Original article

RUNNING HEAD: CORTISOL AND COGNITIVE PROFILE IN DEPRESSION

Title: Cortisol levels and cognitive profile in major depression: A comparison of currently and previously depressed patients.

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Abstract

The association between depressive symptoms and elevated cortisol levels, and depression and cognitive functioning, has been less robust in outpatients with symptoms in the mild to moderate range. Furthermore, the association between elevated cortisol levels and cognitive functioning is unclear. In the present study, currently depressed (n = 37), previously depressed (n = 81) and never depressed controls (n = 50) were assessed on a range of neuropsychological measures. Salivary cortisol was measured in the morning and evening. Participants with current depression were non-hospitalized and had symptoms predominately in the mild to moderate range. Elevated salivary evening cortisol, but not morning cortisol, was significantly related to depressive symptoms. The difference in cortisol levels between the previously depressed group and the never depressed controls was not significant. The groups had significantly different cognitive profiles, with the currently depressed performing poorer on tasks related to working memory compared to the never depressed controls. Both the currently and previously depressed performed worse on attentional tasks. The findings indicate that outpatients with mild to moderate depression have elevated cortisol levels and limited mild cognitive impairments. Furthermore, mild impairments in attention may persist after remission, indicating that this could be a trait-marker in depression. The present study did not find support for a significant relationship between cortisol and cognitive functioning.

Keywords: Major depression; Cortisol; Cognitive function; Neuropsychology; HPA-axis.

1. Introduction

Major depression is a prevalent and impairing disorder (Wittchen and Jacobi, 2005). In addition to disturbances in mood, motivation and vegetative functioning, there is solid evidence indicating that depression is associated with cognitive impairments in its acute phase (Hammar and Årdal, 2009; Rock et al., 2014). Deficits are most common in the domains of memory (Hinkelmann et al., 2013), executive functioning (Snyder, 2013), attention (Rock et al., 2014), and psychomotor speed (Egeland et al., 2005). However, it has been difficult to establish a cognitive profile characterizing depressed patients, and findings are diverse, with some studies failing to find substantial cognitive deficits in depressed individuals (Halvorsen et al., 2012; Krogh et al., 2012). The diversity of results is possibly related to the heterogeneity of depression, and hence, the differences between studied patient groups, for instance with regard to severity, subtype, and the presence of psychotic symptoms and comorbid disorders (Hammar and Årdal, 2009).

Stressful life events, including past or recent traumatic experiences, are associated with an increased risk for developing a depressive episode (e.g., Tennant, 2002). In addition, depression is in itself a stressful event. Thus, several studies have investigated the functioning of the hypothalamic-pituitary-adrenal (HPA) axis in individuals suffering from depression. Upon stress exposure, the HPA-axis becomes activated. This triggers the release of corticotropin-releasing hormone (CRH) from the hypothalamus which stimulates the secretion of adrenocorticotropin (ACTH) from the pituitary gland, which in turn triggers the release of glucocorticoids (cortisol) from the adrenal cortex (Lupien et al., 2007). Under normal conditions, glucocorticoids follow a 24-hour circadian rhythm with peaking concentrations in the morning and a gradual decline during late afternoon, evening and night (Lupien et al., 2007). Free cortisol is commonly measured in saliva. Salivary cortisol levels generally correlate well with free unbound cortisol in blood (Hellhammer et al., 2009). Hypersecretion of cortisol in depression is supported by several studies (Hinkelmann et al., 2013; Vreeburg et al., 2009), but not all (Krogh et al., 2012; Michopoulos et al., 2008). Meta-analyses conclude that cortisol levels are significantly increased in depressed patients compared to controls both in the morning and evening (Knorr et al., 2010; Stetler and Miller, 2011). However, the degree of HPA-hyperactivity varies

substantially and is more pronounced in patients who are hospitalized and whose depression has psychotic, melancholic or endogenous features (Stetler and Miller, 2011).

There is growing evidence that cognitive impairment in depression may persist in a remitted state (e.g., Hasselbalch et al., 2011; Reppermund et al., 2008). Yet others suggest that such impairments may be reversible upon recovery (Biringer et al., 2005). With regard to HPA-axis dysregulation, some research indicates that this is state-dependent and normalizing with successful symptom relief (Hinkelmann et al., 2012; Reppermund et al., 2007). However, several studies show that dysregulation may persist despite recovery (McKay and Zakzanis, 2010; Vreeburg et al., 2009), and may predict recurrence of the disorder (Zobel et al., 2001). This, together with studies showing abnormal HPA-axis functioning in young non-depressed individuals at familial risk (Mannie et al., 2007), poses the question that such abnormalities may represent a trait-marker of depression.

Cortisol binds to two subtypes of receptors throughout the brain, both which are prominent in the hippocampus and prefrontal cortex which are brain areas related to memory and executive functioning (Lupien et al., 2007). The mineralocorticoid receptor (MR) has high affinity for cortisol, and MRs are therefore almost entirely occupied under conditions with basal levels of glucocorticoid secretion (Anacker et al., 2011). The other receptor, the glucocorticoid receptor (GR) has low affinity for cortisol. Thus, under normal conditions, this receptor is more moderately occupied. It becomes fully activated at higher concentrations, such as under stress or at the peak of the circadian rhythm of cortisol secretion (Holsboer, 2000). Due to its activation at higher concentrations, the GR appears to have a crucial role in regulating glucocorticoid levels under stressful circumstances through negative feedback on the HPA-axis inhibiting production and secretion of CRH and ACTH (Juruena et al., 2004). Furthermore, abnormal GR functioning at the limbic-hippocampal level (GR resistance) resulting in impaired negative feedback inhibition and increased release of CRH, is proposed as a mechanism for the overactivity of the HPA-axis in depression and as being involved in causing depression.

