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Review

HPA system in anxiety disorder patients treated with cognitive behavioural therapy: A review

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ABSTRACT

Anxiety disorders (AD) have a complex etiology involving genetic, psychophysiological and environmental factors. Recent biomarker research in AD shows alterations in anatomical, biochemical and physiological pathways as well as in endocrinological processes. Perceived stress is one of the factors often reported in relation to the onset and the course of AD. Hence, the function of the hypothalamus-pituitary-adrenal (HPA) axis, the endogenous system regulating the stress response homeostasis, may serve as biomarker in disease etiology and response to treatment. Vice versa, successful treatment could have an advantageous effect on the function of the HPA system. In the present review, we summarize findings on the HPA system in relation to AD and first results on its modifiability in response to cognitive behavioral therapy (CBT), one of the most efficacious psychotherapeutic treatments for AD. We specifically focus on findings of experimental studies that explored cortisol levels before, during and after exposure-based CBT. A systematic search was conducted in MEDLINE/PubMed, PsycINFO, Web of Science, and in references of retrieved studies until April 2024. The inclusion criteria were studies enclosing keywords related to the HPA axis, an anxiety disorder and CBT techniques. The results of the summarized studies suggest that cortisol levels have the potential to indicate the AD disease status and serve as possible biomarker in outcome prediction. Global dysfunction of the HPA system seems to point to higher symptom burden and less advantageous response to CBT. Furthermore, low cortisol levels elicited in relation to exposure interventions are repeatedly associated with risk for non-response. Additionally, some evidence suggests that successful CBT containing exposure sessions as well as cognitive techniques induces normalization of the HPA system by reducing acute response to fear related stimuli in parallel to normalizing basal cortisol levels. To conclude, cortisol seems to be a promising candidate to depict several aspects of AD-related disease status and CBT effects, however, additional prospective studies are needed to evaluate the mode of applications of this marker in the clinical routine.

1. Introduction

1.1. Anxiety disorders and CBT

Anxiety disorders (AD) such as Panic Disorder (PD) with/without Agoraphobia (AG), Social Anxiety Disorder (SAD), Generalized Anxiety Disorder (GAD) and Specific Phobias are pathological forms of fear and anxiety that are characterized by excessive emotional and physiological responses in the absence of real danger. Cognitive behavioral therapy (CBT) is one of the most efficacious psychotherapeutic treatments (Bandelow et al., 2022; Cuijpers et al., 2016; Hans & Hiller, 2013; Hofmann & Smits, 2008), which includes strategies for modifying dysfunctional cognitions and exposure therapy (ET; Carpenter et al., 2018). However, about a third of the patients do not respond to CBT treatment for unknown reasons (Springer et al., 2018). Since "cause should inform cure" (Uher, 2008), it is important to identify biomarkers that extend the knowledge about the pathology and assesses the severity of the disorder (For a review see Bandelow et al., 2016; Bandelow et al., 2017), as well as to explain and predict differential treatment response as intended in personalized medicine. The assumption that

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psychotherapy is able to target the underlying (biological) cause, not just changing the subjective psychological features (cognitions, emotions) or coping abilities is widely unexplored and needs confirmation. Endogenous stress hormones, e.g. cortisol, that partly mediate the fear reaction and have been found to be elevated during acute fear (Joëls & Baram, 2009), are promising candidates.

