Hippocampal Volume, Memory, and Cortisol Status in Major Depressive Disorder: Effects of Treatment

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Background: *Depression has been linked to stress, memory deficits, and hypercortisolemia. However, the relationships between depression, hippocampal structure and function, and cortisol levels are unclear and the effects of antidepressant treatment on the measures are not well studied.*

Methods: *Whole hippocampal volume, performance on verbal and visual declarative memory function and cortisol status was evaluated in 38 subjects with major depressive disorder (MDD) and 33 healthy subjects. All measures were repeated in a subgroup (*n *= 22) of depressed patients after successful selective serotonin reuptake inhibitor (SSRI) treatment.*

Results: *Hippocampal volume was not significantly different between patients with untreated MMD and healthy subjects, after controlling for whole brain volume, age and gender. However, depressed subjects had significantly greater deficits in delayed memory and percent retention on the verbal portion of the Wechsler Memory Scale—Revised (WMS-R) compared with healthy subjects, without significant differences in visual memory, attention, vigilance, or distractibility. Baseline plasma or urinary free cortisol (UFC) was not related to either hippocampal volume or memory deficits. Successful treatment with antidepressants did not change hippocampal volume but did result in a significant improvement in memory function and a reduction in UFC excretion.*

Conclusions: *Medication-free nonelderly depressed outpatients without alcohol dependence or adverse experiences in childhood had normal hippocampal volume. Focal declarative memory deficits in depression supported localized hippocampal dysfunction in depressed patients. Treatment with antidepressants significantly improved memory and depression but did not alter hippocampal volume, suggesting that antidepressants may improve hippocampal function in the absence of detectable structural changes.*

Key Words: Antidepressants, cortisol, hippocampus, MDD, memory, MRI

Stressful life events are often associated with the onset of depressive episodes (Kendler et al 2000; Maciejewski et al 2001), and hypercortisolemia has been frequently reported in patients with major depressive disorder (MDD; Wirz-Justice 1994; Young et al 2001). These observations, together with reports of hippocampal-mediated declarative memory deficits in MDD (Bemelmans et al 1996; Rubinow et al 1984; Sheline et al 1999), have stimulated research into the relationships between stress, depression, cortisol, and the hippocampus. The findings of stress- and cortisol-induced damage to hippocampal structure and function in animal studies provide further impetus for work in this area (Czeh et al 2001; Duman et al 1999; Gould et al 2000; McEwen 2000; Sapolsky 1996, 2000). Prior studies have not investigated the relationship between hippocampal volume, hippocampal-mediated memory function, and cortisol status in the same group of depressed subjects. The effects of successful antidepressant treatment on these measures also have not been comprehensively evaluated.

Of 14 previous studies of hippocampal volume in MDD (see Figure 1), eight were unable to find significant group differences (Ashtari et al 1999; Axelson et al 1993; Coffey et al 1993; Frodl et al 2002; Pantel et al 1997; Rusch et al 2001; Vakili et al 2000), whereas six found significantly smaller left (Bremner et al 2000a; Mervaala et al 2000) or left and right hippocampus (MacQueen et al 2003; Sheline et al 1996, 1999; Steffens et al 2000). Reduced hippocampal volume was correlated with total duration of depression in some studies (MacQueen et al 2003; Sheline et al 1996, 1999), but not in all (Bremner et al 2000a; Frodl et al 2002). Reports of differences in hippocampal volume in bipolar disorder have also been mixed, with reports of increased (Kemmerer et al 1994), decreased (Swayze et al 1992), and unchanged hippocampal volumes (Hauser et al 1989). Several groups have reported smaller hippocampal volumes in another stress-related illness, posttraumatic stress disorder (PTSD; Bremner et al 2000a; Gurvits et al 1996), as well as in adults with early childhood trauma (Stein et al 1997; Vythilingam et al 2002), depressed women with childhood sexual or physical abuse (Vythilingam et al 2002), and in subjects with alcohol dependence (Jensen and Pakkenberg 1993; Sullivan et al 1995). Because most prior neuroimaging studies in MDD did not systematically exclude subjects with a history of childhood physical or sexual abuse, alcohol and drug use, current antidepressant use, or medical problems, it is possible that these factors may have contributed to the variability in hippocampal findings.

The hippocampus and adjacent medial temporal lobe structures mediate declarative or explicit memory function (Scoville and Milner 2000; Zola et al 2000). Clinical measures of declarative memory such as the Wechsler Memory Scale or the Selective Reminding Test (SRT) are dependent on intact hippocampal functioning. For example, long-term retrieval scores on the verbal SRT as well as percent retention after 30 min on the WMS-R significantly correlate with hippocampal neuronal density (Sass et al 1992).

Impairments in declarative memory have frequently been reported in depressed individuals. Hippocampal-mediated explicit memory deficits in MDD have been reported to occur in the

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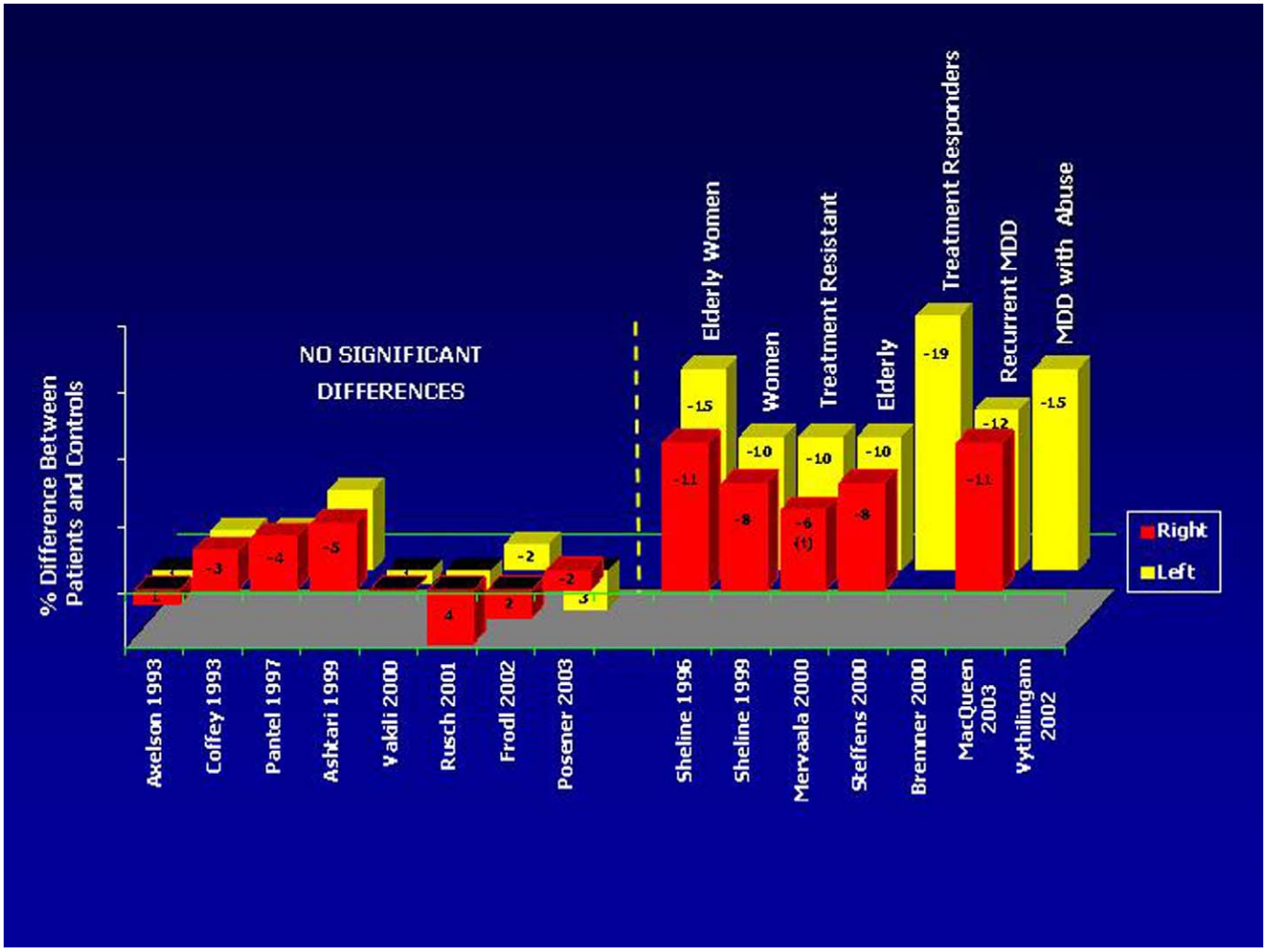

Figure 1. Hippocampal volume findings using structural magnetic resonance studies in unipolar major depressive disorder (MDD). Red and yellow bars indicate percent difference in right and left hippocampal volume between patients and control subjects, respectively. Studies on the right showed significant differences between MDD and healthy subjects.

absence of abnormalities in other neuropsychologic domains, suggesting a selective mesial temporal lobe dysfunction in MDD (Austin et al 2001; Bemelmans et al 1996; Sheline et al 1999; Sweeney et al 2000; Wolfe et al 1987). These memory deficits are reported to improve with effective antidepressant treatment (Cassano et al 2002; La Pia et al 1992; Levkovitz et al 2002). However, widespread impairment in cognitive function (Ravnkilde et al 2002) or impairment of attention and working memory (Landro et al 2001) have also been reported in subjects with MDD, whereas no significant impairment in cognitive functioning was observed in a sample of younger depressed outpatients (Grant et al 2001). As with the hippocampal imaging studies, the inclusion of subjects with varied histories, comorbidities, and treatments has tended to confound the studies, complicate cross-comparisons, and hinder interpretation. It remains unclear whether cognitive deficits associated with depression are indicative of global deficits or focal hippocampal dysfunction.

