Journal of Psychiatric Research 111 (2019) 44–50

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

The cortisol awakening response at admission to hospital predicts depression severity after discharge in MDD patients

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ARTICLE INFO

Keywords:
Cortisol awakening response
Depression
HPA axis
Biomarker
Follow-up

ABSTRACT

Major Depressive Disorder (MDD) is associated with hypothalamic-pituitary-adrenal (HPA) axis dysregulation and altered cortisol awakening response (CAR), a non-invasive biomarker for HPA axis reactivity. We theorized that the CAR resembles the accumulated effects of depression over time, and may therefore predict depressive symptom severity once patients return home following inpatient treatment. Two studies are reported. In Study 1 (n = 101; 57% female), the CAR was measured at intake and self-ratings of depression severity was assessed six weeks following discharge. Study 2 (n = 127; 58% female) was a replication and extension of Study 1 where a follow-up assessment of self-rated depression severity was added at six months following discharge. In Study 1 the CAR at intake showed a tendency towards a negative association with self-reported depression six weeks after discharge. Study 2 extended this finding within a more severely depressed, larger sample, where a blunted CAR predicted self-reported depressive severity six weeks and six month following discharge. These findings suggest that a blunted CAR can predict mood deterioration post treatment in inpatients diagnosed with severe MDD.

1. Introduction

Biological markers that can help in diagnosis and predict post treatment symptom deterioration in Major Depression Disorder (MDD) are still scarce. This may be due to the large heterogeneity of physical symptoms associated with depression and the insufficient measurement validity of many biomarkers (Mayeux, 2004). Whether treatment is to become more effective in the future will depend on gaining a deeper understanding of the etiology and pathophysiology of depression (Saveanu and Nemeroff, 2012). Alterations in the hypothalamic-pituitary-adrenal (HPA) axis is a frequently reported and replicated finding in a large proportion of patients with MDD (Varghese and Brown, 2001). Typically, MDD patients demonstrate hypersecretion of cortisol partly due to an impaired endogenous glucocorticoid feedback regulation of HPA axis activity (Pariante and Lightman, 2008; Sachar et al., 1970; Saveanu and Nemeroff, 2012; Stetler and Miller, 2011). Moreover, evidence suggests that HPA axis hyperactivity may not be a consequence of depression, but may rather be a predisposing factor for developing depression as a result of adverse early life experiences, sensitizing the individual to stress by causing enduring alterations in HPA axis functioning from early on (Pariante and Lightman, 2008).

The CAR refers to the sharp rise in cortisol secretion in response to awakening that peaks after approximately 30–45 min (Fries et al., 2009; Pruessner et al., 1997). This distinct rise in cortisol in response to awakening has been related to one's anticipations for the upcoming day and the corresponding “mobilizing” of energy resources to meet these demands (Fries et al., 2009). This hypothesis is supported by observations of the CAR being higher during weekdays than during weekends, because demands are usually higher during weekdays (Schlotz et al., 2004), and elevated when experiencing higher levels of social stress, worry, and lack of social recognition (Wüst et al., 2000a). The CAR reflects one aspect of HPA axis reactivity that is sensitive to certain

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https://doi.org/10.1016/j.jpsychires.2019.01.002
Received 26 July 2018; Received in revised form 22 December 2018; Accepted 2 January 2019

psychosocial and health factors such as job stress, life stress and fatigue (Chida and Steptoe, 2009; Schmidt-Reinwald et al., 1999; Wüst et al., 2000a).

In spite of the large body of literature relating hypercortisolism to MDD, studies have also reported a blunted CAR in MDD (Dedovic and Ngiam, 2015), suggesting that hypocortisolism may occur in cases of MDD. In the recent years it has been suggested that the CAR is related to depression severity, in which moderate degrees of depression have been associated with heightened CAR, and severe depression with blunted CAR (Chida and Steptoe, 2009; Wardenaar et al., 2011). Several mechanisms for the development of hypocortisolism from hypercortisolism have been outlined (see Fries et al., 2005; Heim et al., 2000). HPA axis downregulation is known to follow persisting chronic stress (Heim et al., 2000), and is related to burnout (Oosterholt et al., 2015), which is a state considered to conceptually overlap with depression (Bianchi et al., 2015).