1.2. HPA system

The hypothalamic-pituitary-adrenal (HPA) axis has been repeatedly shown to play an important role in AD (Elnazer & Baldwin, 2014; Plag et al., 2013). One of the major modulators of the HPA system is the corticotropin releasing hormone (CRH; for a review see Binder & Nemeroff, 2010; Nemeroff & Vale, 2005), which elicits the release of pituitary adrenocorticotropic hormone (ACTH) and subsequently cortisol under basal conditions and in response to stress. Cortisol follows a 24-hour circadian rhythm with highest levels in the morning upon wakening, which is called cortisol awakening response (CAR) with the peak release 30–45 min post-awakening, and lowest levels about mid-night (Lupien et al., 2005; Pruessner et al., 1997). To maintain physiological and behavioral responsiveness to stress, oscillating levels of adrenal glucocorticoid hormones are necessary and were shown to have an ultradian frequency due to a pulsatile secretion pattern (For a review see Spiga et al., 2015; Walker et al., 2012). Latter is impaired by continuous and prolonged stress with exposing the body to regularly high levels of cortisol (Heim et al., 2000), e.g. caused by high-frequency panic attacks and anticipatory anxiety. While cortisol has been shown to basically promote plasticity at the synaptic structural level (Liston et al., 2013) and thus to improve learning and memory, a chronically hyperactivated HPA system respectively long-term stress diminishes neuroplasticity (Surget & Belzung, 2022). Additionally, an inverted-U relationship between activity of endogenous stress hormones and human memory has been shown, with low doses of cortisol not affecting memory, with high doses probably impairing and in between promoting consolidation (Andreano and Cahill, 2006). Elevated cortisol levels seem to inhibit memory retrieval and working memory during emotionally arousing situations, but to enhance memory consolidation of emotionally arousing experiences (For a review see de Quervain et al., 2009; Hood et al., 2014; Lupien et al., 2005; Wingenfeld and Wolf, 2014).

The majority of the available studies assess peripheral cortisol levels in different bio samples as a direct measure of the HPA system activity in humans and animal models. The traditional cortisol assessment strategies like saliva, plasma and urine samples reflect the highly volatile short-term secretory activity of the stress system. Hair steroid analysis (Elnazer and Baldwin, 2014) is a reliable measure of cumulative cortisol concentration over a period of months (Elnazer et al., 2021) and can be used as long-term marker of HPA system functioning. Additionally, distinct HPA system function can be actively tested by administration of 1) glucocorticoids, e.g. dexamethasone (Dex), which assesses the suppression properties of the HPA system (the Dexamethason-Suppression-test, DST) or 2) corticotropin-releasing hormone (CRH), which is used to investigate the activation properties of the HPA system mostly in combination with suppression testing - the combined Dexamethasone suppression/Corticotropin-Releasing Hormone stimulation (Dex/CRH test; Heuser et al., 1994).

1.3. HPA system and anxiety disorders

The hypothesis of the HPA system dysfunction in AD has led to a plethora of studies investigating acute and chronic HPA system changes and its effects on therapeutic interventions, to understand the underlying biological processes and to develop new therapeutic drugs. There is mixed evidence for basal and acute deviations in cortisol levels as well as an association with symptom severity, duration of the disorder, and age in AD patients (for a review see Bandelow et al., 2017; Elnazer and Baldwin, 2014; Elnazer et al., 2021; Hek et al., 2013; Łoś and Waszkiewicz, 2021; Plag et al., 2013; Vinkers et al., 2021). Cortisol elevations in PD patients were either not found compared to controls or shown to be more pronounced during the day or during the night as well as during (induced) panic attacks and to be associated with higher symptom severity. Also, whether GAD or SAD is associated with aberrant increased basal cortisol levels remains unclear (For a review see Bandelow et al., 2017; Caldiroli et al., 2023; Kische et al., 2021).

Studies investigating HPA system dynamics in AD under psychosocial as well as physiological stress induction demonstrated both, hypo- as well as hyperactivation, or no difference to control condition (for a review see Bandelow et al., 2017; Ising et al., 2012). For example, hyporeactivity of the HPA system to psychological stress tests (e.g. Trier Social Stress Test [TSST]; Kirschbaum et al., 1993) at baseline was seen in PD patients (Altamura et al., 2018; Petrowski et al., 2010; Petrowski et al., 2013; Wichmann, Kirschbaum, Bohme, et al., 2017) and SAD patients (Petrowski et al., 2021) as well as a hyperresponsiveness in SAD patients (Roelofs et al., 2009; van West et al., 2008) or no difference to healthy subjects (e.g. Asbrand et al., 2019; Elzinga et al., 2010; Faucher et al., 2016; Grace et al., 2022; Klumbies et al., 2014; Krämer et al., 2012). Most studies suggest an enhanced cortisol increase during exposure to phobic stimuli in specific phobias with no difference to controls in the absence of fear-related situations (Bandelow et al., 2017). The majority of investigations with suppression tests have shown a normal suppression of ACTH and cortisol in the standard DST and Dex/CRH test in AD patients (For a review see Ising et al., 2012; Plag et al., 2013; Vreeburg et al., 2013; Wichmann et al., 2018) and a few found non-suppression e.g. in GAD (Tiller et al., 1988) or in PD patients (Erhardt et al., 2006). Earlier Coryell et al. (1991) demonstrated that non-suppression after DST in 77 medicated and non-medicated PD patients indicated a more persistent and chronically disabling condition three years later. Also, Petrowski et al. (2012) showed with the Dex/CRH test, that the duration of the illness may be a risk factor for hyperreactivity of the HPA system in PD patients.