The relationship between stress, elevated levels of cortisol and hippocampal structure and memory deficits has been a topic of intense discussion. A prospective study in elderly healthy subjects found that elevated levels of plasma cortisol were associated with smaller hippocampal volume and increased memory loss (Lupien et al 1998). Higher post-dexamethasone plasma cortisol was inversely correlated with smaller left hippocampal volume in depressed subjects, although there was no significant difference in either left or right hippocampal volume between depressed patients and healthy subjects (Axelson et al 1993). Elevated urinary cortisol excretion in MDD was associated with a greater number of errors on the Halstead Category Test (Rubinow et al 1984). Healthy subjects who received stress doses of hydrocortisone or dexamethasone demonstrated transient hippocampal-mediated memory loss (Newcomer et al 1994, 1999). Subjects with Cushing's disease were reported to have smaller hippocampal volumes, which were negatively related to hippocampal-mediated memory deficits (Starkman et al 1992). The relationships between hippocampal volume, memory deficits and cortisol status have not been simultaneously evaluated in subjects with MDD.

The findings that the adult primate (Gould et al 1999) and human (Eriksson et al 1998) hippocampus can generate functional neurons may be relevant in the pathophysiology and

treatment of MDD (McEwen and Magarinos 2001). It has been hypothesized that stress-induced impairment of hippocampal neurogenesis precipitates episodes of depression, whereas enhanced neurogenesis results in recovery from the depressive episodes (Jacobs et al 2000). Antidepressants appear to increase neurogenesis and dendritic branching in the adult rodent hippocampus (Czeh et al 2001; D'Sa and Duman 2002; Jacobs et al 2000; Malberg et al 2000; Manev et al 2001) and to prevent stress-induced morphologic changes in hippocampal neurons (Magarinos et al 1999; Watanabe et al 1992). Preliminary evidence in humans suggests that reduction in hippocampal volume may be reversible. A significant increase in hippocampal volume along with improvement in list learning on the SRT was seen in patients with Cushing's disease following postsurgical decreases in plasma cortisol levels (Starkman et al 1999, 2003). A significant increase in hippocampal volume was seen in patients with chronic PTSD after treatment with the selective serotonin reuptake inhibitor (SSRI) paroxetine (Vermetten et al 2003). Conversely, administration of the antidepressant tianeptine prevented reduction of hippocampal volume following psychosocial stress in the tree shrew (Czeh et al 2001).

The present study evaluated hippocampal volume, hippocampal-mediated neuropsychologic performance, and cortisol status in patients with MDD. Because the aim was to examine definitively the relationship between cortisol status, hippocampal structure, and hippocampal-mediated neuropsychologic function, careful attention was paid to exclude subjects with confounding factors such as early childhood trauma, alcohol or drug use, medical problems, or use of psychotropic medications. The effects of antidepressant treatment on hippocampal volume, memory, and cortisol status were also evaluated prospectively in a subgroup of patients.

Methods and Materials

Subjects

Outpatient depressed and healthy control subjects, 18–60 years of age, were recruited through newspaper advertisements and flyers and gave written informed consent before participation in this study. The study was approved by the Human Investigation Committee at the Yale University School of Medicine. After an initial psychiatric interview, all subjects underwent a physical examination and screening tests that included a complete blood count, plasma electrolytes, β-HCG and creatine, liver function tests, thyroid function tests, and blood urea nitrogen. A routine urinalysis and drug screen were also performed.

Depressed patients were included if they met criteria for MDD based on the structured clinical interview for DSM-IV (SCID; First 1995) and scored a minimum 25 on the Yale Depression Inventory (YDI; Mazure et al 1990). Patients and healthy subjects were also evaluated with a measure of state anxiety, the Hamilton Anxiety Rating Scale (Hamilton 1959), and the Early Trauma Inventory (Bremner et al 2000b). Alcohol intake was evaluated using the alcohol section of the Addiction Severity Index (ASI; McLellan et al 1985), in addition to the alcohol and substance abuse section of the SCID. Past history of depressive episodes was obtained through use of SCID-derived information and the National Institute of Mental Health life-charting method (Post et al 1988). This information was used to calculate the total number and duration of depressed episodes in days. The number of days depressed across all episodes was then summed to obtain a total number of days depressed.

Subjects were excluded from the study if they had a history of childhood trauma or other major Axis I disorders, including bipolar disorder, schizophrenia, schizoaffective disorder, and current or past history of alcohol or substance abuse or dependence; however, patients with dysthymia or panic attacks in the context of MDD were included. Subjects were also excluded if they had major medical or neurologic illness, a history of significant head trauma, treatment with ECT, exposure to oral or intravenous steroids, contraindications to magnetic resonance imaging (MRI), or an IQ of less than 90.

None of the subjects had experienced, witnessed, or were confronted with an event that involved actual or threatened death, serious injury, or threat to physical integrity and therefore did not meet criteria for PTSD; however, depressed patients had significantly elevated scores on the clinician-administered Early Trauma Inventory compared with control subjects (240 ± 273 vs. 138 ± 313; $Z = -2.71$, $p = .01$), with trend significance for the general trauma subscale ($p = .06$), emotional trauma subscale ($p = .07$), and sexual trauma subscale ($p = .07$).

Seventeen patients met criteria for dysthymia, three met criteria for social phobia, and one patient had a history of generalized anxiety disorder. Of the 38 subjects, 15 were drug-naive, and the remainder of the sample had been free of antidepressant medications for at least 6 weeks. The median age of onset of the first depressive episode was 25 ± 12 years, the number of lifetime depressive episodes was 2 ± 2, the total duration of the current depressive episode was 13 ± 17 months, and the total number of days depressed was 1201 ± 1202 days. Seven subjects presented with a first episode of depression, and 31 subjects had recurrent MDD. Eleven depressed patients had melancholic features, and six had atypical major depression. The majority of subjects ($n = 21$) did not have a family history of major depression.

Treatment

Out of the 38 depressed subjects, 5 chose to receive treatment elsewhere, 2 chose not to receive treatment with antidepressants, 6 were lost to follow-up, 1 subject was noncompliant with medication because of sexual side effects, 1 subject moved out of the area, and 1 subject had a partial remission of depression after a 3-week vacation and no longer met inclusion criteria. Twenty-two patients with MDD (8 men, 14 women; mean age: 42 ± 13 years; 19 right-handed subjects) were treated with an SSRI and completed pretreatment and posttreatment MRI, neuropsychologic tests, and cortisol measurements. Twenty patients received fluoxetine (mean daily dose 30 ± 10 mg, mean duration 6 ± 2 months). One patient was switched to 150 mg of sertraline after developing sexual side effects with fluoxetine. A nonresponder to fluoxetine improved significantly on 225 mg a day of venlafaxine. The mean duration of antidepressant treatment was 7 ± 3 months.

Neuropsychologic Testing

A neuropsychologic test battery containing measures of immediate and delayed verbal and nonverbal memory was administered to patients and control subjects. Memory tasks were included along with measures of psychomotor speed, attention, and executive functions to separate functional deficits related to the hippocampus from those usually attributed to other, or multiple, regions. All of the neuropsychologic assessment procedures employed (with the exception of alternate form for WMS-R Logical Memory) in this study were standardized clinical measures (reviewed in Lezak 1995; Spreen and Strauss 1998) and

are described in more detail in Bremner et al (1993). The battery consisted of the following tests.

Wechsler Adult Intelligence Scale—Revised. Four subtests were administered to derive an estimate of Full Scale IQ (Wechsler 1981). These included Vocabulary, Similarities, Picture Arrangement, and Block Design.