Prolonged excessive exposure to cortisol due to Cushing's syndrome (Forget et al., 2002) and long-term corticosteroid treatment (Brown et al., 2004) is associated with cognitive impairments;

results suggestive of a neurotoxic effect. The association between HPA-axis activity and cognitive performance in depressed individuals remains unclear. Some studies suggest that there is indeed an association (e.g., Egeland et al., 2005; Gomez et al., 2006; Keller et al., 2016). However, others fail to document a relationship (Krogh et al., 2012; Michopoulos et al., 2008; Vythilingam et al., 2004). Similarly, it has been difficult to confirm the neurotoxicity of cortisol in depression by establishing a direct relationship between the peripheral glucocorticoid system and decreased hippocampal volume, which could further affect cognitive functions (Colla et al., 2007; Kaymak et al., 2010). However, a recent pilot study indicated that the link between cortisol and hippocampal volume may be more complex and rely on the interaction between cortisol and other steroid hormones (Jin et al., 2016). The fact that depression tends to recur for 50 - 80 % of patients, thus inflicting prolonged cortisol hypersecretion, also raises the question as to whether there are different cognitive profiles for patients with single-episode and recurrent depression, as suggested by some studies (Hasselbalch et al., 2013).

1.2. Aims

The aim of this study was fourfold. 1. The association between elevated HPA-axis activity and depressive symptoms in outpatients with symptoms in the mild to moderate range has been less robust in previous studies (Krogh et al., 2012; Stetler and Miller, 2011). Therefore, we firstly aimed to study the relationship between salivary cortisol and *depressive symptoms* in a sample including non-hospitalized mildly to moderately depressed individuals, previously depressed individuals currently in a remitted state, and never depressed healthy controls. Based on previous studies we hypothesised that depressive symptoms will be positively correlated with cortisol levels. 2. Further, we studied group differences in cortisol level, focusing on both potential differences between the currently depressed and never depressed groups, and whether the previously depressed group differed from the other groups. In addition, possible differences in cortisol between individuals having experienced single versus recurrent depression was studied. As earlier research has proposed HPA-axis dysregulation as a trait marker in depression, our hypothesis is that cortisol levels will be elevated both in the currently and previously depressed group. 3. The third aim was to investigate whether there were different cognitive profiles for the groups of currently, previously and never depressed, when assessed on a

range of neuropsychological measures. The neuropsychological data from the sample has previously been analysed for differences using single tests as the main outcome (Halvorsen et al., 2012). The present article builds on this by investigating difference in cognitive profiles using components based on factor analysis as the outcome. Due to the relatively mild severity of the sample, we hypothesised that the currently depressed group would show mild and limited impairments on neuropsychological tests, and that this would be evident in the previously depressed group as well. 4. Lastly, exploratory analyses were performed to study the associations between salivary cortisol and performance on neuropsychological measures.

2. Methods

2.1. Participants

The study included 168 participants comprising currently depressed (CD; n = 37), recovered previously depressed (PD; n = 81) and individuals who had never experienced depression (ND; n = 50). Participants were diagnosed in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association (APA), 2000) using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1997). Exclusion criteria were depression in partial remission as defined in DSM-IV-TR (APA, 2000), dysthymic disorder, current or past manic/hypomanic episode or psychotic symptoms, a history of known brain damage and major depression due to a general medical condition. Based on information from the clinical interview participants were grouped as currently depressed, previously depressed, but in recovery for a minimum of 8 weeks, or never depressed without ongoing or past axis-I disorders. Hearing and vision was normal or corrected to normal in all participants.

Of the 168 participants, 103 were recruited from a previous study of depression and cognitive vulnerability among mildly to moderately depressed outpatient younger adults (CD, *n* = 15; PD, *n* = 62; ND, *n* = 26; Wang et al., 2005). The remaining 65 participants were recruited from general practitioners and through advertisements in a local newspaper. The study was approved by the

Regional Committee for Research Ethics, and written informed consent was obtained from all participants. For further information regarding the sample and study design see Halvorsen et al. (2012; 2011).

2.2. Procedure

Participants were tested over two consecutive days. The clinical interview, the Beck Depression Inventory-II (BDI-II) and neuropsychological testing were conducted during day one, whereas salivary cortisol was measured between the two days of testing. Clinical psychologists or postgraduate psychology students thoroughly trained by a highly qualified supervisor, performed clinical interviews and neuropsychological testing. The clinical interviews were digitally recorded and 30 interviews (10 from each group) were randomly selected for reliability testing. Interrater agreement (kappa) was high both for deciding group allocation (currently, previously or never depressed; $k = 0.9$) and for distinguishing between participants who had or had not been depressed (currently or previously depressed versus never depressed; $k = 1.0$; Halvorsen et al., 2012). Interrater reliability was not assessed for comorbid diagnoses. Therefore, exact numbers for comorbid diagnosis are not reported. The test session lasted 2 – 3 hours including regular breaks. Tests were presented in the same order for all participants. Participants received 150 NOK (~$18) per hour of participation as compensation.

2.3. Cortisol level

Salivary evening and morning cortisol were sampled by having participants chew on a cotton swab (cat.no. 51.1534.500, Salivette®, Sarstedt, Nümbrecht, Germany). Swabs were placed in plastic tubes (Salivette®), centrifuged at 1000 x g for 10 minutes and kept frozen (-20©) until analysis. Participants were instructed to abstain from eating, drinking and brushing their teeth for at least one hour before the evening sample, and to take the morning sample directly after getting up, before eating, drinking or brushing their teeth.

Cortisol was analyzed with an electrochemiluminescence immunoassay (ECLIA) using an automated clinical chemistry analyser (Modular P, Roche Diagnostics, Mannheim, Germany). The

lower detection limit was 0.5 nmol/L, and the inter-assay coefficient of variation (CV) in saliva samples was 2.7 % at a concentration of 11.5 nmol/L, likewise intra-assay CV was 11.5 %. In serum, the within-subject biologic CV is 15.2 %, whereas the between-subject biologic CV is 38.1 % according to the Westgard Quality Control database. Similar variation should be reflected in the saliva that contains the free fraction of the hormone, i.e. the fraction not bound to transcortin and albumin, which is approximately 1/50 of that in serum. The laboratory had a reference interval for morning and evening hours of 6 – 29 and 2 – 15 nmol/L, respectively.