The symptom deterioration that is typically observed between treatment offset and follow-up assessments may be influenced by the continuation of pretreatment stressors (Monroe et al., 2009). Such pretreatment stressors may be driven by interactions between the individual and the environment. For instance, depressed individuals may elicit social rejection through maladaptive social behavior (Van Orden and Joiner, 2013; see also De Rubeis et al., 2017), and it seems plausible that these effects persist even after discharge in remitted MDD patients. Moreover, a higher number of depressive episodes, more residual symptomatology, and daily hassles were related to symptom deterioration after treatment over a 2-year period (Bockting et al., 2006). A follow-up of this study, extending to 5.5 years, identified two maladaptive coping strategies as additional predictors of symptom deterioration: avoidant problem solving and lower ability to distract oneself from negative thoughts (Bockting et al., 2009). Environmental characteristics may include factors related to socio-economic conditions (Monroe et al., 2009).

We argue that — as an index of physiological stress and HPA reactivity — the CAR reflects the body's cumulated response to enduring environmental stressors and is thus an index of an individual's overall level of psychosocial stress prior to hospitalization. Moreover, recent research suggests that the CAR is a predictor for treatment outcomes in MDD (Jones et al., 2015).

This article presents two studies examining the value of the CAR assessed during the first days of hospitalization prior to psychotherapeutic intervention in predicting long-term treatment outcome in patients with MDD. Whereas the first study was exploratory in nature, the second study aimed at replicating and supporting the findings of Study 1. In Study 1, the association between the CAR at time of intake and depressive symptoms six weeks after discharge was examined in a sample of 101 inpatients. Study 2 was an extension of Study 1, involving a larger sample of MDD inpatients ($n = 127$) with an extended follow-up period of six months after discharge. Based on the results of Study 1 and previous research suggesting that a blunted CAR is associated with higher depressive symptom severity, lower treatment response, less favorable prognosis, and chronic stress, (Chida and Steptoe, 2009; Jones et al., 2015; Vreeburg et al., 2013; Wardenaar et al., 2011), we hypothesized in Study 2 that a lower CAR at intake to hospitalized treatment for MDD would predict a higher depressive symptom deterioration six weeks and six months following discharge. To our knowledge these are the first studies investigating the CAR as a biomarker for predicting long-term post treatment depressive symptom deterioration in an inpatient setting.

Both studies were approved by the Ethics committee of the “Medical Association Westfalen-Lippe” and written informed consent was obtained from all participants prior to data collection.

Table 1
Summary of descriptive statistics and cortisol levels in Study 1.

		N	*M*	*SD*	Min	Max
Survey and demographics	Age	101	40.3	13.7	15.9	68.7
	BDI Intake	94	23.8	10.7	0	52.0
	BDI Discharge	78	11.6	8.3	0	40.0
	BDI 6WF	65	13.7	10.6	0	45.2
	Valid N (listwise)	55				
Psychotropic medication use	Total	36 (35.6%)				
	SSRI	13				
	SNRI	12				
	Tricyclics	2				
	MAO inhibitors	8				
	Antipsychotics	6				
	Anticonvulsants	8				
	Other	4				
Cortisol	Cortisol awakening	87	15.7	8.6	1.6	40.4
	Cortisol +30	86	23.2	11.1	2.9	55.0
	CAR	85	7.5	9.5	−21.3	30.9
	Valid N (listwise)	85				

Note. The percentage of total psychotropic medication use refers to the percentage of the total sample. The total number of each psychotropic drug does not add up to the total number of patients taking psychotropic medication because 14 patients were taking more than one drug. Cortisol values in nmol/L. Abbreviations: M = Mean, SD = Standard deviation, Min = Minimum, Max = Maximum, WF = Week Follow-up, SSRI = Selective serotonin reuptake inhibitors, SNRI = Serotonin-norepinephrine reuptake inhibitors, MAO = Monoamine oxidase, CAR = Cortisol awakening response.

2. Study 1

2.1. Method

2.1.1. Participants

One hundred and one inpatients (57% females) admitted for psychotherapy treatment in a German psychosomatic hospital were recruited between 2011 and 2014. Inclusion criteria was MDD as a main diagnosis. Exclusion criteria were glucocorticoid medication use, comorbid addiction disorder, excessive substance abuse, psychosis, autoimmune-thyroiditis, personality disorders due to medical conditions, respiratory disease, hormone or heart conditions. The participants' diagnoses were determined through a structured clinical interview (SCID I, II; Fydrich et al., 1997; Wittchen et al., 1997a; Wittchen et al., 1997b). At intake, 36 patients (35.6%) were on at least one psychotropic drug (Table 1).