Łoś and Waszkiewicz (2021) concluded in their review that cortisol in the initial stage of the AD is elevated, which makes it possible to treat it as a trait biomarker and thus, can be used for early detection of pathological forms of anxiety. Elevated cortisol levels may be a marker for the stress load due to anxiety symptoms itself. They further hypothesized that the cortisol concentration decreases during the course of AD and therefore may be monitored to assess the progress of the disease as state marker showing the level of clinical symptoms. However, it is not clear whether dysfunction of the HPA system is a potential etiological factor, for example for the onset of PD, or a result of continuous stress, for example caused by recurring panic attacks (Łoś and Waszkiewicz, 2021). Also, in SAD an initial increased cortisol reactivity to social exposition may attenuate following chronic exposure to stressful situations (Caldiroli et al., 2023). Taking the assumption into account that AD states exert long-term effects on GC secretion, findings of a recent study assessing hair cortisol indicate an elevated concentration in patients with single-episode AD and low concentration in recurrent-episode AD with a potential desensitisation of HPA response to stress (Elnazer et al., 2021). An alteration of the HPA system activation has also been linked to a worse course of symptoms in AD (Bandelow et al., 2000; Coryell et al., 1991; Petrowski et al., 2012). For example, investigating 837 depressive and anxiety patients in a longitudinal study, a lower salivary cortisol awakening response (CAR), possibly indicative of an underlying exhaustion of the HPA axis, was found to predict an unfavourable course trajectory after 2 years (Vreeburg et al., 2013). Interestingly, a study in 232 healthy individuals showed prospective associations between a higher salivary CAR and first onset of AD in 25 patients, especially of SAD (N = 11), over a six-year period (Adam et al., 2014). Also, higher pre-treatment mean 24-h cortisol levels in PD patients were previously shown to predict a worse outcome two years later (Abelson and Curtis, 1996).

In conclusion, there are contradicting results in the relevant research findings regarding the HPA abnormalities in AD with mixed evidence for

the dysfunction of the HPA system, either hyper- or hyporesponse, as underlying etiological process or as marker of state anxiety. Overall, the status of the HPA system may be indicative on individual level for treatment outcome in AD. In line with this, the present article summarized the findings related to cortisol as HPA axis marker in response to psychotherapy, particularly exposure-based CBT, that focusses on cognitive processes and avoidance behavior. As was pointed out in reviews before (Fischer and Zilcha-Mano, 2022; Laufer et al., 2018) due to the wide range of different cortisol sampling and analysis protocols, the studies existing so far are too heterogeneous for meta-analysis. Further, previous reviews reported only briefly on the specific topic of dynamics in the HPA system in regard to explicit CBT techniques and its implications as well as in context of a broader focus regarding therapy methods, psychiatric disorders, and assessed hormones and other biomarkers (Bandelow et al., 2017; Elnazer and Baldwin, 2014; Fischer and Zilcha-Mano, 2022; Laufer et al., 2018; Łoś and Waszkiewicz, 2021) or had a narrower focus – for example only prediction (e.g. Fischer and Cleare, 2017) not change. Additionally, several recently published studies were not included. Thus, this is the first review that focuses in detail on HPA system assessment with cortisol levels measurement before, during and after exposure-based CBT in AD patients. Here, we emphasize the dynamics over time and factors specific for CBT that may have an effect. First, we examined studies using just one baseline measurement of cortisol predicting response. Second, examinations during exposure are summarized and third, studies with pre/post assessments are reviewed.