2.4. Instruments

The BDI-II is a 21-item self-report measure of severity of depressive symptoms during the last two weeks (Beck et al., 1996). Each item is rated on a 4-point scale ranging from 0 – 3. The validated Norwegian translation was used in the study (Kjærgaard et al., 2014). Studies support the BDI-II as a reliable, internally consistent and valid scale for assessing depression (e.g., Beck et al., 1996).

Beck Anxiety Inventory (BAI) is a 21-item measure of anxiety symptom severity during the last week (Beck and Steer, 1993). Each item is rated from 0 to 3. The inventory has shown high internal consistency and reliability, as well as robust convergent and discriminant validity (Fydrich et al., 1992; Steer et al., 1993).

2.5. Neuropsychological tests

All participants were assessed on executive functioning, memory, attention, psychomotor speed, and information processing; cognitive domains previously found to be sensitive to dysfunction in unipolar depression (Hammar and Årdal, 2009; Rock et al., 2014). *Executive functioning* was assessed using the Delis Kaplan Executive Function System (D-KEFS; Delis et al., 2001); Colour-Word Interference Test (the variables inhibition and inhibition/switching), D-KEFS Verbal Fluency (including the variable category switching; Delis et al., 2001), Wisconsin Card Sorting Test (WCST; Heaton, 1993), and Trail Making Test B (Reitan and Wolfson, 1993). *Working memory* was tested using the Digit Span Backward from the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 2003). Tests of *psychomotor speed and information processing* included the California Computerized

Assessment Package RT (CalCap; Miller, 1993), Digit Symbol Coding from WAIS-III (Wechsler, 2003), Colour-Word Interference Test (the variables color naming and word reading; Delis et al., 2001), and Trail Making Test A (Reitan and Wolfson, 1993). *Attention* was assessed with the Digit Span Forward from WAIS-III (Wechsler, 2003) and the Seashore Rhythm Test from the Halstead-Reitan test battery (Reitan and Wolfson, 1993). *Verbal learning and memory* was evaluated using the California Verbal Learning Test, second edition (CVLT-II; Delis et al., 2004). *Verbal Fluency* was tested with the D-KEFS Verbal Fluency subtests (Delis et al., 2001). In addition, the Picture Completion and Comprehension subtests from the WAIS-III (Wechsler, 2003) were administered as measures of intellectual abilities.

2.6. Statistical analysis

Of the 168 participants in the study, 36 missed the morning cortisol measure and 43 missed the evening measure. Further, four outliers (two morning, two evening) were excluded due to extreme cortisol values (>3 SD above sample mean). For the analyses this leaves a sample of 130 (CD: n = 31; PD: n = 61; ND: n = 38) and 123 participants (CD: n = 27; PD: n = 60; ND: n = 36) with a morning and evening cortisol measure, respectively. Morning samples were collected between 6 and 10.30 am (M = 7.65, SD = 0.78; 91 % collected between 7 am and 9 am), and evening samples were collected between 8 pm and 1.30 am (M = 22.47, SD = 0.80; 89 % collected between 9.30 pm and 11.30 pm). One evening sample was collected at 6.30 pm. For means, time points after midnight were recoded as 24 (midnight) and 25 (1 am) to avoid that these time points would have an undue influence on the means. There was no significant difference between groups on time of measurement, $F_{\text{morning}}(2,131) = 2.09$, $p = .13$, $\eta_p^2 = 0.03$; $F_{\text{evening}}(2,123) = 1.26$, $p = .29$, $\eta_p^2 = 0.02$. As time of measurement did not differ between groups and did not correlate significantly with cortisol levels or any of the neuropsychological indexes (see description below), this variable was not controlled for in the analyses.

All analyses were carried out using IBM SPSS Statistics version 24 for Windows (IBM Corp., Released 2016). Effect sizes were calculated using the spreadsheet provided by Lakens (2013). Differences between groups on demographic and clinical variables were analysed using One-way ANOVAs for continuous variables and for categorical variables Chi square test or Fisher's Exact test when appropriate. The associations between depression and cortisol were analysed using non-parametric tests due to the non-normal distribution of the cortisol-data. We used Spearman's rho correlations with one-tailed significance tests for testing the relationship between depressive symptoms (BDI-II) and cortisol, and independent samples Kruskal-Wallis tests for analysing group differences. An independent-samples Jonckheere-Terpstra test was carried out to determine if there was a significant ordered trend in medians between the three groups. This was based on the hypothesis that there may be an ordering of median cortisol levels from lowest in the healthy control group and highest in the currently depressed group. This pattern of results, albeit non-significant, was found in the present sample for mean scores on neuropsychological tests (Halvorsen et al., 2012).

Power analyses were performed with G*Power 3.1.9.2 (Faul et al., 2007). With an alpha level of 0.05 the study had a statistical power of 0.88 for detecting small correlations (r = 0.25) between BDI-II and cortisol (n = 123 for evening cortisol), and a power of 0.82 for detecting effects of moderate size (f^2 = 0.15) in a multiple regression analysis with 8 predictors. Originally, the study was powered to detect group-differences of moderate effect sizes (d = 0.5, power = 0.80, n = 168), but due to missing cortisol data the achieved power for group-differences in cortisol was less than adequate (power ~0.70). Nevertheless, results are useful for meta-analytic purposes as all effect sizes are reported.