2.1.2. Materials and procedures

2.1.2.1. Beck Depression Inventory-I. The Beck Depression Inventory (BDI) is a 21-item self-report questionnaire assessing the severity of depressive symptoms. Items consist of four response statements that are scored from 0 to 3 representing ascending severity of depressive symptoms (Beck and Steer, 1993; German version: Hautzinger et al., 1995). A score of 0–9 indicates minimal depression, 10–18 indicates mild depression, 19–29 indicates moderate depression, and 30–63 indicates severe depression. Scores were assessed within the first five days after admission (BDI Intake), and during the last five days before discharge (BDI Discharge). The treatment consisted of cognitive behavioral therapy (CBT) with daily individual sessions, and additional group therapies and pharmacotherapy. The BDI follow-up assessment was completed via an online questionnaire with patients being personally contacted by a member of the research/clinical team by email six weeks (BDI 6WF) after discharge. After completing the

Table 2
Correlations between CAR and depressive pathology in Study 1.

Measure		1. CAR	2. BDI Intake	3. BDI Discharge	4. BDI 6WF
1. CAR	Pearson Correlation	–	-.097 (−.310–.125)	-.163 (−.389–.082)	-.255 (−.487–.011)
	Sig. (2-tailed)		.391	.191	.060
	N		80	66	55
2. BDI Intake	Pearson Correlation	-.097 (−.310–.125)	–	**.528** (.343–.674)**	**.520** (.311–.681)**
	Sig. (2-tailed)	.391		.000	.000
	N	80		75	62
3. BDI Discharge	Pearson Correlation	-.163 (−.389–.082)	**.528** (.343–.674)**	–	**.666** (.493–.788)**
	Sig. (2-tailed)	.191	.000		.000
	N	66	75		58
4. BDI 6WF	Pearson Correlation	-.255 (−.487–.011)	**.520** (.311–.681)**	**.666** (.493–.788)**	–
	Sig. (2-tailed)	.060	.000	.000	
	N	55	62	58	

Note. *$p < .05$, **$p < .001$. Two-tailed 95% confidence intervals in parentheses.

online follow-up assessment the participants were also invited back to the clinic to assess their wellbeing and to discuss the results with a clinician. The internal consistency (Cronbach's alpha) of the BDI at all timepoints was good to very good: BDI Intake $\alpha = 0.88$ ($N = 94$); BDI Discharge $\alpha = 0.87$ ($N = 75$); BDI 6WF $\alpha = 0.93$ ($N = 62$) and comparable to a previous validation of the German BDI version (Kühner et al., 2007).

2.1.2.2. Assessment of CAR. Cortisol secretion was assessed during the first five days of admission through saliva sampling using cotton salivettes (manufacturer: Sarstedt AG & Co., Nümbrecht/Germany) at two time points: Directly after awakening in the morning, and 30 min after awakening. The samples were sent to a medical laboratory for Enzyme Immunoassay after collection. The CAR was calculated by subtracting the cortisol measurement 30 min after awakening from the cortisol measurement directly after awakening, such that higher values would indicate a higher CAR.[1] Salivettes were handed out by the therapists the day before the measurements along with instructions about using the first salivette directly after awakening and the second salivette 30 min after awakening. Participants were advised to refrain from brushing their teeth, sucking on drops, exercise, caffeine consumption and smoking between awakening and the second cortisol assessment at 30 min after awakening.

2.1.3. Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics version 24. Prior to analysis, all variables were checked for accuracy of data entry and missing values. The differences in sample size within the tables reflect missing values. Little's MCAR (missing completely at random) Test showed a statistically non-significant result ($\chi^2 = 28.36$, $df = 27$, $p = .393$) indicating that values missing completely at random could be inferred (Tabachnick and Fidell, 2013). All variables were checked for univariate outliers by identifying cases with z-values above 3.29 or below −3.29, and dealt with by deletion. One individual's measurement at awakening and one individual's measurement 30 min after awakening were identified as outliers and deleted. All variables were normally distributed.