Wechsler Memory Scale—Revised. Two subtests of the Wechsler Memory Scale (Wechsler 1987) were administered according to the Russell (1975) revision. WMS-R Logical Memory (LM) consists of two stories that are recalled immediately and following a 30-min delay; it is considered a test of verbal memory. The figural memory or Visual Reproduction (VR) subtest is felt to represent visual memory and involves the reproduction of designs after a 10-sec presentation. Credit is only given for items recalled or their equivalent as detailed in the WMS-R manual. Incorrect recall of story material is disregarded in the score. For both subtests, immediate and delayed reproduction were tested and a percentage of retention was compared (delayed recall divided by immediate recall multiplied by 100) (Bremner et al 1993). The stories used for the paragraph recall subtest of the WMS-R were replaced with new stories for repeat testing after treatment to minimize practice effects (Newcomer et al 1994). Lesion and imaging studies have shown performance on declarative memory portions of the WMS-R (LM and VR) to be mediated by medial temporal lobe structures that include the hippocampus (Martin et al 1999; Trenerry et al 1996).

Verbal and Visual Selective Reminding Test. Two components of the SRT (Buschke and Fuld 1974; Hannay and Levin 1985) were completed. The verbal task is a measure of verbal learning in which 12 words are presented for immediate recall. On subsequent trials, only the words not recalled on the prior test are presented. The task is complete after two consecutive perfect recall trials or 12 presentations. The visual component of the SRT (Buschke and Fuld 1974; Hannay and Levin 1985) is modeled on the verbal test; 12 designs are presented one at a time for 3 sec each, followed by an opportunity to draw all from memory. Each design that is not accurately reproduced on a given trial is shown again until perfect recall is attained or 12 trials are reached. Five indexes of learning and memory are obtained from each of the selective reminding tasks: total recall, long-term retrieval, long-term storage, list learning (continuous long-term retrieval), and delayed recall (Bremner et al 1993, pp. 1016–1017).

Continuous Performance Task. The Gordon Diagnostic System (Gordon and Mettelman 1987, 1988) was employed to assess attention and concentration using an AX paradigm (subjects were asked to respond to the target *X* only if preceded by the letter *A*). In the distraction condition, distracting digits appeared on either side the target; in the vigilance condition, there were no such distracting digits.

Trail-Making Test. Part A of this test measures visual scanning, sequencing, and psychomotor speed; Part B has an additional set-shifting and executive component (Reitan 1955).

Magnetic Resonance Imaging

MRI Acquisition and Processing. Subjects were imaged with a 1.5-Tesla General Electric Signa device using a tilted coronal three-dimensional volume spoiled gradient recoil (SPGR) sequence; repetition time = 25 msec, echo time = 5 msec, number of excitations = 2, matrix 256 × 192, field of view = 24 cm. This resulted in 60 coronal 1.5-mm contiguous slices through the hippocampus. Images were transferred via computer network to a Sun Sparc Ultra 80 workstation (Sun Microsystems, Palo Alto, California), and region boundaries were traced manually with a mouse-driven cursor using the ANALYZE program (Mayo Foundation, Rochester, Minnesota). An initial sagittal localizing sequence was obtained to determine the long axis of the hippocampus, and axial images through the brain were also obtained.

Measurement of Hippocampal Volume. Anatomic guidelines for defining the hippocampus and amygdala were based on prior work in the field (Bronen 1992; Bronen and Cheung 1991a, 1991b, 1991c; Duvernoy 1998; Kim et al 1994; Watson et al 1992) and have been described in detail (Vythilingam et al 2002). The boundaries for the body of the hippocampus are described in Bremner et al (1995). The sections anterior to the body were classified as the head, and those posterior to the last slice of the body were classified as the tail of the hippocampus. A rater with extensive training in hippocampal anatomy and blind to the diagnosis of subjects (MV) traced the hippocampal boundaries of patients and healthy control subjects. Interrater reliability was assessed by comparing hippocampal volumes determined by two raters (MV and Thomas Lam) for a set of 12 subjects; intraclass correlation coefficients of .920 and .891 were observed for left and right hippocampal volumes, respectively.

Measurement of Other Brain Regions. The temporal lobe of patients and healthy subjects was measured using the methods previously described (Vythilingam et al 2000). Whole brain volume was assessed using the autotrace mode in the ANALYZE program and included gray matter, white matter, cerebrospinal fluid of both cerebral hemispheres, the cerebellum, and the brainstem above the level of the pons.

Cortisol Status

Urinary Cortisol. One 24-hour sample of urine was collected from each subject using the method described in Mason et al (2001). Subjects were asked to empty their bladder at 8 AM on the first day and start urine collection immediately after. Urine excreted over a period of 24 hours was collected in a designated container. Subjects were asked to void at 8 AM the next day and include this final sample in the 24-hour collection. The total urine volume was measured and a portion stored at –20°C until analyzed for free cortisol by radioimmunoassay (DSL-2100 Active Cortisol Coated-Tube RIA Kit, Diagnostic System Laboratories, Webster, Texas). Day-to-day coefficients of variation of 8.4%–11% were observed (MDD: $n = 32$, Healthy Subjects: $n = 24$).

Plasma Cortisol. Baseline and post-dexamethasone plasma cortisol concentrations were determined using a commercially available radioimmunometric assay kit (Incstar, Stillwater, Minnesota); within-day and day-to-day coefficients of variation of 5%–9% were observed. (MDD patients: $n = 29$ for baseline and 28 for post-DST cortisol; healthy subjects: $n = 27$ for baseline and 24 for post-DST cortisol)

Dexamethasone Suppression Test. A subgroup of subjects (MDD patients: $n = 28$, healthy subjects: $n = 24$) underwent a standard DST with collection of a baseline plasma cortisol sample at 4 PM. Dexamethasone (1 mg) was administered at 11 PM, and a second plasma cortisol sample was obtained at 4 PM the following day. Subjects with postdexamethasone cortisol levels > 5 μg/dL were categorized as nonsuppressors.

Statistical Analysis

All data are presented as raw means and standard deviations unless otherwise specified. Distributions for each variable were examined for normality using Shapiro and Wilks' *W*. When

Table 1. Sociodemographic and Clinical Variables of Patients with Major Depressive Disorder (MDD) and Healthy Subjects

	MDD ($n = 38$)	Healthy Subjects ($n = 33$)	F	df	p
Mean Age (years)	41 ± 11	34 ± 10	6.76	1,69	.01
IQ	113 ± 16	119 ± 18	1.89	1,66	.17
Height (inches)	66 ± 4	67 ± 3	.72	1,62	.40
Weight (pounds)	171 ± 42	154 ± 35	3.00	1,62	.09
Education (years)	15 ± 2	16 ± 2	2.53	1,68	.16
			χ^2	df	p
Gender (male/female)	15/23	12/21	.07	1	.81
Race (Caucasian/African American/other)	37/1/0	30/1/2	2.39	2	.30
Handedness (right/left/no preference)	32/6/0	27/5/1	1.17	2	.56
Addiction Severity Index	.2 ± .9	0	2.14	1	.27
			U	Z	p
Yale Depression Inventory	34 ± 7	2 ± 3	0	−6.90	<.001
Hamilton Anxiety Scale Score	17 ± 6	1 ± 1	1	−6.89	<.001

IQ, intelligence quotient.

significant deviations from normality were found ($p < .01$), nonparametric statistics were applied.

Analysis of variance (ANOVA) was used for most continuous variables; when deviations from normality occurred, the Mann–Whitney U score was used for group comparisons. For categoric variables, chi-square analysis was used. To handle age adjustments, analysis of covariance was performed with normally distributed data and logistic regression used with nonnormal distributions. Pre–post comparisons were performed with repeated-measures ANOVA for normally distributed data and Wilcoxen's signed rank test for nonnormally distributed data. Correlations were calculated using Spearman's rho. p values were not corrected for multiple comparisons. To examine possible nonlinear relationships between hippocampal volume and duration of depression, quadratic, cubic, logarithmic, exponential and power curves were tested. Practice effects were evaluated using a 95% confidence interval around the SE of prediction as in Charter (1996).

Results

Sociodemographic and clinical information of depressed patients and healthy subjects are given in Table 1. Thirty-eight depressed patients (15 men, 23 women) and 33 healthy subjects (12 men, 21 women) formed the study sample. The mean age of the depressed patients was significantly higher than that of healthy subjects (41 ± 11 vs. 34 ± 10 years; $F = 6.76$, $df = 1,69$ $p = .01$). The height, weight, and education in years were not significantly different between patients and subjects. The gender and racial distribution were similar in patients and healthy subjects, and there was a similar number of right- and left-handed subjects in the depressed and healthy groups (see Table 1). The Addiction Severity Index score was similar in both patients and healthy subjects. The mean YDI score was significantly greater in depressed subjects (34 ± 7 vs. 2 ± 3; $Z = -6.90$, $p < .001$), as were Hamilton Anxiety Scores (17 ± 6 vs. 1 ± 1; $Z = -6.89$, $p < .001$). Of the 38 depressed patients, 31 (82%) had multiple episodes. The mean number of episodes and the duration of episodes was 2.1 ± 2.5 and 39.5 ± 39.5 months, respectively.