Further, we performed a principal components analysis (PCA) for the neuropsychological test items (22 variables). Oblique oblimin rotation was chosen because we assumed a certain degree of dependency between the underlying factors. We used 1.0 as prior communality estimates. Variables with communalities below 0.5 were excluded in order to ensure that the factor solution would account for a substantial proportion of variance of included variables. One variable (Simple Reaction Time from CalCap) was excluded on this basis. The final analysis including 21 variables retained 6

components with eigenvalues above the Kaiser's criterion of 1. Factor solutions based on the scree plot (5 to 6 factors) and parallel analyses were also considered (3 factors). However, the 6 factor solution provided the most theoretically sound alternative. The Kaiser-Meyer-Olkin measure indicated good sampling adequacy, KMO = .86, and a significant Bartlett's test of sphericity ($p<.001$) suggested sufficient correlations between variables. Mean index-scores for each of the 6 dimensions were calculated using z-transformed variable scores. Only variables with strong factor loadings (≥0.50) were included for the index-scores. No variables had strong loadings on more than one factor. The correlations between the index-scores and the factor scores from the analysis ranged from .97 to 1.00, indicating minimal loss of information.

Mean index-scores were subsequently used as dependent variables in repeated-measures MANOVAs investigating differences in cognitive profiles between the groups of CD, PD and ND. Group was included as the between-subjects variable and mean-scores on the 6 cognitive indexes as the within-subjects variable. An interaction-effect between group and cognitive index would indicate significant different profiles. Index-scores did generally not deviate substantially from normality based on histograms and measures of skewness and kurtosis. Further, a non-significant Box-test suggested that the assumption of homogeneity of variance-covariance matrices was met. The omnibus MANOVA was followed-up by individual ANOVAs for each index. Lastly, the mean index scores were used as independent variables in hierarchical regression analyses. Cortisol measures were entered as independent variables controlling for demographic variables (gender, age and education), medication use, and BDI-II and BAI scores. Bootstrapping (2000 samples) was used to generate confidence intervals (percentile) and *p*-values that do not rely on the assumptions of normality of residuals or homoscedasticity.

3. Results

3.1. Sample characteristics

The total sample included 37 currently depressed individuals, 81 previously depressed individuals and 50 never depressed controls. Demographic and clinical information for the three groups are shown in Table 1. There were no significant differences between the groups on any demographic variables, including age, gender, education, intellectual abilities and handedness. On the BDI-II there were significant differences between all groups in the expected direction (ND < PD < CD; $F(2,165) = 133.42$, $p = <.001$, $\eta_p^2 = 0.62$). The mean BDI-II score in the PD and ND groups were well below the clinical threshold of 14 as defined by Beck, Steer and Brown (see Table 1; 1996), but 13 individuals in the PD-group had BDI-II score above 13. The depressive severity in the CD-group ranged from mild to severe (BDI-II score 12 - 45), with a mean score of moderate severity (see Table 1). There was also a significant difference between the groups on the BAI, $F(2,164) = 58.75$, $p < .001$, $\eta_p^2 = 0.42$ (see Table 1), with post hoc analyses finding significant differences between all groups, ND < PD, $p = .002$, ND < CD, $p < .001$, PD < CD, $p < .001$. The mean BAI-scores were minimal in the ND and PD groups and within the mild to moderate range in the CD-group (Beck and Steer, 1993). The majority of participants in the CD and PD groups had recurrent depression. There was no significant difference on BDI-II, $F(1,116) = 1.74$, $p = .19$, $\eta_p^2 = 0.01$, between participants with single ($M = 11.17$, $SD = 12.08$) versus recurrent depression ($M = 14.10$, $SD = 10.65$), nor was there a difference in BAI-scores, $F(1,116) = 1.75$, $p = .19$, $\eta_p^2 = 0.01$, Single episode: $M = 8.19$, $SD = 9.97$; Recurrent: $M = 10.60$, $SD = 8.67$. Participants were non-hospitalized, and only 7 % in the PD and 19 % in the CD group used antidepressant medication.

Comorbidity in the sample was limited. Anxiety diagnoses were most common, with social phobia or mild generalized anxiety being reported by approximately 10 participants in each of the depressed groups. Post-traumatic stress disorder (PTSD) was reported by only one participant. There were no significant differences between the depression groups on clinical variables other than BDI-II and BAI (see Table 1).

Table 1. Demographic and clinical characteristics of the participants (n = 168).

Variable	Never depressed (n = 50)	Previously depressed (n = 81)	Currently depressed (n = 37)	Significance tests

Female, *n* (%)	39 (78.0)	71 (87.7)	27 (73.0)	χ^2 (2) = 4.23, *p* = .12
Age, *M* (*SD*)	38.1 (12.7)	37.4 (9.6)	37.5 (12.0)	*F*(2,165) = 0.06, *p* = .95
Education, years, M (SD)	15.1 (3.6)	15.1 (2.6)	13.8 (3.8)	*F*(2,165) = 2.53, *p* = .08
BDI-II [a], M (SD)	3.1 (2.9)	7.7 (6.7)	25.3 (9.2)	*F*(2,165) = 133.42, *p* < .001
BAI [b,c]	2.3 (2.8)	6.4 (6.3)	17.4 (9.8)	*F* (2,164) = 58.75, *p* < .001
Right handed, n (%)	45 (90.0)	75 (92.6)	35 (94.6)	Fisher's Exact Test = 0.65, *p* = .81
Intellectual abilities [c], M (SD)				
Comprehension	23.4 (5.7)	23.0 (4.5)	22.2 (4.6)	*F*(2,164) = 0.68, *p* = .51
Picture Completion	21.0 (2.7)	21.0 (2.9)	20.9 (3.1)	*F*(2,164) = 0.03, *p* = .97
Medication, n (%)	0	6 (7.4)	7 (18.9)	Fisher's Exact Test: *p* = .11 [d]
Recurrent depression, n (%)	0	55 (67.9)	27 (73.0)	χ^2 (1) = 0.31, *p* = .58 [d]
≥ 3 depressive episodes, n (%)	0	36 (44.4)	19 (51.4)	χ^2 (1) = 0.49, *p* = .49 [d]
≥ 5 years in remission		51 (63.0)		

[a]BDI-II = Beck Depression inventory, second edition; [b] BAI = Beck Anxiety Inventory, [c]Missing: n = 1; [d]only depressed groups analysed.