The associations between CAR and BDI measurements (intake, discharge and 6WF) were assessed using Pearson's correlations. One patient had bipolar depression (F31.4), and therefore a second correlation analysis was performed excluding this patient to explore how this would affect the results. The results from this second correlation analysis are reported separately.

[1] Following a request from one of the reviewers, the analysis was repeated using the Area Under the Curve ground (AUGg) method, in line with (Pruessner et al. (2003), but the overall pattern of results remained unchanged. For this reason and for ease of exposition, these results are not reported.

2.2. Results

Descriptive statistics are presented in Table 1. No significant associations were found between the CAR at intake and BDI Intake, BDI Discharge, and BDI 6WF (Table 2). However, the strength of the associations increased at each time point, and a tendency towards a negative linear association emerged between CAR and BDI 6WF. Age was negatively associated with BDI Discharge. Consistent with the literature, neither age ($r = -0.028$, $p = .801$, two-tailed) nor sex ($r = -0.037$, $p = .741$, two-tailed) were associated with the CAR (see Fries et al., 2009). The results from the separate correlation analysis with the exclusion of one patient with bipolar depression yielded similar non-significant associations between CAR and the BDI assessments: CAR*BDI Intake: $r = -0.096$, $p = .400$, two-tailed; CAR*BDI Discharge: $r = -0.157$, $p = .212$, two-tailed; and CAR*BDI 6WF: $r = -0.249$, $p = .069$, two-tailed.

2.3. Discussion

The tendency towards a negative association between CAR and BDI 6WF did not support the CAR as a predictor of follow-up symptom deterioration, but indicated the need for further research on this topic. A blunted CAR is suggested to be associated with high depression severity (Dedovic and Ngiam, 2015), and the low proportion of severely depressed MDD patients in the present sample might account for the relatively weak association between CAR and depression (Dedovich and Ngiam, 2015; Wardenaar et al., 2011). Furthermore, it is unclear at which time after discharge from inpatient treatment the cumulative effect of exposure to internal and external risk factors maximizes. We therefore replicated the previous study with a larger sample of depressed inpatients, and utilized a longer follow-up period of six months after discharge. We were also able to retrieve data on body mass index (BMI) from the sample in Study 2 which was not possible in Study 1.

3. Study 2

Study 2 is a replication and extension of Study 1 where we increased the number of participants, added an additional follow-up measure of BDI at six months after discharge (BDI 6MF), updated the diagnostic tool from BDI-I to BDI-II, collected data on BMI, and retrieved inter- and inter assay coefficients for the cortisol analyses which were not available for Study 1. Improvements and differences from BDI to BDI-II are outlined below. The same procedures for measuring CAR and BDI at different timepoints were used as described in Study 1. Based on the findings of Study 1, we hypothesized that the CAR at intake would be negatively associated with follow-up depressive symptoms and predict symptom deterioration six weeks and six months following discharge.

Table 3
Summary of descriptive statistics and mean cortisol levels in Study 2.

		N	*M*	*SD*	Min	Max
Survey and demographics	Age	123	42.9	13.7	17.0	68.0
	BDI Intake	122	28.9	11.9	1.0	52.0
	BDI Discharge	118	13.3	10.7	0.0	47.0
	BDI 6WF	89	15.1	12.0	0.0	49.0
	BDI 6MF	88	15.9	12.6	0.0	53.0
	Valid N (listwise)	66				
Psychotropic medication use	Total	71 (57.7%)				
	SSRI	30				
	SNRI	23				
	Tricyclics	13				
	MAO inhibitors	9				
	Antipsychotics	7				
	Anticonvulsants	17				
	Other	9				
Cortisol	Cortisol awakening	114	26.2	14.3	2.9	81.1
	Cortisol +30	114	40.9	19.2	3.2	88.1
	CAR	112	14.4	16.6	−19.7	61.4
	Valid N (listwise)	112				

Note. The percentage of total psychotropic medication use refers to the percentage of the total sample. The total number of each psychotropic drug does not add up to the total number of patients taking psychotropic medication because 25 patients were taking more than one drug. Cortisol values in nmol/L. Abbreviations: M = Mean, SD = Standard deviation, Min = Minimum, Max = Maximum, WF = Week Follow-up, MF = Month Follow-up, SSRI = Selective serotonin reuptake inhibitors, SNRI = Serotonin-norepinephrine reuptake inhibitors, MAO = Monoamine oxidase, CAR = Cortisol awakening response.