2. Methods

The sources for the current review were journal articles. Methods were based on the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The inclusion criteria were studies examining the HPA axis, cortisol respectively, in all varieties of sampling methods (saliva, blood, hair) in patients with an anxiety disorder before, during, and after treatment with CBT techniques. English and German experimental studies published until April 2024 were considered. Articles using other psychotherapy methods (e.g. psychodynamic) or examining healthy subjects were excluded. Several steps were taken to identify usable studies. First, we went through the citations list of all relevant reviews mentioned here to identify studies that examined related topics. Next, a literature search was conducted using the database MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), PsycINFO (American Psychological Association), and Web of Science. The search strategy using MeSH (Medical Subject Headings) was based on the following different combinations of keywords: cortisol, hypothalamic-pituitary-adrenal axis or system, dexamethasone, behavior therapy (BT), cognitive therapy (CT), cognitive behavior therapy, exposure therapy and the anxiety disorders PD/AG, SAD, GAD as well as specific phobias. Also, the references of retrieved studies were screened in search of additional articles that met the topic. We repeated this process until no further study could be found. In total, 29 studies have been identified that investigated cortisol as marker for HPA system function within exposure-based CBT or related interventions which due to the narrative nature and range of the review were all included. The examinations were grouped by study designs: a) just one baseline measure of cortisol, b) examinations during exposure and c) studies with pre/post measure. For an overview and determination of type and quality, study details were collected by the first author and sorted by type of anxiety disorder, patient sample, treatment characteristics, cortisol measure and results.

3. Results

3.1. Baseline cortisol levels and stress reactivity as predictor of CBT outcome

Cortisol as HPA system biomarker with a basal measurement before treatment has been evaluated as outcome predictor for CBT in AD; studies are summarized in Table 1. Short-term salivary or plasma basal cortisol levels were not found to predict CBT response in AD in a meta-analysis (Fischer and Cleare, 2017) containing data of 6 studies also described below (Brand et al., 2011; Dierckx et al., 2012; Lass-Hennemann and Michael, 2014; Meuret et al., 2014; Siegmund et al., 2011; see Table 1). Other investigations showed an association of an attenuated cortisol stress response in PD patients to a stress task with CBT non-response in regard to agoraphobic avoidance behavior (Wichmann, Kirschbaum, Lorenz, et al., 2017) and in children with AD only with less decrease in depressive symptoms but not anxiety at one year follow up (Dieleman et al., 2016). Non-suppression to the Dex/CRH test, hypo-responsiveness of the HPA system to CRH respectively, was shown to predict an unfavorable CBT outcome in PD patients (Wichmann et al., 2018). One recent study demonstrated higher baseline cortisol plasma levels in 21 pharmacotherapy- and comorbidity-free PD patients to be significantly associated with a worse CBT outcome, especially in female participants (Masdrakis et al., 2021). However, the study included only a small number of PD patients having different phases of disease, which limits the generalizability of the findings. One study observed higher hair cortisol concentrations as a predictor of improved therapy response in a mixed sample of 89 depressive and AD patients, while lower cortisol levels might reflect a failure to raise sufficient cortisol responses over the course of treatment (Fischer et al., 2018). In another study in 36 spider phobic individuals hair and saliva cortisol at baseline did not predict CBT outcome (Steudte-Schmiedgen et al., 2021). In summary, results regarding basal and stress-exposure related cortisol as predictor of CBT outcome are inconsistent but point to a detrimental effect of insufficient HPA system responsiveness.

3.2. Cortisol dynamics during exposure sessions

Some studies examined cortisol levels directly before, during and after exposure to phobic situations with inconsistent results regarding cortisol reactivity: they either found elevated levels or no response (Abelson and Curtis, 1989; Alpers et al., 2003; Curtis et al., 1976; Curtis et al., 1978; Woods et al., 1987; see Table 1). In an earlier investigation with 10 animal phobic women, elevated cortisol response to an exposure session decreased in the second session, though not significantly (Nesse et al., 1985). A study in 15 patients with spider phobia receiving one to three exposure sessions found increased levels of cortisol compared to healthy controls as well as a normalization over treatment (Gaab et al., 2005). Interestingly, these psychobiological effects were mediated by changes of cognitive appraisal. Concordantly, Abelson et al. (2005) showed that a short cognitive intervention (9 Minutes) to reduce novelty, increase cognitive coping and providing a sense of control prior to stimulation with pentagastrin (experimental panicogenic compound) reduced blood cortisol as well as ACTH levels and anxiety responses of PD patients compared to no intervention. Siegmund et al. (2011) showed, that a blunted cortisol reaction of PD patients at repeated exposures despite high anxiety levels was related to a worse therapeutic outcome. Additionally, Meuret et al. (2014) found that absolute cortisol levels over a period of several hours in patients with PD/AG moderated the extinction of panic, fear and avoidance. In this study, elevated cortisol response to exposure was associated with better outcome. Higher pre-exposure levels and CAR had a positive impact on outcome. In contrast, when elevated on a “normal” control day, higher CAR was associated with poorer outcome. They point out, that anticipation of a demanding task and an according adaptive process of the HPA system seems to be advantageous. However, conclusions from this study are