Looking at all groups together, there were no significant differences in demographic or clinical variables between participants providing or missing cortisol measures, *F*(1,166) = 0.12 – 1.40, *p* = .24 – .73, χ^2 (1) = 0.004 - .58, *p* = .23 -.95). Furthermore, there were no differences between the groups in proportion of participants missing cortisol samples, χ^2 (2) = 0.80, *p* = .67. When looking at patterns of missingness in the separate groups there were no significant differences in the ND and PD groups. However, in the CD group participants missing one or both cortisol measures had significantly higher scores on the BDI-II, *F*(1,35) = 12.35, *p* = .001, η_p^2 = 0.26 (*M*: 22.44 vs. 32.90). In addition, they tended to be younger, *F*(1,35) = 8.26, *p* = .007, η_p^2 = 0.19 (*M*: 40.63 vs. 29.00), and have lower education, *F*(1,35) = 4.29 , *p* = .046, η_p^2 = 0.11 (*M:* 14.52 vs. 11.70 years).

3.2. The association between salivary cortisol and depressive symptoms

Analyses of the full sample of participants indicated a small, but significant positive relationship between BDI-II scores and salivary cortisol measured in the evening, r_s = 0.22, *p* = .007. The association between BDI-II scores and salivary morning cortisol was non-significant, r_s = 0.01, *p* = .44.

The correlation between depressive symptoms and cortisol was also analysed separately within the three groups. There were no significant relationships between BDI-II and any cortisol measure within any group (morning cortisol: r_s = -0.04 – 0.11, *p* = .42 - .85; evening cortisol: r_s = -0.05 – 0.22,

p = .21 - .72). However, these analyses were restricted by limited sample size, especially in the CD (n = 31) and ND (n = 42) groups.

As the groups differed significantly on anxiety symptoms measured with BAI, analyses were performed to investigate if anxiety mediated the association between BDI-II and evening cortisol. The Sobel test indicated that there was no significant mediation effect of BAI, Z_s = -0.60, SE = 0.01, p = .55. Therefore, BAI is not controlled for in the following analyses of group-differences.

3.3. Group-differences in salivary cortisol

A comparison of salivary cortisol in the three groups (CD, PD and ND) using an independent Samples Kruskal-Wallis Test found no significant differences between the groups on morning cortisol, n = 130, $\chi^2(2) = 1.08$, p = .58, $r_{ND\text{-}CD}$ = -0.02, $r_{ND\text{-}PD}$ = 0.09, $r_{CD\text{-}PD}$ = -0.08. However, for evening cortisol there was a significant difference between the groups, n = 123, $\chi^2(2) = 8.59$, p = .01, with a mean rank cortisol score of 78.00, 60.93, 51.78 for the CD, PD and ND groups, respectively. Pairwise comparisons indicated a significant difference after adjustment for multiple tests between the ND and CD group (CD > ND, p = .01, r = 0.35; $r_{ND\text{-}PD}$ = 0.13, $r_{CD\text{-}PD}$ = 0.23). Furthermore, an independent-samples Jonckheere-Terpstra test of ordered alternatives showed a statistically significant trend of higher median cortisol levels across groups with higher level of depression (CD >PD >ND), T_{JT} = 2979.50, z = 2.89, p = .004. Pairwise comparisons found that there was a significant difference between CD and ND (CD > ND, p = .01), and between the CD and PD groups (CD >PD, p = .04). Since some previously depressed participants had elevated scores on BDI-II, the analysis was re-run excluding 13 individuals with BDI-II scores above 13. This did not alter the results.

Similarly, an independent Samples Kruskal-Wallis Test indicated no significant differences between the groups based on frequency of depression (never, single, recurrent) in morning cortisol, n = 130, $\chi^2(2) = 0.58$, p = .75, $r_{ND\text{-}Single}$ = 0.10, $r_{ND\text{-}Recurrent}$ = 0.08, $r_{Single\text{-}Recurrent}$ = -0.05. The difference for evening cortisol was marginally significant, n = 123, $\chi^2(2) = 6.08$, p = .048, with a mean rank cortisol score of 69.57, 58.38, 51.78 for the groups with recurrent, single or no depression, respectively. Pairwise comparisons showed that the largest difference in evening cortisol was between the ND and

recurrent depression group, p = .02, r = 0.24. However, this difference did not reach significance after adjustment for multiple tests (p =.05). The other pairwise comparisons did not reach significance, ND = Single, p = .47, r = 0.11; Recurrent = Single, p = .18, r = 0.15. Looking at the Jonckheere-Terpstra test of ordered alternatives, there was a statistically significant trend for higher median levels of evening cortisol across the groups, T_{JT} = 2879.50, z = 2.50, p = .01. Evening cortisol was significantly higher in the recurrent depression group compared to the ND group, p = 03.

3.4. Neuropsychological profiles in current and previous depression

To reduce the number of neuropsychological test-variables a PCA was performed. This analysis yielded the following 6 components: 1. Psychomotor speed, 2. Verbal memory, 3. Executive function, 4. Working memory, 5. Verbal fluency, and 6. Attention (see Table 2 for factor loadings for all the included neuropsychological variables). Index-scores were calculated using z-transformed variable scores.

Table 2. Factor loadings for the 6 neuropsychological components. Based on the principal components analysis with oblimin oblique rotation.