3.1. Method

3.1.1. Participants

One hundred and twenty-seven patients (57.7% females) admitted to the same inpatient psychotherapeutic treatment as in Study 1 were recruited between 2014 and 2015. Study 2 had the same inclusion and exclusion criteria and assessed the patients' clinical diagnoses as in Study 1. None of the participants had a bipolar disorder diagnosis. At intake, 71 (57.7%) patients were on at least one psychotropic drug (Table 3).

3.1.2. Materials and procedures

3.1.2.1. Beck Depression Inventory-II. The Beck Depression Inventory-II (BDI-II) measures the intensity of depressive symptoms and attitudes in accordance with the DSM-IV criteria (Beck et al., 1996a; German version: Kühner et al., 2007). Several changes were made in the BDI-II to increase its psychometric properties, such as eliminating four items (e.g. items involving changes in body image), adding four diagnostic specific items (e.g. items involving concentration difficulties, agitation, loss of energy and worthlessness), and reformulating items involving eating and sleeping problems (Beck et al., 1996a). Participants were asked to rate the past two weeks instead of the past week as in BDI-I (Beck et al., 1996b). The cutoff scores differ in BDI-I and BDI-II. In BDI-II, scores between 0 and 13 indicate minimal depression, 14–19 indicate mild depression, 20–28 indicate moderate depression, and 29–63 indicate severe depression. In our sample, the scale had very good internal consistency at all timepoints: BDI-II Intake $\alpha = 0.92$ ($N = 127$); BDI-II Discharge $\alpha = 0.93$ ($N = 120$); BDI-II 6WF $\alpha = 0.94$ ($N = 96$); BDI-II 6 MF $\alpha = 0.95$ ($N = 83$).

As in Study 1, the follow-up assessments were completed via an online questionnaire with patients being personally contacted by a member of the research/clinical team by email six weeks (BDI 6WF) and six months (BDI 6MF) after discharge. After completing the online follow-up assessments, the participants were invited back to the clinic to discuss their results with a clinician.

3.1.2.2. Assessment of CAR. The same materials, measurements, and procedures as described in Study 1 were used to assess the CAR. Intra- and inter assay coefficients were 3.05% and 4.15%, respectively.

3.1.3. Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics version 24. The same procedures as in Study 1 were followed prior to analysis, in addition to checking the assumptions for multiple regression analysis. The differences in sample size within the tables reflect missing values. Little's MCAR (missing completely at random) Test showed a statistically non-significant result ($\chi^2 = 80.54$, $df = 78$, $p = .400$) indicating that values missing completely at random could be inferred (Tabachnick and Fidell, 2013). Four individuals' cortisol measurement after awakening, one individual's cortisol measurement 30 min after awakening and one CAR difference value were identified as univariate outliers and deleted. All variables were normally distributed.

The associations between CAR and the BDI-II measurements (BDI-II Intake, BDI-II Discharge, BDI-II 6WF, and BDI-II 6MF) were assessed using Pearson's correlations. In addition, four hierarchical multiple regression analyses were conducted to examine whether CAR predicted follow-up depression at six weeks and six months after discharge, controlled for initial depression (either at intake or at discharge). BMI was entered in step 1 in all hierarchical regression analyses.

3.2. Results

Descriptive statistics for age, BDI-II measurements and cortisol measurements are presented in Table 3. CAR was negatively associated with both BDI-II follow-ups (Table 4). As in Study 1, age ($r = -0.051$, $p = .595$, two-tailed) and sex ($r = -0.039$, $p = .686$, two-tailed) were not associated with CAR. BMI was correlated with age ($r = 0.318$, $p < .001$, two tailed), sex ($r = 0.279$, $p = .002$), BDI 6WF ($r = 0.268$, $p = .011$, two-tailed), and BDI 6MF ($r = 0.269$, $p = .012$, two-tailed), but not with the CAR ($r = -0.093$, $p = .332$, two-tailed).

