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Changes in cortisol secretion during antidepressive treatment and cognitive improvement in patients with major depression: A longitudinal study

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Summary
Objectives: We have previously reported that cognitive deficits are cross-sectionally associated with elevated cortisol in depressed patients. Here, we longitudinally examined if changes in cortisol secretion during treatment are associated with improvement of cognition.
Methods: Cognitive function and salivary cortisol levels were longitudinally examined in 52 patients with major depression before and after 3 weeks of standardized selective serotonin reuptake inhibitor (SSRI) and an add-on treatment modulating the mineralocorticoid receptor and compared to a healthy control group ($n = 50$) matched for age, gender and years of education.
Results: Across add-on treatment groups, SSRI treatment reduced salivary cortisol in patients to levels of healthy controls (time $\times$ group interaction $p = .05$). In patients, reduction of cortisol significantly correlated with improvement in depressive symptoms ($r = .52$, $p < .01$), speed of information processing ($r = .50$, $p < .01$), and cognitive set-shifting ($r = .34$, $p = .03$). Improved depressive symptoms were only associated with improved attention and working memory.
Conclusions: Improvement of some cognitive domains during SSRI treatment was associated with decreasing cortisol secretion and was only to a lesser extent associated with improved depressive symptoms.
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1. Introduction

Cognitive deficits are characteristic features of depression and increased activity of the hypothalamus—pituitary—adrenal axis (HPA) leading to elevated cortisol is often reported in major depression (Belanoff et al., 2001; de Kloet et al., 2005a,b) although this depends on type and severity of depression as well as on sample characteristics (Stetler

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and Miller, 2011; Knorr et al., 2010). We have recently shown in a cross-sectional study that cognitive deficits are related to elevated cortisol in depressed patients (Hinkelmann et al., 2009) and several studies have shown a normalization of HPA axis function during the course of treatment (McKay and Zakzanis, 2010).

However, whether HPA normalization is related to improvement of cognitive deficits, is still under debate. To our knowledge, only two studies have longitudinally examined the association between HPA normalization and improvement of cognition in depressed patients compared to healthy subjects: O'Brien et al. (2004) found a decrease of free cortisol in older depressed patients (mean age 74 years) during treatment, which was not correlated with cognitive improvement (O'Brien et al., 2004). Compared to healthy subjects, patients showed only slight cognitive improvement and about half of them fulfilled formal criteria for Mild Cognitive Impairment (MCI) during follow-up.

Vythilingam et al. (2004) investigated a younger and medication free sample of depressed patients in comparison to healthy subjects. During SSRI treatment, patients showed a decrease of cortisol and an improvement in memory function. However, at baseline, patients did not exhibit greater cortisol levels compared to healthy controls and cortisol was not associated with cognition before treatment. During follow-up no healthy subjects were included and no association between cognition and cortisol was found.

Two further studies longitudinally investigated the relationship of cortisol and cognition in depressed patients without including a healthy control group: Zobel et al. (2004) demonstrated an association of the decrease in cortisol and the improvement of working memory function, which was independent of symptom severity. In contrast, Reppermund et al. (2007) did not find such associations but reported that a high rate of depressed inpatients remained cognitively impaired at discharge.

In summary, the few existing studies regarding HPA-axis function and cognition during treatment in patients with major depression have come to inconclusive results and exhibit several limitations. In our previous cross-sectional report from the same sample (Hinkelmann et al., 2009), elevated cortisol was specifically associated with cognitive deficits in verbal and non-verbal memory and in executive function. Here, we aimed to further investigate the longitudinal association between changes of HPA-axis activity and cognition in depressed patients during treatment. We hypothesized that decreases in cortisol secretion during antidepressant treatment would be associated with improvement of cognitive function in the same domains, i.e. in verbal and non-verbal memory and in executive function.

2. Methods

2.1. Subjects

Clinical and demographic characteristics of the participants are shown in Table 1. In brief, we recruited 52 in- and outpatients (15 men and 37 women, mean age 35 ± 11.5 years, mean years of education 11.3 ± 1.6 years, Hamilton Rating Scale for Depression score mean 27.2 ± 4.5, mean number of episodes 1 ± 1.2) 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 MINI-interview and a minimum baseline score of 18 points on the

Table 1 Demographic variables.

	Patients ($N = 52$) M (SD)	Controls ($N = 50$) M (SD)	p
Age	35 (11.6)	35 (11.6)	n.s.
Male/female	15/37	15/35	n.s.
Education (years)	11.3 (1.6)	11.5 (1.5)	n.s.
BMI (SD)	24.3 (6.1)	23.2 (3.7)	n.s.
Smokers	50%	28%	.02*
BDI (SD)	30.9 (9.9)	3.3 (2.8)	<.01*
Inpatients	654%		
Non-psychotropic concomitant medication	$N = 6$	$N = 5$	
Beta blocker	2	–	
Calcium antangonists	1	–	
Statins	–	2	
Levothyroxine	3	–	
Iodine	–	1	
Warfarin	–	1	
Non-steroidal anti-inflammatory medication	–	1	
Escitalopram dosage (mean mg/day 21)**	13.2 (3.8)	n.a.	
Lorazepam dosage (mean mg/day 21)	0.18 (0.4)	n.a.	
Zolpidem/Zopiclon dosage (mean no. tablets/day)	0.2 (0.5)	n.a.	

Abbreviations: BMI: Body Mass Index, BDI: Beck Depression Inventory.

* Based on independent t-test for continuous variables and chi-square for dichotomous variables.

** At baseline all patients were free of psychotropic medication and were all started on escitalopram after the baseline assessment.

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