Variables	Components					
	1	2	3	4	5	6
Trail Making Test A	-.816					
Trail Making Test B	-.663					
Colour-Word Interference Test – Inhibition	-.657					
Digit Symbol Coding	.645					
Color-Word Interference Test – Inhibition/Switching	-.569					
Color-Word Interference Test – Colour Naming	-.456					
CVLT-II[a] - Short Delay Free Recall		.961				
CVLT-II[a] - Long Delay Free Recall		.935				
CVLT-II[a] - Trials 1-5 Total		.879				
WCST[b] - Perseverative Responses			-.869			
WCST[b] - Categories Completed			-.825			
Seashore Rythm Test				.800		
Digit Span Backward				.767		
Digit Span Forward				.748		
Color-Word Interference Test – Word Reading				-.425		
Verbal Fluency – Category Switching					.880	
Verbal Fluency – Category Fluency					.771	
Verbal Fluency – Letter Fluency					.550	
CalCAP[c] - Sequential Reaction Time 1						-.946
CalCAP[c]- Sequential Reaction Time 2						-.775
CalCAP[c] - Choice Reaction Time						-.630

[a]CVLT-II = California Verbal Learning Test, second edition, [b]WCST = Wisconsin Card Sorting Test, [c]CalCAP = California Computerized Assessment Package RT.

Results from the repeated-measures MANOVA showed different cognitive profiles between the three groups (CD, PD, ND) as indicated by a significant interaction between group and the within-subjects factor cognitive component, $\Lambda_{Pillai} = 0.15$, $F(10,318) = 2.48$, $p = .007$, $\eta_p^2 = 0.03$, $\eta_G^2 = 0.02$ (see Table 3 for mean index-scores for the groups and Figure 1 for plots). The interaction was significant irrespective of which multivariate test statistic was used. Pillai's trace provided the most conservative estimate. Including medication as a covariate did not substantially alter the overall results, with the interaction between group and cognition being significant, $\Lambda_{Pillai} = 0.14$, $F(10,316) = 2.42$, $p = .009$. There was no significant interaction between medication and the cognitive components.

Separate univariate ANOVAs yielded significant differences between the groups on the Working memory and Attention components (see Table 3). Bonferroni corrected post hoc analyses showed that the ND group scored significantly higher on Working memory compared to the CD group ($p = .04$). The PD group also performed better than the CD group, but this difference did not reach significance ($p = .06$). In addition, the ND group performed significantly better than both the CD and PD groups on Attentional tasks (ND > CD, $p = .003$; ND > PD, $p = .01$). Re-running the analysis without previously depressed participants with BDI-II scores above 13 (total $n = 152$) confirmed the findings (Working memory: ND > CD, $p = .04$; PD > CD, $p = .048$; Attention: ND > CD, $p = .003$; ND > PD, $p = .002$).

Table 3. Mean index scores for the never, previously or currently depressed groups, and results from follow-up ANOVAs comparing the cognitive components across groups.

Component *M* (*SD*)	Never depressed ($n = 48$)	Previously depressed ($n = 81$)	Currently depressed ($n = 36$)	ANOVA F (2,162)
Psychomotor speed	.03 (.92)	.05 (.72)	-.09 (.62)	0.46, $p = .63$, $\eta_p^2 = 0.01$
Verbal memory	-.10 (.94)	.07 (.91)	.002 (.98)	0.47, $p = .63$, $\eta_p^2 = 0.01$
Executive function (reversed direction)	-.17 (.78)	.07 (.89)	.01 (.88)	1.21, $p = .30$, $\eta_p^2 = 0.01$
Working memory	.14 (.94)	.07 (.76)	-.31 (.68)	3.68, $p = .03$, $\eta_p^2 = 0.04$
Verbal fluency	.18 (.84)	-.03 (.78)	-.15 (.78)	2.00, $p = .14$, $\eta_p^2 = 0.01$
Attention	.33 (.78)	-.08 (.72)	-.23 (.87)	6.51, $p = .002$, $\eta_p^2 = 0.07$

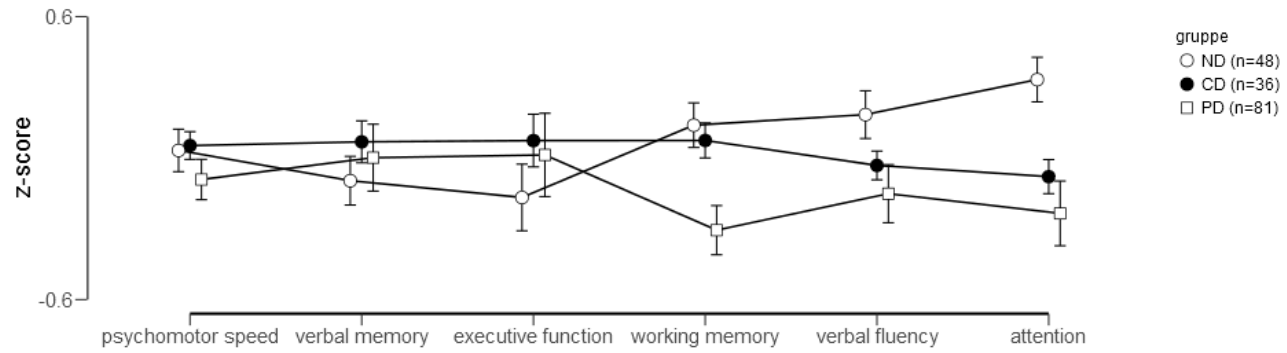

Figure 1: Neuropsychological profiles of cognitive index scores for the Never depressed (ND), Previously depressed (PD) and Currently depressed (CD) groups.