Table 1
Summary of studies investigating associations between HPA system variation and course of symptoms in AD treated with cognitive and/or exposure therapy.

Studies with baseline cortisol levels and stress reactivity as predictor of CBT outcome

Authors	Diagnosis	Sample	Treatment	Measures	Results	Study Quality[a]	Effect size
Wichmann et al. (2017)	PD±AG	N = 28 (20 women, age: M=35.71 ± 13.18 yrs.) N = 32 matched HC (21 women, age: M=34.66 ± 12.07 yrs.)	CBT (five weeks individual and group sessions)	Plasma cortisol and ACTH before and during the TSST (within first two weeks of therapy) VAS, PASA, MI, BSQ, ACQ, BDI	Decreased cortisol concentrations in PD patients in comparison to HC and association of attenuated cortisol stress response with CBT non-response (avoidance behaviour)	+++	r = −0.345 to −0.396
Dieleman et al. (2016)	AD	N = 152 children (age: 8–12 yrs.)	CBT (10 child sessions and 4 separate parent sessions)	Salivary cortisol prior and post a stress task at baseline, SCL, HRV MASC, CDI	Lower cortisol reactivity predicted less decrease in depressive symptoms at one-year follow-up	+++	R^2_{change}= .03
Wichmann et al. (2018)	PD±AG	N = 34 patients (23 women; age: M=35.50 ± 12.74) N = 34 matched HC (25 women; age: M=33.82 ± 12.50)	CBT (five weeks individual and group sessions)	Cortisol and ACTH during DEX/CRH test at baseline PAS, ACQ, BSQ, MI	Patients with inadequate cortisol suppression showed less improvement in agoraphobic cognitions after CBT	+++	r = 0.489
Masdrakis et al. (2021)	PD±AG	N = 21 (16 women; age; M=35 yrs; medication-free)	CBT (8 weekly sessions)	Plasma cortisol and ACTH at baseline SCL−90; CGI, ACQ, MI	Non responders to CBT as compared to responders demonstrated significantly higher cortisol and ACTH basal plasma concentrations	++	-
Fischer et al. (2018)	AD, MDD	N = 89 (93 % women; age: M=34)	CBT	Hair cortisol at baseline CTQ, PHQ−9, GAD−7	Non-responders in terms of anxiety (48 %) had lower pre-treatment hair cortisol as well as higher levels of trauma	+++	η^2= .079
Steudte-Schmiedgen et al. (2021)	Spider Phobia	N = 36 (26 women; age: M=25)	ET (1 session)	Hair and saliva cortisol and cortisone at baseline SAS, FSQ, BAT, EAST	No association of cortisol and treatment response	+++	-