Two hierarchical multiple regression analyses were conducted to predict BDI-II 6WF (Table 5), one controlling for BDI-II Intake (left column) and one controlling for BDI-II Discharge (right column). BDI-II Intake was entered in step 1 and the CAR at step 2, which added a significant amount of explained variance to the prediction of BDI-II 6WF. The final model as a whole was statistically significant: F (3, 77) = 9.10, $p < .001$. When BDI-II Discharge was entered in step 1, the CAR predicted less variance in BDI-II 6WF, but remained statistically significant. The final model was statistically significant: F (3, 77) = 56.78, $p < .001$.

Table 4
Correlations between CAR and depressive pathology in Study 2.

Measure		1. CAR	2. BDI-II Intake	3. BDI-II Discharge	4. BDI-II 6WF	5. BDI-II 6MF
1. CAR	Pearson Correlation	–	.012 (−.174–.197)	-.090 (−.277–.104)	**-.259*** **(−.451 - -.044)–**	**-.223*** **(−.423 - -.002)**
	Sig. (2-tailed)		.897	.366	.020	.048
	N		111	104	81	79
2. BDI-II Intake	Pearson Correlation	.012 (−.174–.197)	–	**.530**** **(.384–.650)**	**.396**** **(.204–.559)**	**.472**** **(.288–.622)**
	Sig. (2-tailed)	.897		.000	.000	.000
	N	111		114	88	85
3. BDI-II Discharge	Pearson Correlation	-.090 (−.277–.104)	**.530**** **(.384–.650)**	–	**.797**** **(.703–.863)**	**.760**** **(.652–.837)**
	Sig. (2-tailed)	.366	.000		.000	.000
	N	104	114		84	84
4. BDI-II 6WF	Pearson Correlation	**-.259*** **(-.451—.044)**	**.396**** **(.204–.559)**	**.797**** **(.703–.863)**	–	**.842**** **(.758–.898)**
	Sig. (2-tailed)	.020	.000	.000		.000
	N	81	88	84		71
5. BDI-II 6MF	Pearson Correlation	**-.223*** **(-.423—.002)**	**.472**** **(.288–.622)**	**.760**** **(.652–.837)**	**.842**** **(.758–.898)**	–
	Sig. (2-tailed)	.048	.000	.000	.000	
	N	79	85	84	71	

Note. *$p < .05$, **$p < .001$. Two-tailed 95% confidence intervals in parentheses.

Table 5
Summary of hierarchical multiple regression analyses predicting BDI 6WF.

Controlling for BDI Intake			Controlling for BDI Discharge		
Predictor	ΔR^2	Standardized β	Predictor	ΔR^2	Standardized β
Step 1	**.202****		Step 1	**.657****	
BMI		**.214***	BMI		**.148***
BDI Intake		**.365***	BDI Discharge		**.774****
Step 2	**.060***		Step 2	**.031***	
BMI		.190	BMI		**.134***
BDI Intake		**.371****	BDI Discharge		**.761****
CAR		**-.246***	CAR		**-.178***
Total R^2	**.262****		Total R^2	**.689****	
Total Adjusted R^2	**.233****		Total Adjusted R^2	**.677****	
N	80		*N*	80	

Note. * $p < .05$, ** $p < .001$.

In a similar vein, two hierarchical multiple regression analyses were conducted to predict BDI-II 6MF (Table 6). In the first hierarchical multiple regression model for BDI-II 6MF, BDI-II Intake was entered in step 1 and CAR was entered in step 2. Adding the CAR as an additional predictor to the model in step 2 significantly increased the model's explanatory power. The final model as a whole was statistically significant: $F\,(3, 75) = 11.14$, $p < .001$, where both BDI-II Intake and the CAR were statistically significant individual predictors of BDI-II 6MF. In the second hierarchical model BDI-II Discharge was entered in step 1 and the CAR at step 2 leading to further explained variance. The final model as a whole was statistically significant: $F\,(3, 75) = 41.17$, $p < .001$, and both variables made unique contributions to the prediction of BDI 6MF.[2]

3.3. Discussion

The results supported our hypothesis that a lower CAR would predict a higher depressive symptom deterioration following discharge from hospitalized treatment in patients with MDD. We found that BDI-II scores at discharge explained more than half of the variance in both BDI-II 6WF and BDI-II 6MF. Adding the CAR into the model explained additional variance beyond the self-reported data, illustrating its predictive value in both follow-up measurements after discharge. Beta weights indicate that the additional explanatory power of the CAR remained very similar over the 6 week- and 6 month-period.