Brain Volumetrics Results

Hippocampal Volume in Patients with MDD and Healthy Control Subjects. Hippocampal and brain region volumetric data are given in Table 2 and Figure 2. Group mean hippocampal volumes in patients and in healthy subjects were similar (left: 3305 ± 380 vs. 3334 ± 390 mm^3; $F = .10$, $df = 1,68$, $p = .75$; right: 3132 ± 417 vs. 3235 ± 407 mm^3; $F = .74$, $df = 1,68$, $p = .39$; mean: 3219 ± 380 vs. 3285 ± 389 mm^3; $F = .39$, $df = 1,68$, $p = .54$). Hippocampal volumes normalized to whole brain volumes were also similar between patients and healthy subjects. There was no significant difference in the right or left body or head of the hippocampus between patients and healthy subjects. Left or right hippocampal volume was not correlated with the severity of depression; however, left, right, and mean hippocampal volumes were inversely correlated with the severity of anxiety ($r = -.40$, $p = .02$; $r = -.35$, $p = .04$; $r = -.39$, $p = .02$, respectively). There was no significant difference in hippocampal volumes between subjects with first-episode MDD or with multiple episodes MDD when compared with healthy subjects (mean hippocampal volume = 3194 ± 412 mm^3; 3224 ± 380

Table 2. Mean Hippocampal and Brain Regions Volume (mm^3) in Major Depressive Disorder Patients (MDD) and Healthy Subjects

	MDD ($n = 38$)	Healthy Subjects ($n = 33$)	F	p
Hippocampus Whole				
Left	3305 ± 380	3334 ± 390	.1	.75
Right	3132 ± 417	3235 ± 407	.74	.39
Mean	3219 ± 380	3285 ± 389	.39	.54
Hippocampus/WB Ratio[a]				
Left	2.79 ± .39	2.69 ± .24	.93	.34
Right	2.64 ± .36	2.62 ± .27	.05	.82
Mean	2.72 ± .36	2.66 ± .25	.38	.54
Hippocampus Body				
Left	1241 ± 186	1239 ± 162	0	.98
Right	1261 ± 158	1299 ± 157	1.91	.17
Mean	1251 ± 161	1269 ± 150	.46	.50
Hippocampus Head				
Left	1233 ± 305	1235 ± 294	.01	.94
Right	1013 ± 337	1020 ± 315	.14	.70
Mean	1123 ± 283	1127 ± 284	.03	.86
Temporal Lobe				
Left	15,396 ± 1586	16660 ± 1935	8.25	.01
Right	16,269 ± 1669	17092 ± 2485	1.18	.28
Mean	15,832 ± 1492	16876 ± 2031	4.31	.04
WB	1,194,407 ± 131,457	1,239,475 ± 120,821	1.54	.22

WB, whole brain. $df = 1,68$.
[a]Ratio × 1000.

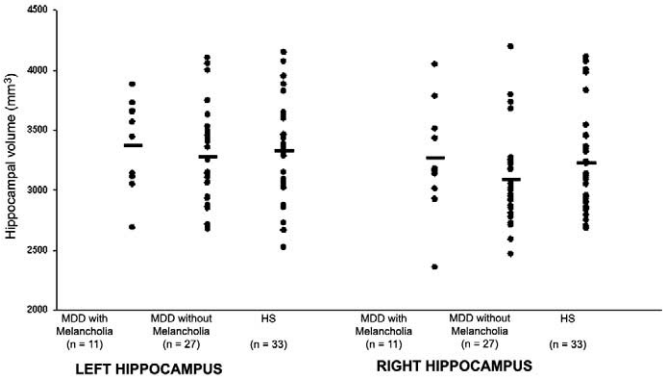

Figure 2. Mean hippocampal volume (mm^3) in patients with major depressive disorder (MDD) and healthy subjects (HS).

mm^3; 3285 ± 389 mm^3, respectively). When curve-fitting analysis was performed to evaluate nonlinear associations between variables (MacQueen et al 2003), there was no significant relationship between duration of depression in days and hippocampal volume. Drug-free duration before MRI measurement did not affect hippocampal volume in depressed patients. There was no significant difference between total brain volume or right temporal lobe volume between patients and control subjects. The left temporal lobe was significantly smaller in patients compared with healthy subjects after covarying for whole brain volume (15491 ± 1694 vs. 16549 ± 1701 mm^3; $F = 6.49$, $df = 1,67$, $p = .01$).

Effect of Antidepressant Treatment on Hippocampal Volume

There was a significant improvement in symptoms of depression (YDI: pre = 34 ± 9 vs. post = 5 ± 4; $Z = -4.11$, $p < .001$) and anxiety (HAMA: pre = 17 ± 6 vs. post = 3 ± 3; $Z = -4.02$, $p < .001$) after 7 ± 3 months of antidepressant treatment. Hippocampal and brain region volumes before and after successful antidepressant treatment are given in Table 3. There were no significant differences in left (3284 ± 422 vs. 3218 ± 418 mm^3; $F = 1.34$, $p = .25$), right (3110 ± 424 vs. 3191 ± 427 mm^3; $F = 1.51$, $p = .23$), or mean hippocampal volume (3197 ± 407 vs. 3205 ± 408 mm^3; $F = .03$, $p = .87$) before and after treatment with antidepressants. There were also no significant changes in subregion volumes of the hippocampus before and after successful antidepressant treatment (mean body: 1251 ± 183 vs. 1255 ± 208 mm^3; mean head: 1097 ± 286 vs. 1104 ± 260 mm^3). Whole brain volume and temporal lobe volume were also unchanged after treatment (whole brain: 1,187,745 ± 135,989 vs. 1,211,246 ± 160,581 mm^3; mean temporal lobe: 16,026 ± 1578 vs. 16,337 ± 1535 mm^3). Similar results were obtained when the analyses of drug treatment effects were restricted to subjects receiving fluoxetine ($n = 20$).

Table 3. Mean (± SD) Hippocampal Volume (mm^3) Before and After Successful Antidepressant Treatment

	Pretreatment MDD ($n = 22$)	Posttreatment MDD ($n = 22$)	F	p
Hippocampus Whole				
Left	3284 ± 422	3218 ± 418	1.34	.25
Right	3110 ± 424	3191 ± 427	1.51	.23
Mean	3197 ± 407	3205 ± 408	.03	.87
Hippocampus/WB Ratio[a]				
Left	2.79 ± .44	2.68 ± .31	2.56	.13
Right	2.64 ± .38	2.65 ± .33	.05	.82
Mean	2.71 ± .40	2.66 ± .31	.59	.45
Hippocampus Body				
Left	1251 ± 217	1222 ± 227	.86	.36
Right	1251 ± 167	1287 ± 212	1.51	.23
Mean	1251 ± 183	1255 ± 208	.03	.88
Hippocampus Head				
Left	1189 ± 321	1164 ± 307	.16	.69
Right	1006 ± 300	1045 ± 274	.41	.53
Mean	1097 ± 286	1104 ± 260	.02	.90
Temporal Lobe				
Left	15668 ± 1748	15881 ± 1835	1.04	.32
Right	16384 ± 1647	16795 ± 1540	3.17	.09
Mean	16026 ± 1578	16337 ± 1535	2.67	.12
WB	1187745 ± 135989	1211246 ± 160581	1.46	.24

WB, whole brain. $df = 1,67$.
[a]Ratio × 1000.

Neuropsychologic Test Results

Neuropsychologic Measures in Patients with MDD and Healthy Control Subjects. Table 4 presents descriptive and inferential statistics on neuropsychologic measures for unmedicated MDD patients and healthy subjects. No significant difference was found between MDD patients and control subjects on an estimate of Full Scale IQ and on either verbal or visual versions of the SRT. Delayed memory and percent retention on the verbal subtest of the WMS-R were significantly lower in MDD patients compared with healthy subjects, whereas a significant difference was not found for visual recall. The significant differences in delayed verbal memory and percent retained at 30 min persisted after covarying for age. In the vigilance condition of the Continuous Performance Test, there was a significantly slower response in depressed patients compared with healthy subjects after covarying for age (46.1 ± 11.7 vs. 37.4 ± 11.0 sec; Wald = 4.12, $p = .04$), but this was not found in the distraction condition. There was no difference between groups in the number of omission or commission errors in either the distraction or vigilance condition. The time taken to complete the Part A of the Trail Making Test was trend increased in depressed patients compared with healthy subjects (28.3 ± 8.4 vs. 23.0 ± 7.9 sec; $F = 3.19$, $df = 1,38$, $p = .08$); however, no significant difference was found for Part B. No significant differences were seen in Digit Span recall.

Neuropsychologic Test Performance After Successful Treatment with Antidepressants. Measures of performance on tests of memory, attention, and psychomotor speed before and after successful antidepressant treatment are given in Table 5. There was significant improvement in verbal immediate and delayed memory and trend level improvement in verbal percent retention; however, there was no significant improvement in immediate, delayed, or percent retention in the visual subtest of the WMS-R. Verbal and visual components of the SRT were also significantly improved after antidepressant treatment. There were no significant differences in measures of attention and concentration or for the Trail Making Test.