3.5. Cortisol and neuropsychological functioning

The last aim was to investigate the association between salivary cortisol and performance on neuropsychological measures. Results of six hierarchical regression analyses using mean index-scores for each of the components as dependent variables, showed no significant effects of cortisol measures (morning or evening samples) on neuropsychological performance when controlling for demographic variables (gender, age and education), medication use, depressive symptoms (BDI-II) and anxiety symptoms (BAI; See Supplementary Table 1 for coefficients for the cortisol measures). Including depression frequency (no, single or recurrent episodes) as a covariate did not alter the results of the regression analyses. Age and education were the two variables with the most significant impact on performance on the neuropsychological tests. The only clinical variable showing significant effects on neuropsychological performance was medication use, which had a significantly negative effect on Executive function (B = .88, SE_B = .29, β = .25, *p* = .002, CI = 0.30 – 1.44). The included variables could explain 32.0 % (adjusted R^2 = .27) of the Psychomotor speed component, 34.3 % (adjusted R^2 = .29) of the Verbal memory component, and 24.8 % (adjusted R^2 = .19) of the component Working memory. However, the model explained only 16.6 % (adjusted R^2 = .10) of Executive function, 14.0 % (adjusted R^2 = .07) of the Verbal fluency component and 11.4 % (adjusted R^2 = .05) of the Attention component.

4. Discussion

The main finding of the present study is that an elevation in salivary evening cortisol, but not morning cortisol, was significantly related to depressive symptoms in a sample including non-hospitalized, mildly to moderately depressed individuals. There was no significant difference between individuals with previous depression and the never depressed controls. However, the results indicated that evening cortisol levels might be higher in individuals who had experienced recurrent depressive episodes, irrespective of current symptoms, compared to those who had never experienced depression or only had a single episode. There were significantly different cognitive profiles for the currently, previously and never depressed groups. The currently depressed group showed impaired working memory compared to the group with no depression, and both the currently and previously depressed performed poorer on attentional tasks. Despite findings indicating a relation between depression and cortisol levels, and depression and cognition, there was no support for relationship between morning or evening cortisol levels and cognitive functioning.

4.2. Salivary cortisol and depression

The relation between evening cortisol level and depression was supported in the group comparisons showing significantly elevated evening cortisol in the currently depressed group compared to the never depressed controls and by a small, but significant correlation between BDI-II scores and evening cortisol. These results are in line with several other studies and meta-analyses supporting hypersecretion of cortisol in depression (Knorr et al., 2010; Stetler and Miller, 2011; Vreeburg et al., 2009). Elevations in cortisol are found to be more pronounced in patients who are hospitalized or have a depression characterized by psychotic, melancholic or endogenous symptoms (Keller et al., 2016; Stetler and Miller, 2011). In fact, some previous studies have failed to find evidence for different salivary cortisol profiles when comparing outpatients with mild to moderate depression (Krogh et al., 2012), or patients with non-psychotic depression (Keller et al., 2016) to healthy controls. In contrast, the present study indicates that cortisol levels may be significantly elevated, at least in the evening, also in patient groups with less severe depression. This is consistent with a recent study including outpatients with depression of moderate severity and remitted depressed

patients (Salvat-Pujol et al., 2017). They found a significant difference in evening cortisol between depressed patients and healthy controls, but no differences between groups on other cortisol measures.

Contrary to two previous meta-analyses (Knorr et al., 2010; Stetler and Miller, 2011), the present study found no significant differences in morning cortisol between depressed and non-depressed individuals. Several studies have also found that the cortisol awakening response (CAR); that is, the sharp rise in cortisol secretion after waking, can be greater in depression (e.g., Vreeburg et al., 2009). Measuring the CAR reflects the distinct features of morning cortisol activity in a more exact manner. Our null-finding concerning morning cortisol, therefore, should be interpreted cautiously due to the use of only one measurement point and the uncertainty of the exact timing in relation to awakening.

The present study also included a group of previously depressed individuals in a remitted state. This group had evening cortisol levels at an intermediate level compared to the currently and never depressed, but were not significantly different from the never depressed group. Thus, consistent with some previous studies (Hinkelmann et al., 2012; Reppermund et al., 2007), our results indicate that cortisol levels may tend to normalize with symptom remittance. However, when comparing groups with recurrent and single depression, irrespective of current symptoms, the results were more ambiguous. The group with recurrent depression had higher levels of evening cortisol compared to the never depressed group, although when adjusting for multiple tests, the difference was only significant on the Jonckheere-Terpstra test. This finding may lend preliminary support to the notion that elevated cortisol levels is not solely related to the depressive state, but rather may be affected by repeated exposure to depression, or may be a trait marker predisposing individuals for a more recurrent course of depression. The latter has been suggested by earlier research showing that sustained HPA-axis dysregulation is predictive of future relapses (Zobel et al., 2001). Furthermore, as our study only measured cortisol level, it cannot be ruled out that HPA-axis dysregulation measured with the CAR or the dexamethasone suppression/corticotropin-releasing-hormone (DEX/CRH) challenge test may persist despite symptom remission, as indicated by some studies (Bhagwagar et al., 2003; Vreeburg et al., 2009).

4.3. Neuropsychological functioning in current and previous depression

The search for a neuropsychological profile characteristic for major depression has proven difficult, due to the heterogeneity of the disorders. The present results indicate specific impairments in the depressed group related to working memory and attention, with significantly poorer results on attentional tasks persisting in a remitted state. This result contradicts previous findings supporting generalized impairments across multiple neuropsychological domains both in the acute phase of depression (e.g., Egeland et al., 2005; Faust et al., 2017; Reppermund et al., 2008; Rock et al., 2014; Salvat-Pujol et al., 2017) and upon remission (Hasselbalch et al., 2013; Reppermund et al., 2008). The present study included outpatients with symptoms predominately in the mild to moderate range. More severe depression (e.g. psychotic depression) has been related to more substantial cognitive impairments both in the acute and remitted state (Gomez et al., 2006; Hasselbalch et al., 2013; Keller et al., 2016; McDermott and Ebmeier, 2009). In fact, a previous study of outpatients with mild to moderate depression failed to find any differences on memory-related tasks (Krogh et al., 2012). Thus, the inclusion of a sample of milder severity in the present study, may possibly explain the absence of more widespread impairments.