Studies with cortisol assessment during exposure sessions

Authors	Diagnosis	Sample	Treatment	Measures	Results	Study Quality[a]	Effect size
Abelson and Curtis (1989)	Height Phobia	N = 2 patients (men; age: 19 and 34 yrs.)	ET (17 and 9 sessions)	Plasma cortisol and norepinephrine, HR before and during ET sessions SUD	Both subjects showed rising cortisol responses and stable, non-extinguishing norepinephrine responses to height exposure	+	-
Alpers et al. (2003)	Driving Phobia	N = 11 patients (women; age: M=48.4 ± 9.4 yrs.) N = 13 matched HC (age: M=48.6 ± 98.6 yrs.)	ET (3 driving sessions) within 7–15 days	Salivary cortisol before, during, and after exposure Driving Self-efficacy Inventory, SUD, FQ, STAI	Phobics had significantly greater cortisol response scores during driving exposure and during quiet sitting periods before and afterward exposure	++	d= 1.14 to d= 1.29 (exposures 1 and 2)
Curtis et al. (1976)	Physical Objects Phobia	N = 7	2 ET sessions (3 and 4), 3 control sessions (1, 2 and 5) in the early evening	Plasma cortisol 10 times (20-minute intervals) during sessions SUD	Anxiety elevation and successful ET effect, but no cortisol response	+	-
Curtis et al. (1978)	Physical Objects Phobia	N = 6 (5 women; age: 23–52)	2 ET sessions (3 and 4), 3 control sessions (1, 2 and 5) in the morning	Plasma cortisol 10 times (20-minute intervals) during sessions SUD	Moderate elevations of plasma cortisol above control levels in some subjects	+	-
Woods et al. (1987)	PD±AG	N = 18 patients (14 women, age: M=40.5 yrs.; medication: placebo 4 weeks prior exposure) N = 13 matched HC	CBT (weekly group therapy and in-vivo exposure)	HR, BP, plasma free MHPG, growth hormone, and prolactin levels before, during, and after exposure session HAMA, CGI, PASS, VAS	No significant differences in cortisol between groups	++	-
Nesse et al. (1985)	Animal Phobia	N = 10 (women; age: 25–43 yrs.) N = 15 controls	2 ET sessions (2 and 3), 2 control sessions (1 and 4)	Plasma cortisol 10 times (20 minute intervals) during sessions, pulse, BP, epinephrine, norepinephrine, growth hormone, insulin, glucagon, and pancreatic	Almost all variables increased during anxiety/ ET. Cortisol response was significantly elevated during ET and decreased (n.s.) to second exposure session	++	-

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Table 1 (*continued*)

Studies with cortisol assessment during exposure sessions

Authors	Diagnosis	Sample	Treatment	Measures	Results	Study Quality[a]	Effect size
				polypeptide SUD, STAI			
Gaab et al. (2005)	Spider Phobia	N = 15 (14 women; age: M=26.3, 20–40 yrs.) N = 15 controls	ET (3 sessions)	7 saliva cortisol samples and HR before and during ET SUD, FSQ, SPQ, STAI, avoidance behaviour	Significantly increased levels of cortisol compared to controls and heart rate during exposure normalized significantly over sessions	+++	Increase: f^2= 0.56; Reduction: f^2= 0.78
Abelson et al. (2005)	PD±AG	N = 14 Patients (9 men; age: M=27.5 ± 5.78 yrs.) N = 14 matched HC	9-minute cognitive intervention before pharmacological panicogenic stimulation for half the group (randomly assigned)	Blood cortisol and ACTH before and after pharmacological activation (pentagastrin) Panic symptom intensity, VAS	The cognitive intervention significantly reduced cortisol and ACTH levels, despite pentagastrin's robust stimulation of both hormones. Patients' exaggerated anxiety responses to pentagastrin were normalized by the intervention	++	-
Siegmund et al. (2011)	PD±AG	N = 10 (6 women; age: M=36.9 ± 9.7 yrs.; 3 medicated) N = 10 matched HC	CBT including 3 in-vivo exposures	Plasma cortisol and ACTH before, during and after exposure PAS, MI, BAI	Low concentration of cortisol during exposure was moderately correlated with poorer therapeutic outcome	++	mean r = −0.49
Meuret et al. (2014)	PD±AG	N = 26 (88.5 % women; age: M=33.1 ± 9.12 yrs.; >3 months stable medication=65.4 %)	ET (3 weekly sessions + 2 months follow-up session)	Salivary CAR and cortisol prior, during and after exposure; control day MI, BSQ, ASI	Higher absolute cortisol levels during exposures moderated clinical improvement. Greater morning rises in cortisol on exposure day predicted greater treatment gains, but greater rises on the control day were associated with poorer outcomes	++	-
Lass-Hennemann (2014)	Spider Phobia	N = 60 (women; age: M=25.40, 18–50 yrs.)	ET (one 3 h session)	Hair and saliva cortisol before, during and after ET in the morning (8 am group) vs. in the evening (6 pm group) SUD, FSQ, BAT before, 1 week after and 3 months after ET	Cortisol was significantly higher in the morning group. Patients treated in the morning showed significantly less fear in the BAT after treatment and at follow up	+++	Cortisol difference: partial η^2= .71
Sopp et al. (2024)	Snake Phobia	N = 71 (60 women; age: M=22.3, 18–40 yrs.)	ET (one-hour video session)	Sleep quality (actigraphy), vigilance, salivary CAR and cortisol before, during and after ET in the morning (8 am group) vs. in the evening (6 pm group); EDA, ECG SNAQ, STAI, ASI, PSQI, BDI-II, rMEQ, PHQ-D, BAT, PVT, BAT before, 1 and 4 weeks after ET	Cortisol levels were not found to predict treatment outcome. Higher vigilance was found to be correlated with lower post and follow-up snake anxiety. Pre-exposure sleep efficiency moderated follow-up decrease in snake anxiety	+++	-
Meuret et al. (2016)	PD±AG	N = 26 (87.5 % women; age: M=32.4 ± 9.1 yrs.; >3 months stable medication=62.5 %)	ET (3 weekly sessions + 2 months follow-up session)	Salivary cortisol prior, during and after exposure MI, ACS, PDSS and ASI	Earlier sessions were associated with higher pre-exposure cortisol levels and in turn greater clinical improvement	++	ds> 1.05 and ds> 0.95
Wintermann et al. (2022)	PD±AG	N = 20 patients (12 women; age: M=29.8, 22.7–43.3) N = 20 matched HC (8 women; age: M=24.1, 22.0–28.9)	CBT	Salivary cortisol and HR before and after interoceptive exposure (low intensity exercise) PAS, ACQ, BSQ, MI	Cortisol decreased over time, especially in male patients.Significant negative correlation of cortisol response with therapy outcome	++	η^2= .177 and r = −.554 to −.738
Kuhlman et al. (2020)	SAD	N = 60 (58.3 % women)	Virtual reality ET (7 sessions)	Scopolamine-augmentation or placebo during sessions. 4 saliva cortisol samples during sessions 1, 4, 7, and a post-treatment extinction test LSAS	Elevated endogenous in-session cortisol during exposure sessions was associated with less symptom improvement from pre- to post-treatment and at 1-month follow-up	+++	Fear: d= 3.27 and avoidance: d= 1.66

