Cognitive Impairment in Major Depression: Association with Salivary Cortisol

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Background: Cognitive deficits and elevated cortisol are hallmarks of depression. Cortisol acts via mineralocorticoid and glucocorticoid receptors, which have their highest density in the hippocampus, a brain area closely related to cognitive function. Several studies have separately examined cortisol secretion and cognitive deficits in depression. However, only few studies have assessed their association in the same patients producing inconclusive results.

Methods: We examined 52 medication-free patients with major depression (37 women, 15 men; mean age 35 ± 11 years; Hamilton Depression Scale mean score 27 ± 5) and 50 healthy control subjects, matched for age, gender, and years of education. We applied several neuropsychological tests. Salivary cortisol levels were measured on the same day at 08:00, 12:00, 16:00, and 22:00 hours.

Results: Compared with healthy subjects, patients had significantly higher cortisol levels and were impaired in verbal memory, visuospatial memory, working memory, and selective attention. In depressed patients, but not in healthy control subjects, we found a negative correlation between salivary cortisol levels (area under the curve) and hippocampus-related neuropsychological domains (verbal memory, visuospatial memory) and executive function.

Conclusions: Cognitive deficits, especially those closely related to hippocampus function, appear to be related to cortisol secretion in depressed patients. Elevated cortisol may downregulate mineralocorticoid and glucocorticoid receptors in the hippocampus, which could, in part, be responsible for cognitive deficits in depressed patients.

Key Words: Cognitive function, cortisol, depression, HPA axis, neuropsychology, stress

Cognitive deficits and increased activity of the hypothalamus-pituitary-adrenal (HPA) axis leading to elevated cortisol are hallmarks of depression (1–3). Cortisol binds to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). These receptors show their highest density in the hippocampal area, which is closely related to cognitive function, especially verbal and visuospatial memory (4).

Previous literature assumes a close relationship between depression and HPA alterations on the one hand and depression and cognitive function on the other hand. However, only few studies investigated depression, HPA activity, and cognitive impairment simultaneously, producing inconclusive results. Some studies found an association between high cortisol levels and cognitive impairment in depressed patients (5,6) or predominantly in depressed patients with psychotic symptoms (7), while most studies failed to find an association in cross-sectional analyses (8–12). A limitation to all these previous studies is that patients were either treated with antidepressants or other medications or that no healthy control group was included.

To our knowledge, only two studies investigated HPA axis dysfunction and cognition simultaneously in unmedicated depressed patients compared with healthy control subjects (13,14). Although patients were impaired in memory, no association of cortisol and cognitive function was found in the first study (13). Gomez *et al.* (14) found a negative association between cortisol and verbal memory in a sample of depressed patients and healthy subjects independent of group and, surprisingly, a negative correlation between cortisol and executive function in healthy control subjects but not in depressed patients. Furthermore, depressed patients did not exhibit higher cortisol levels or worse memory performance than healthy control subjects.

To further investigate the association between cortisol and cognitive function in depression, we examined 52 nonpsychotic, drug-free patients with major depression and 50 healthy subjects who were carefully matched for age, sex, and years of education. We hypothesized that 1) patients would exhibit significantly higher cortisol levels and would be impaired in neuropsychological function, and 2) there would be a negative correlation between cortisol and hippocampus-dependent cognitive function in depressed patients.

Methods and Materials

Subjects

We recruited 52 inpatients and outpatients (15 men and 37 women) from a specialized depression clinic at the Department of Psychiatry and Psychotherapy, University Medical Center, Hamburg. Inclusion criteria were 1) a diagnosis of major depressive disorder, single or recurrent according to DSM-IV criteria, according to assessments by two experienced psychiatrists (K.H. and C.O.); 2) a minimum baseline score of 18 points on the Hamilton Rating Scale for Depression, 17-item version (HAMD-17); 3) age from 18 to 70 years; and 4) a period of at least 5 days free from antidepressants, antipsychotics, mood stabilizers, and other medications influencing HPA activity. About half of the patients referred were first-episode patients and therefore drug naïve. The remaining patients were referred either untreated or with major depression despite medication. The latter group went through a 5-day washout and was switched to a different medication immediately after the examination.

Criteria for exclusion were 1) dementia, schizophrenia spectrum disorder, bipolar disorder, substance dependence <6

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Received Apr 30, 2009; revised Jun 23, 2009; accepted Jun 30, 2009.

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.06.023

months according to the Mini-International Neuropsychiatric Interview (MINI) (15); 2) serious medical conditions, especially those associated with adrenal dysfunctions, steroid use, or well-known impact on HPA activity (e.g., diabetes mellitus) or cognitive function; 3) pregnancy and nursing; and 4) fluoxetine medication due to long half-life time.

A control group of 50 healthy subjects (15 male and 35 female) recruited by public postings and matched for age, sex, and years of education were enrolled in the study. Subjects were free of former and present DSM-IV Axis I disorders according to the MINI, had no physical illness, and had been free of any medication at least 3 months.