The finding of significantly poorer performance in the previously depressed compared to the never depressed group on attentional tasks, but not on the working memory component may be a bit surprising at first glance. However, the working memory component included only one task (out of four) requiring participants to manipulate information, as opposed to tasks requiring maintenance of information in memory. A meta-analysis found that the effect size for the difference between depressed and healthy individuals was small for maintenance working memory and significantly larger for manipulation tasks (Snyder, 2013). Therefore, the working memory component of this study had relatively low complexity. In addition, the tasks loading on the attention component were challenging, as they relied on speed of information processing and required participants to sustain attention for approximately 10 minutes.

Consistent with the present results, it has been suggested that attentional deficits may play an important role in cognitive dysfunction in depression, as performance in all cognitive domains

depends on the ability to maintain a certain level of attention (Reppermund et al., 2008). In addition, attention has been proposed as a possible trait marker in depression (Douglas and Porter, 2009; Hasselbalch et al., 2011). Our results support that this conclusion may hold also for patient groups with less severe depression.

4.4. Cortisol and neuropsychological functioning

The role of cortisol as a possible mechanism for cognitive impairment in depression has so far been an unresolved issue. Findings have been mixed, both for studies looking at the association between cognitive performance and cortisol levels (e.g., Egeland et al., 2005; Gomez et al., 2006; Keller et al., 2016; Krogh et al., 2012; Michopoulos et al., 2008; Vythilingam et al., 2004), and HPA-axis reactivity measured with the DEX(/CRH) challenge test (Reppermund et al., 2007). In the present study hierarchical regression analyses using cognitive indexes as dependent variables, did not support a significant association between morning or evening cortisol levels and neuropsychological performance, when important covariates such as age and education were controlled for. Again, it is possible that the relationship between cortisol and cognition is stronger for patient groups with more severe types of depression, in which HPA-axis disturbances may be more pronounced than in the present sample. This would be consistent with some studies comparing psychotic and non-psychotic depressed patients (Gomez et al., 2006; Keller et al., 2016). However, in a recent study including moderately depressed patients and remitted patients, a blunted CAR was associated with poorer performance in the patient groups on some cognitive tasks, and the diurnal cortisol slope also showed relations to cognitive performance, although the direction of this association differed between remitted and non-remitted patients (Salvat-Pujol et al., 2017).

The null-finding of the present study must be interpreted with some caution due to methodological issues. Cortisol was measured at only two time-points. In addition, the neuropsychological testing was not performed at the same specific time of day for all participants, which would have been preferable considering the circadian rhythm of cortisol. Further, due to the limited sample size, it cannot be ruled out that there are small effects that the analyses were not powered to detect. Nevertheless, peripheral cortisol measures alone may not adequately tap into the

complexity of mechanisms relating the glucocorticoid system and cognition, and looking at the relation to other steroid hormones and genetic factors may provide a fuller picture.

4.5. Limitations

The present study has some limitations. The cross-sectional design of the study precludes interpretation of how cortisol levels or cognitive functioning develops during the course of the disorder, as well as the development of the disorder over time with regard to severity and chronicity. Further, cortisol was measured only once in the morning and once in the evening. More measurement points over more than one day would have increased the reliability. In addition, ambulatory salivary cortisol measurements impose challenges related to compliance with sampling instructions. In this study, the timing of measurement varied, and the relation to time of waking was uncertain. This especially challenges the reliability of the morning measure, considering the characteristics of the CAR. However, time of measurement was not significantly correlated with neither cortisol level nor neuropsychological functioning, and was therefore not controlled for in the analyses. Another limitation is that exclusion criteria did not include somatic disorders that may influence HPA-axis functioning or the use of corticosteroid treatment. Furthermore, cortisol levels may be influenced by a number of confounding factors (Hellhammer et al., 2009), including cycle phase, oral contraceptives and menopause, tobacco consumption, body mass index, intense exercise and stress. These variables were not assessed, and thus, cannot be controlled for. Another issue is the severity of past depressive episodes in the PD-group which was not thoroughly assessed. However, participants were all outpatients, and 77 % (n = 62) of the PD-group were recruited from a previous study among mildly to moderately depressed outpatient younger adults (Wang et al., 2006). Based on this and the fact that so few participants used antidepressant medications, we consider it reasonable to characterize the previously depressed sample as mildly to moderately previously depressed. Although the proportion of currently or previously depressed participants using psychotropic medications was small, medication use did affect neurpsychological performance. Lack of information about medication type and doses limited further explortation of this relationship. Further, the present study did not control for childhood traumas, which may be related to cortisol hypersecretion irrespective of depressive symptoms (Lu et

al., 2016). Furthermore, PTSD can be related to reduced cortisol concentrations (Wingenfeld and Wolf, 2011). The uncertain interrater reliability of comorbid diagnoses is a limitation. However, it provides an estimate, indicating that comorbidity in the present study was limited and mainly included social and generalized anxiety disorders, and not PTSD. In addition, anxiety symptoms (BAI) did not mediate the association between BDI-II and cortisol. Thus, it is unlikely that comorbidity had a large effect on the results. Finally, the analysis of patterns of missingness indicated that participants lacking cortisol measures had more severe depression symptoms compared to those completing the cortisol measurements. Due to these non-random missing data, the results should be interpreted with caution. In addition, the study was not powered to detect small effects, and missing cortisol data reduced the sample size, and thus the achieved power for group-comparisons for cortisol was less than adequate. This increases the probability of a type-II error. However, the effect sizes gives an indication of the size of the effects and indicates that non-significant effects were generally small ($r < 0.2$).

4.6. Conclusion

The present study indicates that also patient groups with depression of mild to moderate severity may have significantly elevated evening cortisol levels. In addition, their cognitive profile is significantly different from that of never depressed individuals, but only with specific mild impairments on working memory and attentional tasks. Impairments in attention were also evident in a group of previously depressed individuals, indicating that this could be a trait-marker in depression. Despite the relation between depression and cortisol and depression and specific cognitive impairments, the present study did not find a significant association between morning or evening cortisol levels and cognitive performance.

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