Based on a 95% confidence interval using the SE of prediction (Charter 1996), significant practice effects were found only with the visual long-term storage component of the selective reminding task.

Evaluation of Cortisol Status

Differences in Cortisol Status Between Patients with MDD and Healthy Control Subjects. Depressed patients ($n = 32$) did not have significantly higher levels of 24-hour urinary free cortisol (UFC) compared with healthy control subjects ($n = 24$;

Table 4. Neuropsychological Test Performance in Major Depressive Disorder Patients (MDD) and Healthy Subjects

	MDD (n = 38)	Healthy Subjects (n = 33)	Wald	df	p
Wechsler-Memory Scale—Revised					
Verbal/Logical Memory					
Immediate	27 ± 7	31 ± 6	3.54[a]	1,64	.06
Delayed	20 ± 8	28 ± 7	18.28[a]	1,66	<.001
% Retention	75 ± 35	89 ± 11	4.32	1	.04
Visual Reproduction					
Immediate	33 ± 8	33 ± 6	.72	1	.40
Delayed	27 ± 12	29 ± 9	.02	1	.89
% Retention	81 ± 29	86 ± 21	.19	1	.67
Selective Reminding Test					
Verbal LTR	104 ± 28	107 ± 18	.14[a]	1,40	.71
Verbal LTS	110 ± 25	114 ± 14	.09	1	.76
Verbal CLT	88 ± 36	86 ± 32	.74[a]	1,40	.39
Verbal DEL	9 ± 3	10 ± 2	.22	1	.64
Visual LTR	115 ± 21	120 ± 21	.08	1	.78
Visual LTS	120 ± 18	123 ± 18	.03	1	.87
Visual CLT	104 ± 29	111 ± 31	.08	1	.77
Visual DEL	11 ± 2	12 ± 1	.95	1	.33
Continuous Performance Test (total scores)					
Correct vigilance	29 ± 1	30 ± 1	.06	1	.81
Commission vigilance	0 ± 1	0 ± 1	.02	1	.89
Latency vigilance (msec)	46.1 ± 11.7	37.4 ± 11.0	4.12	1	.04
Correct distractability	22 ± 11	27 ± 6	1.73	1	.19
Commission distractability	1 ± 2	1 ± 5	.13	1	.72
Latency distractability (msec)	45.4 ± 21.6	37.8 ± 16.8	1.95	1	.16
Trail Making Test					
A	28 ± 8	23 ± 8	3.19[a]	1,38	.08
B	64 ± 27	66 ± 41	.84	1	.36
Digit Span					
Forward	8 ± 2	9 ± 2	2.95[a]	1,39	.09
Backward	7 ± 2	8 ± 3	.17[a]	1,39	.68
Total	15 ± 3	17 ± 4	1.34[a]	1,39	.25

CLT, continuous long-term retrieval (list learning); DEL, delayed recall; LTR, long-term recall; LTS, long-term storage.
[a] F value for analysis of covariance.

47.8 ± 24.8 μg/day vs. 41.3 ± 18.6 μg/day; F = 1.15, df = 1,54, p = .29). There were no significant differences in the 24-hour urine collection volumes between depressed subjects and healthy control subjects (1013 ± 817 vs. 1265 ± 834 mL; p = ns); however, plasma cortisol at baseline (4 PM) was significantly different between MDD (n = 29) and healthy control subjects (n = 27; 7.16 ± 3.72 μg/dL vs. 10.39 ± 6.40 μg/dL; F = 5.40, df = 1,54, p = .02). The mean 4 PM baseline plasma cortisol level was not significantly different between depressed subjects with and without melancholia and atypical depression (MDD without melancholia: 8.25 ± 4.70 μg/dL, MDD with melancholia: 5.84 ± 1.93 μg/dL and atypical depression was 6.78 + 2.79μg/dL). The MDD and control groups did not differ in levels of post-DST plasma cortisol (1.46 ± 1.73 μg/dL [n = 28] vs. 1.82 ± 1.84 μg/dL [n = 24]; F = .54, df = 1,50, p = .47). One subject in the depressed group (n = 28) was a nonsuppressor, whereas two subjects in the healthy control group (n = 24) were nonsuppressors to a standard DST.

Cortisol Measures in Patients with MDD Before and After Successful Treatment with Antidepressants. There was a significant decrease in UFC after successful antidepressant treatment in patients with MDD (52.1 ± 28.3 μg/day vs. 41.9 ± 19.6 μg/day; t = 2.17, p = .04). There were no significant changes in baseline plasma cortisol levels (7.32 ± 3.50 μg/dL vs. 7.19 ± 2.71 μg/dL; t = .14, p = .90) or post-DST plasma cortisol levels (1.23 ± 1.90 μg/dL vs. 1.14 ± .87 μg/dL; t = .27, p = .79) following antidepressant treatment.

Correlations Between Cortisol Status and Hippocampal Volume and Memory Function. There was a negative correlation between 24-hour UFC and both the right (r = −.505, p = .02) and left hippocampus (r = −.540, p = .01) in healthy subjects; however, this negative correlation was not seen in depressed patients. There was no correlation between hippocampal volume and post-DST plasma cortisol or baseline DST plasma cortisol. There was a trend for positive correlation between visual immediate and delayed recall with right hippocampus in depressed patients (visual immediate recall: r = .30, p = .07; visual delayed recall: r = .28, p = .09). There were no correlations between hippocampal volume and other measures of memory on the WMS-R or the SRT, and none of the correlations were significant after correction for multiple tests. p values were not corrected for multiple comparisons.

Patients and control subjects who had cortisol data were not different in mean, left, or right hippocampal volume from those who did not have cortisol data [Mean: F(1,67) = .04, p = .85; Left: F(1,67) = .06, p = .81; Right: F(1,67) = .02, p = .89]. Furthermore, there was no interaction between diagnostic status and presence of cortisol data [Mean: F(1,67) = .14, p = .71; Left: F(1,67) = .37, p = .55; Right: F(1,67) = .02, p = .89]. Also, the proportion of patients who had cortisol data were the same for

Table 5. Neuropsychological Test Performance Before and After Successful Antidepressant Treatment

	Pretreatment MDD ($n = 22$)	Posttreatment MDD ($n = 22$)	Z	p
Wechsler Memory Scale				
Verbal/Logical Memory				
Immediate	27 ± 7	32 ± 6	−3.01	.00
Delayed	18 ± 9	27 ± 8	−3.48	.001
% Retention	69 ± 36	85 ± 16	−1.93	.05
Visual Reproduction				
Immediate	33 ± 9	35 ± 4	−.17	.86
Delayed	27 ± 12	30 ± 9	−1.30	.19
% Retention	83 ± 27	85 ± 21	−.50	.62
Selective Reminding				
Verbal LTR	103 ± 32	116 ± 25	−.25	.01
Verbal LTS	108 ± 30	120 ± 22	−2.75	.01
Verbal CLT	90 ± 37	104 ± 34	−2.12	.03
Verbal DEL	10 ± 3	11 ± 2	−2.05	.04
Visual LTR	117 ± 20	133 ± 16	−2.94	.00
Visual LTS	121 ± 18	135 ± 11	−2.93	.00
Visual CLT	109 ± 24	130 ± 26	−2.76	.01
Visual DEL	10 ± 3	12 ± 1	−1.63	.10
Continuous Performance Test (total scores)				
Correct vigilance	30 ± 0	30 ± 0	−.58	.56
Commission vigilance	0 ± 0	0 ± 0	−1.41	.16
Latency vigilance (msec)	45.4 ± 12.9	43.7 ± 8.9	−.20	.84
Correct distractability	23 ± 12	23 ± 10	−.17	.87
Commission distractability	1 ± 2	2 ± 3	−1.51	.13
Latency distractability (msec)	44.1 ± 21.0	45.6 ± 11.3	−.36	.72
Trails Making Test				
A	28 ± 10	28 ± 8	.00	1.00
B	63 ± 32	67 ± 37	−.24	.81
Digit Span				
Forward	8 ± 2	9 ± 2	−1.70	.09
Backward	8 ± 3	9 ± 2	−1.34	.18

CLT, continuous long-term retrieval (list learning); DEL, delayed recall; LTR, long-term recall; LTS, long-term storage; MDD, major depressive disorder.

patients (26%) and control subjects (27%; $\chi^2(n = 71) = .01$, $p = .93$).

Exploratory Analysis of Subgroups Differences

When subjects were divided into familial pure depressive disorder ($n = 9$) and depression spectrum disorder ($n = 13$; Winokur et al 1978), there were no significant differences between the two subgroups in hippocampal (left, right, or whole) or brain volumes. There were no significant differences in volumes when patients with melancholic symptoms ($n = 11$) were compared with subjects without melancholic symptoms ($n = 27$) or when atypical patients were compared with nonatypical patients.

