optimal management regimens for preventing hippocampal deterioration and retrieving cognitive skills are clinical concerns waiting to be highlighted.

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References

1. Aboitiz F (1992) Brain connections: interhemispheric fiber systems and anatomical brain asymmetries in humans. Biol Res 25:51–61
2. Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynold CF 3rd, Becker JT (2002) Brain morphometric abnormalities in geriatric depression. Am J Psychiatry 159:1424–1427
3. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000) Hippocampal volume reduction in major depression. Am J Psychiatry 157:115–118
4. Caetano SC, Hatch JP, Brambilla P, Sassi RB, Nicoletti N, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2004) Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. Psychiatry Res 132:141–147
5. Campbell S, Marriott M, Nahmias C, MacQueen GM (2004) Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 161:598–607
6. Carrol BJ (1982) The dexamethasone supression test for melancholia. Br J Psychiatry 140:292–304
7. Chapman JP, Chapman IJ (1987) Handedness of hypotlletically psychosis-prone subjects. J Abnonn Psychol 96:89–93
8. Colla M, Kronenberg G, Deuchle M, Meichel K, Hagen T, Bohrer M, Heuser I (2007) Hippocampal volume reduction and HPA-system activity in major depression. J Psychiatr Res 41:553–560
9. Cyranowski JM, Frank E, Young E, Shear MK (2000) Adolescant onset of the gender difference in lifetime rates of major depression: a theoretical model. Arch Gen Psychiatry 57:21–27
10. Czeh B, Michaelis T, Watanabe T, Frahm J, de Biumuı G, van Kampen M, Bartalomucci A, Fuchs E (2001) Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci USA 98:12796–12801
11. Czeh B, Lucassen PJ (2007) What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? Eur Arch Psychiatry Clin Neurosci 257:250–260
12. Dehaene S, Changeux JP (1991) Wisconsin Card Sorting Test: theoretical analysis and modeling in a neuronal network. Cereb Cortex 1:62–79
13. Ehnvall A, Sjögren M, Zachrisson OC, Agren H (2004) HPA axis activation determined by the CRH challenge test in patients with few versus multiple episodes of treatment-refractory depression. Eur Arch Psychiatry Clin Neurosci 254:349–355
14. First RLS, Gibbon M, Williams JBW (1995) Structured clinical ınterview of DSM IV axis I disorders. New York State Psychiatric Institute: Biometrics Research Department, New York
15. Frodl T, Meisenzahl E, Zetzsche T, Born C, Groll C, Jager M, Leinsinger G, Bottlender R, Hahn K, Moller H (2002) Hippocampal change in patients with a first episode of major depression. Am J Psychiatry 159:1112–1118
16. Frodl T, Meisenzahl EM, Zill P, Baghai T, Rujescu D, Leinsinger G, Bottlender R, Schule C, Zwanzger P, Engel RR, Rupprecht R, Bondy B, Reiser M, Moller HJ (2004) Reduced hippocampal volumes associated with the long variant of the serotonin transporter polimorphism in major depression. Arch Gen Psychiatry 61:177–183
17. Hamilton M (1967) Development of a rating scale: for primary depressive illness. Br J Soc Clin Psychol 6:278–296
18. Heaton RK (1981) Wisconsin Card Sorting Test Manual. Psychologycal Assessment Resources, Odessa
19. Janssen J, Hulshoff Pol HE, Lampe IK, Schnack HG, de Leeuw FE, Kahn RS, Heeren TJ (2004) Hippocampal changes and white matter lesions in early-onset depression. Biol Psychiatry 56:825–831
20. Joffe RT, Gatt JM, Kemp AH, Grieve S, Dobson-Stone C, Kuan SA, Schofield PR, Gordon E, Williams LM (2009) Brain-derived neurotrophic factor Val66Met polymorphism, the five-factor model of personality and hippocampal volume: implications for depressive illness. Hum Brain Mapp 30(4):1246–1256

21. Kessler RC, McGonagle KA, Swart M, Blazer DG, Nelson CB (1993) Sex and depression in the National Comorbiditty Survey, I: lifetime prevalance, chronicity and recurrence. J Affect Disord 29:85–96
22. Kirschbaum C, Pirke KM, Hellhammer DH (1993) The 'Trier Social Stress Test' a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 28:76–81
23. Klempin F, Kempermann G (2007) Adult hippocampal neurogenesis and aging. Eur Arch Psychiatry Clin Neurosci 257:271–280
24. Kumsta R, Entringer S, Koper JW, van Rossum EF, Hellhammer DH, Wüst S (2007) Sex-specific associations between common glucocorticoid receptor gene variants and hypothalamus–pituitary–adrenal axis responses to psychosocial stress. Biol Psychiatry 62:863–869
25. MacQueen GM, Campbell S, McEwen BS, Macdonald C, Amano S, Joffe RT, Nahmias C, Young T (2003) Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci USA 100:1387–1392
26. Mason BL, Pariante CM (2006) The effects of antidepressants on the hypothalamic–pituitary–adrenal axis. Drug News Perspect 19:603–608
27. Nalcaci E, Kalaycioglu C, Gunes E, Cicek M (2002) Reliability and validity of a handedness questionnaire. Turk Psikiyatri Derg 13:99–106
28. O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N (2004) A longitudinal study of hippocampal volume, cortisol levels and cognition in older depressed subjects. Am J Psychiatry 161:2081–2090
29. Reitan R (1955) The relation of the Trail Making Test to organic brain damage. J Consult Psychol 193:393–394
30. Sapolsky RM (1986) Glucocorticoid toxicity in the hippocampus: reversal by supplementation with brain fuels. J Neurosci 6:2240–2244
31. Sapolsky RM (2000) Glucocorticoids and hippocampal atrophy in neuro-psychiatric disorders. Arch Gen Psychiatry 57:925–935
32. Shah BJ, Ebmeier KP, Glabus MF, Goodwin GM (1998) Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. Br J Psychiatry 172:527–532
33. Shalev I, Lerer E, Israel S, Uzefovsky F, Gritsenko I, Mankuta D, Ebstein RP, Kaitz M (2009) BDNF Val66Met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and gender interactions. Psychoneuroendocrinology 34:382–388
34. Sheline YI, Wang P, Gado M, Csernansky J, Vannier M (1996) Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci USA 93:3908–3913
35. Sheline YI, Sanghavi M, Mintun M, Gado M (1999) Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 19:5034–5043
36. Sheline YI, Gado M, Kraemer H (2003) Untreated depression and hippocampal volume loss. Am J Psychiatry 160:1516–1518
37. Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF, MacFall JR, Krishnan KR (2000) Hippocampal volume in geriatric depression. Biol Psychiatry 48:301–309
38. Taylor WD, Steffens DC, Payne ME, MacFall JR, Marchuk DA, Svenson IK, Krishnan RR (2005) Influence of serotonin transporter promoter region polymorphisms on hippocampal volumes in late life depression. Arch Gen Psychiatry 62:537–544
39. Videbech P, Ravnkilde B (2004) Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 161:1957–1966
40. Vythilingam M, Vermetten E, Anderson GM, Luckenbaugh D, Anderson E, Snow J, Staib LH, Charney DS, Bremner DJ (2004) Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biol Psychiatry 56:101–112
41. Wechsler D (1987) Wechsler Memory Scale Revised (manual). Psychological Corporation, San Antonio
42. World Health Organization (1993) WHO/MNH Battery of cognitive assessment instrumentre pilot battery. WHO, Geneva
43. Yu S, Holsboer F, Almeida OF (2008) Neuronal actions of glucocorticoids: focus on depression. J Steroid Biochem Mol Biol 108:300–309