It should be noted that the unique explained variance in follow-up depression by the CAR after controlling for BMI and BDI either at intake or discharge was small. However, considering the strong associations between the repeated BDI assessments, it is especially noteworthy that pretreatment CAR contributes with additional explained variance in posttreatment follow-up depression, regardless of the magnitude. Moreover, the association between the CAR and depression (Dedovic and Ngiam, 2015) implies that there will be a substantial overlap between the predictive values of pretreatment CAR and depressive symptoms assessed with the BDI.

4. General discussion

The search for biomarkers to enhance diagnosis, treatment and prognosis of mental disorders has received increasing attention in recent years, but the findings are somewhat equivocal (Strawbridge et al., 2017). In this paper two studies were conducted to examine the value of the CAR in predicting follow-up depressive symptoms in hospitalized patients with MDD. In Study 1, the CAR was measured at intake before treatment initiation, with self-reported depressive symptoms (BDI-I) assessed at intake, discharge and six weeks after discharge. Study 2 was a replication and extension of Study 1 adding a follow-up assessment of depression severity at six months after discharge with a larger sample and the revised version of BDI (BDI-II).

[2] As requested by one of the reviewers, the associations between the CAR and anxiety at different time points were also explored. This was done by re-running the analyses in Study 1 and 2 by replacing the BDI-assessments with the anxiety subscale of the Symptom Checklist-90 (SCL-90). The CAR was only associated with SCL-90 Anxiety at the six month follow-up in Study 2: r = -0.284, 95% *CI*s: 0.475—0.068, p = .011. Two hierarchical multiple regressions were conducted predicting SCL-90 Anxiety at six month follow-up with BMI and either SCL-90 Anxiety at intake or discharge in Step 1 and CAR in Step 2. In both hierarchical regression models, the CAR was not a significant predictor of six month follow-up SCL-90 Anxiety.

Table 6
Summary of hierarchical multiple regression analyses predicting BDI 6MF.

Controlling for BDI Intake			Controlling for BDI Discharge		
Predictor	ΔR^2	Standardized β	Predictor	ΔR^2	Standardized β
Step 1	**.264****		Step 1	**.602****	
BMI		**.204***	BMI		**.156***
BDI Intake		**.442****	BDI Discharge		**.736****
Step 2	**.044***		Step 2	**.021***	
BMI		.183	BMI		**.144***
BDI Intake		**.448****	BDI Discharge		**.725****
CAR		**-.212***	CAR		**-.145***
Total R^2	**.308****		Total R^2	**.622****	
Total Adjusted R^2	**.280****		Total Adjusted R^2	**.607****	
N	78		*N*	78	

Note. * $p < .05$, ** $p < .001$.

In Study 1, the CAR had a tendency towards being negatively associated with depression severity at the six week follow-up. In Study 2, the CAR predicted depression severity at six weeks and six months adjusting for depression (BDI-II ratings) at intake or at discharge. The observed negative associations between the CAR and the BDI in both studies indicate that a blunted CAR is associated with greater severity of follow-up self-reported depressive symptoms. To our knowledge, this is the first study to investigate the value of the CAR in predicting post-treatment symptom deterioration in depressed inpatients. Nonetheless, our results are in line with previous work that has found the CAR to predict treatment outcome in inpatients with MDD, where a higher CAR at admission was associated with a greater treatment response (Jones et al., 2015). Despite the different follow-up periods, with depressive symptoms being assessed at six weeks and six months after discharge in our study, rather than directly at discharge as in the study by Jones et al. (2015), both studies indicate that lower CAR is associated with less favorable outcomes in inpatients with MDD. Interestingly, in our study, the CAR was not associated with depressive symptoms at discharge. However, based on the premise that CAR reflects the accumulated effects of stress over time prior to hospitalization, it is not surprising to find that the association between CAR and depressive symptoms does not become evident until the patients have spent time in their home environments, where it is likely that pretreatment stressors still are present. Similarly, in a study with healthy controls and individuals with depression and/or anxiety disorders, a blunted CAR was associated with a less favorable prognosis over a two year period (Vreeburg et al., 2013). Taken together, these and our findings illustrate that a blunted CAR is associated with a less favorable prognosis in MDD.