A significant interactive effect of depression subtype and antidepressant treatment on hippocampal volume was seen ($F = 7.54$, $df = 2,18$, $p = .004$). Post hoc paired t analysis showed that subjects with atypical depression had a significant 21% increase in whole hippocampal volume after treatment with antidepressants (2893 ± 172 vs. 3492 ± 316 mm^3, $p = .004$). This interactive effect was not seen for other depression subgroups; for example, pre- and posttreatment hippocampal volumes in MDD patients with (3193 ± 488 vs. 3212 ± 488 mm^3) or without melancholia (3121 ± 442 vs. 3112 ± 417 mm^3).

Discussion

In this study, patients with unipolar MDD demonstrated specific impairment in verbal memory, despite normal hippocampal volume. Urinary free cortisol (UFC) excretion and plasma cortisol levels in depressed patients were unrelated to either memory deficits or hippocampal volume. Immediate and delayed verbal memory improved and UFC decreased after successful treatment with antidepressant drugs without an accompanying increase in hippocampal volume.

A major finding of our study was the normal hippocampal volume observed in patients with major depression compared with healthy subjects. Disparate findings in MRI studies of the hippocampus in MDD may be related to differences in the sample characteristics between studies as well as MRI methodologic issues such as differences in slice thickness and varied definitions of hippocampal landmarks. Prior studies that evaluated hippocampal volume in medication-free depressed subjects with sociodemographic and clinical variables similar to our study also did not observe significant differences between patients and healthy subjects (Axelson et al 1993; Rusch et al 2001; Vakili et al 2000). Most studies reporting hippocampal structural abnormalities have been restricted to certain subgroups of depressed subjects: patients with treatment resistant depression (Hsieh et al 2002; Mervaala et al 2000; Shah et al 1998), particularly women (Vakili et al 2000), elderly depressed patients (Sheline et al 1999; Sheline et al 1996; Steffens et al 2000), those with multiple episodes (MacQueen et al 2003), and patients with a childhood history of chronic and severe physical or sexual abuse (Vythilingam et al 2002); however, not all studies have found changes in hippocampal structure in MDD (Ashtari et al 1999; Pantel et al 1997).

Exposure to elevated levels of glucocorticoids in older primates does not result in hippocampal neuronal loss (Leverenz et al 1999). Social subordinance in an unstressful setting is also not associated with hippocampal neuronal loss (Brooke et al 1994). Sapolsky (1996) suggested that a combination of stress and hypercortisolemia may be necessary for hippocampal volume reduction. The absence of either early childhood trauma or hypercortisolemia in this group of outpatients with mild to moderate depression makes it less likely that they will have smaller hippocampal volume compared with healthy subjects. Alternatively, structural MRI methods may not have the required resolution to detect hippocampal neuronal and glial changes reported in MDD (Stockmeier, unpublished data). Taken together, prior research suggests that mild to moderately depressed, medically healthy nonelderly subjects, without alcohol or drug use or a history of childhood abuse have normal hippocampal volume.

It is possible that the cumulative and additive effects of several insults (such as early childhood trauma, elevated levels of cortisol, increasing age, medical problems, or alcohol use) together contribute to smaller hippocampal volume in major depression. Although the effect of each contribution may not be sufficient to reach the threshold of MRI detection, it is possible that hippocampal volume loss resulting from combined insults crosses this threshold. This "combined insult hypothesis" for MDD may provide an explanation for our previous finding that

depressed women with early childhood abuse had reduced hippocampal volume whereas depressed women without early childhood abuse had normal hippocampal volume (Vythilingam et al 2002). Depressed women with early childhood abuse also have greater cortisol response to psychosocial stress (Heim et al 2000) and increased levels of cerebrospinal fluid and corticotropin-releasing hormone compared with depressed women without abuse and healthy subjects (Carpenter et al 2002, presented at Biological Psychiatry Fifty-Seventh Annual Convention and Scientific Program, Philadelphia, Pennsylvania, May), suggesting a pathophysiologic basis for the reduction in hippocampal volume (Brunson et al 2001).

In contrast to the absence of discernable differences in hippocampal structure in the depressed subjects, their neuropsychologic test profile was strongly suggestive of specific hippocampal function deficits. Depressed patients demonstrated focal deficits in delayed memory and percent retention in a task that involved recall of a paragraph containing a story; however, verbal memory for a reinforced list-learning task and visual memory were within normal limits. The absence of deficits in vigilance, distractibility, and attention in the Continuous Performance Task suggests that impairments in hippocampal mediated verbal recall in depressed patients occur in the absence of global cognitive deficits. It is unlikely that psychomotor slowing as indicated by increased latency on a vigilance task contributed to focal memory difficulties in depressed patients in this study. The neuropsychologic data from this study are consistent with most previous studies in finding deficits in hippocampal-mediated tasks in MDD (Landro et al 2001; MacQueen et al 2003; Ravnkilde et al 2002) in the absence of widespread cognitive deficits (Burt et al 1995; Veiel 1997; Zakzanis et al 1998).

The lack of difference in post-DST plasma cortisol levels between healthy subjects and depressed patients is consistent with the previous literature demonstrating lower rates of DST nonsuppression in outpatients with MDD compared with inpatients with severe depression (Nelson and Davis 1997; Rush et al 1996). Similarly, there was no significant difference in 24-hour urinary free cortisol excretion levels between patients and healthy subjects; however, the 4 PM baseline plasma cortisol levels were significantly lower in depressed patients compared with healthy subjects. The mean 4 PM baseline plasma cortisol level was not significantly different between depressed subjects with and without melancholia and atypical depression, suggesting that atypical depression status did not contribute to differences in plasma cortisol levels. Previous studies have not specifically reported 4 PM baseline cortisol levels in outpatient MDD before the standard DST; however, 24-hour studies in MDD have reported either elevated (Halbreich et al 1985; Linkowski et al 1985; Wong et al 2000) or normal (Young et al 2001) plasma cortisol levels.

In contrast to prior studies in healthy aging subjects and subjects with Cushing's disease (Lupien et al 1998; Starkman et al 1992), we were unable to demonstrate relationships between cortisol status, hippocampal volume, and memory function in subjects with MDD consistent with the glucocorticoid cascade hypothesis (Sapolsky et al 1986). The absence of hypercortisolemia in our patients may be an important factor in our failure to observe such relationships. It remains to be determined how much of a role cortisol plays in those situations in which reductions in hippocampal volume have been reported.

The extensive preclinical literature and preliminary clinical studies in humans support the possibility that damage to the hippocampus is reversible (Czeh et al 2001; D'Sa and Duman 2002; Malberg et al 2000; Starkman et al 2003). Successful treatment with antidepressants in this study led to significant improvement in verbal and visual memory, a result similar to that reported in prior studies (Cassano et al 2002; Levkovitz et al 2002). The lack of change in hippocampal volume after antidepressant treatment, despite significant improvement in mood and hippocampal function, deserves comment. First, the MRI resolution of the human hippocampus may not be adequate to detect previously reported SSRI-induced increase in new neurons and changes in the microscopic neuronal morphology. It is possible that these antidepressant-induced changes seen in animal studies could be detected clinically by using methods that evaluated shape (Posener et al 2003) or metabolic functioning (Mayberg 2002a, 2002b) of the hippocampus. This possibility is supported by the substantial improvement of verbal memory in the depressed patients. Second, several studies have reported that serotonin (5-HT) stimulates the production of new neurons in the dentate gyrus of the hippocampus (Gould 1999); however, it appears that fluoxetine-induced up-regulation of neurogenesis is mediated through the stimulation of the 5-HT_{1A} receptors on granule cell precursors in the dentate gyrus (Radley and Jacobs 2002). The reported 27% reduction in 5-HT_{1A} binding potential in the mesial temporal region in unipolar depressed subjects (Drevets et al 1999) raises the possibility that this route to enhanced neurogenesis may not be fully operational in depressed patients. It is possible that structural changes after antidepressant treatment may be most easily detected in those depressed subjects with the smallest pretreatment hippocampal volumes. The observation of treatment-induced increases in hippocampal volume in atypical depression, although extremely tentative because of the post hoc nature of the analysis, does suggest that study of subgroup response could be fruitful.

In summary, changes in hippocampal volume were not seen in depression or with antidepressant treatment. Functional changes in the hippocampus occurred in patients with MDD in the absence of structural changes and were ameliorated with antidepressant treatment. Joint consideration of neuropsychologic, behavioral, and biological phenotypes, as well as genetic and environmental influences, are recommended to elucidate this area.

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Ashtari M, Greenwald BS, Kramer-Ginsberg E, Hu J, Wu H, Patel M, et al (1999): Hippocampal/amygdala volumes in geriatric depression. *Psychol Med* 29:629–638.