The study was approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained.

Hormonal Assessment

Salivary cortisol reflects the free, biologically active fraction of cortisol and correlates very well with the amount of free cortisol in blood (16,17). Salivary cortisol was collected at 08:00 hours, 12:00 hours, 16:00 hours, and 22:00 hours. All participants received oral and written instructions on the correct use of the Salivette salivary collection device (Sarstedt AG, Nümbrecht, Germany). Participants were advised not to eat, drink, smoke, brush their teeth, or use mouthwash in the 30 min before salivary collection. Cortisol was determined by radioimmunoassay (DRG, Marburg, Germany). Interassay and intra-assay coefficients of variation were below 8%. Detection limits were .5 ng/mL for cortisol.

Neuropsychological Assessment

Neuropsychological tests comprised the Auditory Verbal Learning Test (AVLT), the Digit Span Test, Rey-Osterrieth Complex Figure Test (RCFT) and Taylor Complex Figure Test (TCFT), letter cancellation test (Test d2), and the Trail Making Test A (TMT-A) and B (TMT-B).

The AVLT (18) is a measure of short-term and long-term verbal memory. The experimenter reads a list of 15 words (list A), which the participant is requested to repeat in loose order. After list A has been presented five times, the subject is asked to reproduce words from a newly presented list (list B). Following this, the subject is instructed to recall the words from list A without renewed presentation. After 30 min, the subject is again asked to repeat the words from list A.

Psychomotor slowness was assessed with the TMT-A (19). In this task, the subject has to connect encircled numbers in ascending order as quickly as possible. Part B (TMT-B) assesses cognitive set shifting and requires the alternation between numbers and letters in ascending order.

The forward and backward digit span (20) task forms part of the Wechsler Adult Intelligence Scale (WAIS). During the forward digit span task, participants are asked to remember a series of digits and repeat them back in the same order. During the backward digit span task, they are asked to repeat the digits in reverse order, which taps working memory.

The RCFT and TCFT (21) measure visuospatial memory. The participant is first required to copy a complex figure. Immediately thereafter and 20 min later, the figure has to be redrawn from memory.

Test d2 (22) is a letter cancellation test that taps selective attention/concentration. In this task, the subject is instructed to cross out the letter d whenever it is accompanied by two small lines; d's with more than or less than two lines or any stimuli containing the character p serve as distracters. Subsequent to a practice trial, 14 rows with target and distracter stimuli are presented.

Statistical Analyses

Differences in demographic characteristics between patients and healthy control subjects were compared using *t* tests for continuous variables and chi-square tests for dichotomous variables. Since patients and healthy control subjects differed significantly in their smoking habits, all analyses were adjusted for smoking.

Mixed analyses of variance (analysis of covariance [ANCOVA]) were conducted to investigate differences in cortisol levels, AVLT, and RCFT, and TCFT, with group as between-subjects factor and time as within-subjects factor. For cortisol secretion during the day, we also calculated the area under the curve (AUC). Area under the curve values in depressed patients and healthy control subjects were compared with ANCOVA.

We applied multivariate analysis of variance (MANOVA) statistics for correlated measures such as forward and backward digit span and the Test d2 tests that share similar but nonredundant information. An analysis of variance (ANOVA) was preferred for tasks with single measures or where steps were less related (e.g., for the RCFT where the first variable relates to the copy and the two others relate to memory).

Partial correlation analyses controlling for age, sex, years of education, and smoking were conducted in the total sample and in each group separately to examine the association between cortisol secretion and cognitive function. Within the depressed group, we also controlled for symptom severity.

In all analyses, two-sided tests were used and as nominal level of significance, $\alpha = .05$ was accepted.

Results

We recruited moderately to severely depressed patients with a mean Hamilton Rating Scale for Depression score of 27.5 ± 4.5 (66.7% inpatients). There were no significant differences between patients and healthy control subjects in demographic variables except smoking, which was more frequent in patients (Table 1).

Cortisol Secretion

Patients exhibited significantly higher salivary cortisol levels compared with control subjects [main effect of group: $F(1,101) = 3.9$, $p = .03$, Figure 1]. We also found a group × time interaction, indicating a differential cortisol secretion between groups over time [$F(3,99) = 5.1$, $p < .01$]. Indeed, post hoc tests revealed a significantly higher morning cortisol in patients compared with

Table 1. Demographic Variables

	Patients ($n = 52$) M (SD)	Control Subjects ($n = 50$) M (SD)	*p*
Age	35 (11.6)	35 (11.6)	ns
Male/Female	15/37	15/35	ns
Education (Years)	11.3 (1.6)	11.5 (1.5)	ns
BMI (SD)	24.3 (6.1)	23.2 (3.7)	ns
Smokers	50%	28%	.02[a]
BDI (SD)	30.9 (9.9)	3.3 (2.8)	<.01[a]

BDI, Beck Depression Inventory; BMI, body mass index.
[a]Based on independent *t* test for continuous variables and chi-square for dichotomous variables.