Two reasons might explain the nonsignificant association between CAR and follow-up depression in Study 1. First, the relatively smaller sample size in Study 1 compared to Study 2 may have resulted in a lack of power preventing the association to reach statistical significance. Second, compared to the sample in Study 2, the severity of depression at intake in Study 1 was lower. When applying the BDI cut-off criteria for severe depression, Study 1 consisted of 25.8% severely depressed patients, compared to 45.7% in Study 2. Due to the various differences between the BDI-I and the later published BDI-II, a statistical comparison of both samples would be questionable. It could be speculated however, that the weaker and nonsignificant negative association between the CAR and the BDI 6WF in Study 1, was related to the lower proportion of severely depressed patients and thus a less accentuated profile of blunted CAR in Study 1.

4.1. Limitations

Findings of the present study should be interpreted in light of some limitations. A blunted CAR was observed in teachers high in work-related rumination (Cropley et al., 2015). The authors explained their findings in terms of the high ruminators having sleep disturbances, leading to the cortisol secretion occurring before the actual awakening (Cropley et al., 2015; see also Chida and Steptoe, 2009). Sleep disturbance is a symptom of MDD (American Psychiatric Association, 2013) and poor sleep quality may affect the CAR and therefore have influenced our results. As all patients were woken at the same time each morning, we did not assess actual sleep time or quality of sleep. Although the subjects received instructions for conducting the saliva samplings, compliance was not assessed. The CAR has shown to peak between 30 and 45 min after awakening, and by sampling only at awakening and 30 min after awakening, we cannot be sure to have captured the true CAR peak. However, at least 50% mean cortisol increase occurs within the first 30 min after awakening (Pruessner et al., 1997; Wüst et al., 2000b) which indicates that a substantial proportion of the CAR magnitude was captured in the present studies. Even though the CAR is considered a reliable measure of HPA-axis functioning (Schmidt-Reinwald et al., 1999), we also know that it is influenced by short term changes in relation to anticipations for the upcoming day (see Schlotz et al., 2004), and ideally, future research should assess the CAR on two consecutive days to reduce variance attributable to situational effects (Hucklebridge et al., 2005; Wüst et al., 2000b). Finally, as this study was based on a relatively heterogeneous naturalistic sample of depressed inpatients it was not possible to systematically examine comorbid mental disorders or subtypes of depressive disorders. However, the tradeoff from less control over such factors also entails the benefit of greater ecological validity with the naturalistic properties of our two studies.

4.2. Future directions

Further studies on the CAR as a predictor of future depressive symptoms should include measurements of the CAR in the follow-up periods or during treatment to examine how the CAR changes over time in relation to depressive symptoms, and how depression severity at intake influences this relationship over time. Such studies would benefit from incorporating diary reports to control for psychosocial predictors of symptom changes after discharge and thus have better control over the environments the patients return to after discharge. A main focus for future studies should lie in mapping the most important factors contributing to alterations in the CAR so that its relation to MDD can be fully understood. This may include comparing the CAR and depression severity between the broader diagnostic subtypes of depression (e.g. melancholic and atypical depression) and between degrees of illness chronicity. Indeed, different subtypes of depression have been associated with differences in HPA axis dysregulation, where melancholic, endogenous and psychotic subtypes have been associated with higher cortisol secretion while atypical depression has been associated with lower cortisol secretion (Stetler and Miller, 2011).

5. Conclusion

To our knowledge this is the first study investigating the CAR as a biomarker for predicting post treatment depressive symptom deterioration in an inpatient setting. The CAR assessed at intake before treatment initiation predicted depressive symptoms six weeks and six months after discharge. In addition to being an index of depression severity, an abnormal CAR may also be a reflection of more adverse psychosocial factors prior to hospitalization that may increase the probability for symptom deterioration after discharge. The possibility of identifying at intake which patients will suffer from greater symptom deterioration in the follow-up period could contribute to lowering the high relapse and recurrent rates seen in MDD.

Conflicts of interest

No further conflicts of interest are to be reported.

Funding

We emphasize that our research complies with all APA's ethical standards. This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors. We confirm that our manuscript has not been published elsewhere and is not currently under consideration by any other journal. All authors listed have agreed to Psychiatric Research's terms and conditions and agree with submission of the manuscript in this form.

Disclosure

The authors Sabrina Denninghaus and Markus Pawelzik are employed at the Eos-Klinik Münster, the psychosomatic hospital were the data were collected.

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