Austin MP, Mitchell P, Goodwin GM (2001): Cognitive deficits in depression: Possible implications for functional neuropathology. *Br J Psychiatry* 178:200–206.

Axelson DA, Doraiswamy PM, McDonald WM, Boyko OB, Tupler LA, Patterson LJ, et al (1993): Hypercortisolemia and hippocampal changes in depression. *Psychiatry Res* 47:163–173.

Bemelmans KJ, Goekoop JG, van Kempen GM (1996): Recall performance in acutely depressed patients and plasma cortisol. *Biol Psychiatry* 39:750–752.

Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000a): Hippocampal volume reduction in major depression. *Am J Psychiatry* 157:115–118.

Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al (1995): MRI-based measurement of hippocampal volume in patients with combat- related posttraumatic stress disorder. *Am J Psychiatry* 152:973–981.

Bremner JD, Scott TM, Delaney RC, Southwick SM, Mason JW, Johnson DR, et al (1993): Deficits in short-term memory in posttraumatic stress disorder. *Am J Psychiatry* 150:1015–1019.

Bremner JD, Vermetten E, Mazure CM (2000b): Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: The early trauma inventory. *Depress Anxiety* 12:1–12.

Bronen RA (1992): Hippocampal and limbic terminology. *Am J Neuroradiol* 13:943–5.

Bronen RA, Cheung G (1991a): MRI of the normal hippocampus. *Magn Reson Imaging* 9:497–500.

Bronen RA, Cheung G (1991b): MRI of the temporal lobe: Normal variations, with special reference toward epilepsy. *Magn Reson Imaging* 9:501–507.

Bronen RA, Cheung G (1991c): Relationship of hippocampus and amygdala to coronal MRI landmarks. *Magn Reson Imaging* 9:449–457.

Brooke SM, de Haas-Johnson AM, Kaplan JR, Sapolsky RM (1994): Characterization of mineralocorticoid and glucocorticoid receptors in primate brain. *Brain Res* 637:303–307.

Brunson KL, Eghbal-Ahmadi M, Bender R, Chen Y, Baram TZ (2001): Long-term, progressive hippocampal cell loss and dysfunction induced by early-life administration of corticotropin-releasing hormone reproduce the effects of early-life stress. *Proc Natl Acad Sci* 95:279–283.

Burt DB, Zembar MJ, Niederehe G (1995): Depression and memory impairment: A meta-analysis of the association, its pattern, and specificity. *Psychol Bull* 117:285–305.

Buschke H, Fuld PA (1974): Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology* 24:1019–1025.

Cassano GB, Puca F, Scapicchio PL, Trabucchi M (2002): Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. *J Clin Psychiatry* 63:396–402.

Charter RA (1996): Revisiting the standard errors of measurement, estimate, and prediction and their application to test score. *Percept Motor Skills* 82:1139–1144.

Coffey CE, Wilkinson WE, Weiner RD, Parashos IA, Djang WT, Webb MC, et al (1993): Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. *Arch Gen Psychiatry* 50:7–16.

Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, et al (2001): Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. *Proc Natl Acad Sci U S A* 98:12796–12801.

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, et al (1999): PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 46:1375–1387.

D'Sa C, Duman RS (2002): Antidepressants and neuroplasticity. *Bipolar Disord* 4:183–194.

Duman RS, Malberg J, Thome J (1999): Neural plasticity to stress and antidepressant treatment. *Biol Psychiatry* 46:1181–1191.

Duvernoy C (1998): *The Human Hippocampus. Functional Anatomy, Vascularization and Serial Sections with MRI*, 2nd ed. Berlin: Springer.

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al (1998): Neurogenesis in the adult human hippocampus. *Nat Med* 4:1313–1317.

First RLS, Gibbon M, Williams JBW (1995): *Structured Clinical Interview of DSM IV Axis I Disorders*. New York: Biometrics Research Department.

Frodl T, Meisenzahl EM, Zetzsche T, Born C, Groll C, Jager M, et al (2002): Hippocampal changes in patients with a first episode of major depression. *Am J Psychiatry* 159:1112–1118.

Gordon M, Mettelman B (1987): *Technical Guide to the Gordon Diagnostic System*. Dewitt, NY: Gordon Systems.

Gordon M, Mettleman BB (1988): The assessment of attention: I. Standardization and reliability of a behavior-based measure. *J Clin Psychol* 44:682–690.

Gould E (1999): Serotonin and hippocampal neurogenesis. *Neuropsychopharmacology* 21(suppl 1):46S–51S.

Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E (1999): Hippocampal neurogenesis in adult Old World primates. *Proc Natl Acad Sci U S A* 96:5263–5267.

Gould E, Tanapat P, Rydel T, Hastings N (2000): Regulation of hippocampal neurogenesis in adulthood. *Biol Psychiatry* 48:715–720.

Grant MM, Thase ME, Sweeney JA (2001): Cognitive disturbance in outpatient depressed younger adults: Evidence of modest impairment. *Biol Psychiatry* 50:35–43.

Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al (1996): Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry* 40:1091–1099.

Halbreich U, Asnis GM, Shindledecker R, Zumoff B, Nathan RS (1985): Cortisol secretion in endogenous depression. I. Basal plasma levels. *Arch Gen Psychiatry* 42:904–908.

Hamilton M (1959): The assessment of anxiety states by rating. *Br J Med Psychol* 32:50–55.

Hannay HJ, Levin HS (1985): Selective reminding test: An examination of the equivalence of four forms. *J Clin Exp Neuropsychol* 7:251–263.

Hauser P, Altshuler LL, Berrettini W, Dauphinais ID, Gelernter J, Post RM (1989): Temporal lobe measurement in primary affective disorder by magnetic resonance imaging. *J Neuropsychiatry Clin Neurosci* 1:128–134.

Heim C, Newport DJ, Miller AH, Nemeroff CB (2000): Long-term neuroendocrine effects of childhood maltreatment. *JAMA* 284:2321.

Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC (2002): Hippocampal volume and antidepressant response in geriatric depression. *Int J Geriatr Psychiatry* 17:519–525.

Jacobs BL, Praag H, Gage FH (2000): Adult brain neurogenesis and psychiatry: A novel theory of depression. *Mol Psychiatry* 5:262–269.

Jensen GB, Pakkenberg B (1993): Do alcoholics drink their neurons away? *Lancet* 342:1201–1204.

Kemmerer M, Nasrallah H, Sharma S, Olson S, Martin R, Lynn M (1994): Increased hippocampal volume in bipolar disorder [abstract]. *Biol Psychiatry* 35:626.

Kendler KS, Thornton LM, Gardner CO (2000): Stressful life events and previous episodes in the etiology of major depression in women: An evaluation of the "kindling" hypothesis. *Am J Psychiatry* 157:1243–1251.

Kim JH, Tien RD, Felsberg GJ, Osumi AK, Lee N (1994): MR measurements of the hippocampus for lateralization of temporal lobe epilepsy: Value of measurements of the body vs the whole structure. *Am J Roentgenol* 163:1453–1457.

La Pia S, Giorgio D, Ciriello R, Sannino A, De Simone L, Paoletti C, et al (1992): Double-blind controlled study to evaluate the effectiveness and tolerability of fluoxetine versus mianserin in the treatment of depressive disorders among the elderly and their effects on cognitive behavioural parameters. *New Trends Exp Clin Psychiatry* 8:136–139.

Landro NI, Stiles TC, Sletvold H (2001): Neuropsychological function in nonpsychotic unipolar major depression. *Neuropsychiatry Neuropsychol Behav Neurol* 14:233–240.

Leverenz JB, Wilkinson CW, Wamble M, Corbin S, Grabber JE, Raskind MA, et al (1999): Effect of chronic high-dose exogenous cortisol on hippocampal neuronal number in aged nonhuman primates. *J Neurosci* 19:2356–2361.

Levkovitz Y, Caftori R, Avital A, Richter-Levin G (2002): The SSRIs drug Fluoxetine, but not the noradrenergic tricyclic drug desipramine, improves memory performance during acute major depression. *Brain Res Bull* 58:345–350.

Lezak MD (1995): *Neuropsychological Assessment*, 3rd ed. New York: Oxford University Press.

Linkowski P, Mendlewicz J, Leclercq R, Brasseur M, Hubain P, Golstein J, et al (1985): The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. *J Clin Endocrinol Metab* 61:429–438.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, et al (1998): Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci* 1:69–73.

Maciejewski PK, Prigerson HG, Mazure CM (2001): Sex differences in event-related risk for major depression. *Psychol Med* 31:593–604.

MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, et al (2003): Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc Natl Acad Sci U S A* 100:1387–1392.

Magarinos AM, Deslandes A, McEwen BS (1999): Effects of antidepressants and benzodiazepine treatments on the dendritic structure of CA3 pyramidal neurons after chronic stress. *Eur J Pharmacol* 371:113–122.

Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000): Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* 20:9104–9110.

Manev H, Uz T, Smalheiser NR, Manev R (2001): Antidepressants alter cell proliferation in the adult brain in vivo and in neural cultures in vitro. *Eur J Pharmacol* 411:67–70.

Martin RC, Hugg JW, Roth DL, Bilir E, Gilliam FG, Faught E, et al (1999): MRI extrahippocampal volumes and visual memory: correlations independent of MRI hippocampal volumes in temporal lobe epilepsy patients. *J Int Neuropsychol Soc* 5:540–548.

Mason J, Wang S, Yehuda R, Riney S, Charney D, Southwick S (2001): Psychogenic lowering of urinary cortisol levels linked to increased emotional numbing and a shame-depressive syndrome in combat-related posttraumatic stress disorder. *Psychosom Med* 63:387–401.

Mayberg H (2002a): Depression, II: Localization of pathophysiology. *Am J Psychiatry* 159:1979.

Mayberg HS (2002b): Modulating limbic-cortical circuits in depression: Targets of antidepressant treatments. *Semin Clin Neuropsychiatry* 7:255–268.

Mazure CM, Nelson JC, Jatlow PI (1990): Predictors of hospital outcome without antidepressants in major depression. *Psychiatry Res* 33:51–58.

McEwen BS (2000): Effects of adverse experiences for brain structure and function. *Biol Psychiatry* 48:721–731.

McEwen BS, Magarinos AM (2001): Stress and hippocampal plasticity: Implications for the pathophysiology of affective disorders. *Hum Psychopharmacol* 16(suppl 1):S7–S19.

McLellan AT, Luborsky L, Cacciola J, Griffith J, Evans F, Barr HL, et al (1985): New data from the Addiction Severity Index. Reliability and validity in three centers. *J Nerv Ment Dis* 173:412–423.

Mervaala E, Fohr J, Kononen M, Valkonen-Korhonen M, Vainio P, Partanen K, et al (2000): Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychol Med* 30:117–125.

Nelson JC, Davis JM (1997): DST studies in psychotic depression: A meta-analysis. *Am J Psychiatry* 154:1497–1503.

Newcomer JW, Craft S, Hershey T, Askins K, Bardgett ME (1994): Glucocorticoid-induced impairment in declarative memory performance in adult humans. *J Neurosci* 14:2047–2053.

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, et al (1999): Decreased memory performance in healthy humans induced by stress-level cortisol treatment. *Arch Gen Psychiatry* 56:527–533.

Pantel J, Schroder J, Essig M, Popp D, Dech H, Knopp MV, et al (1997): Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J Affect Disord* 42:69–83.

Posener JA, Wang L, Price JL, Gado MH, Province MA, Miller MI, et al (2003): High-dimensional mapping of the hippocampus in depression. *Am J Psychiatry* 160:83–89.

Post RM, Roy-Byrne PP, Uhde TW (1988): Graphic representation of the life course of illness in patients with affective disorder. *Am J Psychiatry* 145:844–848.

Radley JJ, Jacobs BL (2002): 5-HT1A receptor antagonist administration decreases cell proliferation in the dentate gyrus. *Brain Res* 955:264–267.

Ravnkilde B, Videbech P, Clemmensen K, Egander A, Rasmussen NA, Rosenberg R (2002): Cognitive deficits in major depression. *Scand J Psychol* 43:239–251.

Reitan R (1955): The relation of the Trail Making Test to organic brain damage. *J Consult Psychol* 193:393–394.

Rubinow DR, Post RM, Savard R, Gold PW (1984): Cortisol hypersecretion and cognitive impairment in depression. *Arch Gen Psychiatry* 41:279–283.

Rusch BD, Abercrombie HC, Oakes TR, Schaefer SM, Davidson RJ (2001): Hippocampal morphometry in depressed patients and control subjects: Relations to anxiety symptoms. *Biol Psychiatry* 50:960–964.

Rush AJ, Giles DE, Schlesser MA, Orsulak PJ, Parker CRJ, Weissenburger JE, et al (1996): The dexamethasone suppression test in patients with mood disorders. *J Clin Psychiatry* 57:470–484.

Russell E (1975): A multiple scoring method for the assessment of complex memory functions. *J Consult Clin Psychol* 43:800–809.

Sapolsky RM (1996): Stress, glucocorticoids, and damage to the nervous system: The current state of confusion. *Stress* 1:1–19.

Sapolsky RM (2000): Stress hormones: Good and bad. *Neurobiol Dis* 7:540–542.

Sapolsky RM, Krey LC, McEwen BS (1986): The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Endocr Rev* 7:284–301.

Sass KJ, Sass A, Westerveld M, Lencz T, Novelly RA, Kim JH, et al (1992): Specificity in the correlation of verbal memory and hippocampal neuron loss: Dissociation of memory, language, and verbal intellectual ability. *J Clin Exp Neuropsychol* 14:662–672.

Scoville WB, Milner B (2000): Loss of recent memory after bilateral hippocampal lesions. *1957 J Neuropsychiatry Clin Neurosci* 12:103–113.

Shah PJ, 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.

Sheline YI, Sanghavi M, Mintun MA, Gado MH (1999): Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 19:5034–5043.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW (1996): Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci U S A* 93:3908–3913.

Spreen O, Strauss E (1998): *Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*, 2nd ed. New York: Oxford University Press.

Starkman MN, Gebarski SS, Berent S, Schteingart DE (1992): Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biol Psychiatry* 32:756–765.

Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Schteingart DE (1999): Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biol Psychiatry* 46:1595–1602.

Starkman MN, Giordani B, Gebarski SS, Schteingart DE (2003): Improvement in learning associated with increase in hippocampal formation volume. *Biol Psychiatry* 53:233–238.

Steffens DC, Byrum CE, McQuoid DR, Greenberg DL, Payne ME, Blitchington TF, et al (2000): Hippocampal volume in geriatric depression. *Biol Psychiatry* 48:301–309.

Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B (1997): Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 27:951–959.

Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A (1995): Anterior hippocampal volume deficits in nonamnesic, aging chronic alcoholics. *Alcohol Clin Exp Res* 19:110–122.

Swayze VW 2nd, Andreasen NC, Alliger RJ, Yuh WT, Ehrhardt JC (1992): Subcortical and temporal structures in affective disorder and schizophrenia: A magnetic resonance imaging study. *Biol Psychiatry* 31:221–240.

Sweeney JA, Kmiec JA, Kupfer DJ (2000): Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol Psychiatry* 48:674–684.

Trenerry MR, Jack CR Jr, Cascino GD, Sharbrough FW, So EL (1996): Bilateral magnetic resonance imaging-determined hippocampal atrophy and verbal memory before and after temporal lobectomy. *Epilepsia* 37:526–533.

Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, et al (2000): Hippocampal volume in primary unipolar major depression: A magnetic resonance imaging study. *Biol Psychiatry* 47:1087–1090.

Veiel HO (1997): A preliminary profile of neuropsychological deficits associated with major depression. *J Clin Exp Neuropsychol* 19:587–603.

Vermetten E, Vythilingam M, Southwick S, Charney D, Bremner J (2003): Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry* 54:693–702.

Vythilingam M, Anderson ER, Goddard A, Woods SW, Staib LH, Charney DS, et al (2000): Temporal lobe volume in panic disorder—a quantitative magnetic resonance imaging study. *Psychiatry Res* 99:75–82.

Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, et al (2002): Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 159:2072–2080.

Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS (1992): Tianeptine attenuates stress-induced morphological changes in the hippocampus. *Eur J Pharmacol* 222:157–162.

Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A, et al (1992): Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology* 42:1743–1750.

Wechsler D (1981): *The Wechsler Adult Intelligence Scale—Revised (WAIS-R)*. San Antonio, TX: Psychological Corporation.

Wechsler D (1987): *Wechsler Memory Scale—Revised [manual]*. San Antonio, TX: Psychological Corporation.

Winokur G, Behar D, Vanvalkenburg C, Lowry M (1978): Is a familial definition of depression both feasible and valid? *J Nerv Ment Dis* 166:764–768.

Wirz-Justice A (1994): Biological rhythms in affective disorders. In: Kupfer FEB, editor. *ACNP Fourth Generation of Progress*. New York: Raven Press, 999–1017.

Wolfe J, Granholm E, Butters N, Saunders E, Janowsky D (1987): Verbal memory deficits associated with major affective disorders: A comparison of unipolar and bipolar patients. *J Affect Disord* 13:83–92.

Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, et al (2000): Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: Relation to hypercortisolism and corticotropin-releasing hormone. *Proc Natl Acad Sci U S A* 97:325–330.

Young EA, Carlson NE, Brown MB (2001): Twenty-four-hour ACTH and cortisol pulsatility in depressed women. *Neuropsychopharmacology* 25:267–276.

Zakzanis KK, Leach L, Kaplan E (1998): On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry Neuropsychol Behav Neurol* 11:111–119.

Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo EA, Clark RE (2000): Impaired recognition memory in monkeys after damage limited to the hippocampal region. *J Neurosci* 20:451–463.