Studies with cortisol assessment pre/post CBT

Authors	Diagnosis	Sample	Treatment	Measures	Results	Study Quality[a]	Effect size
Brand et al. (2011)	Mask Phobia	N = 46 patients (male army recruits; age: M=19.46 ± 1.64) N = 39 HC (age: M=19.69 ± 1.54)	CBT (two-day intensive treatment course)	Salivary CAR before and after CBT; cortisol prior, during and after exposure in the afternoon and control day STAI, GAS	Cortisol secretion was significantly higher in patients and decreased after therapy	+ +	AUC total: d= 0.86 AUC basal: d= 0.43 AUC net: d= 0.66
Hemyari et al. (2020)	Rat Phobia	N = 40 students (women; age: M=20.97, 18–24 yrs.)	One- (n = 20) and multi-session (n = 20) exposure based CBT	Plasma cortisol, pro-inflammatory cytokines, and interleukin−6 at baseline and during a BAT before and after CBT DPSS-R, FRQ, STAI, BAT	Cortisol levels and cytokines were significantly reduced after CBT in both types of treatment	++	-
Tafet et al. (2005)	GAD	N = 17 outpatients (9 women; age: M=42.4 ± 8.5 yrs.), N = 8 waitlist controls (4 women)	CT (24 sessions), no medication	Plasma cortisol before and after CT or after 24 weeks in the morning and afternoon HAMA	Significant decrease in afternoon cortisol levels along decrease in anxiety symptoms	++	-
Wang et al. (2013)	GAD, MDD, OCD	N = 54 patients (30 women; age: M=29.31 ± 9.78 yrs.) N = 55 medicated controls (29 women; age: M=30.95 ± 10.18 yrs.)	CT (attribution retraining group therapy, 8 sessions/weeks) or SSRI	Plasma cortisol in the morning before and after treatment HAMA, HAMD	Patients in the CT group had significantly lower plasma cortisol concentrations compared to baseline	+++	-
Dierckx et al. (2012)	AD	N = 116 children and adolescents (male ≈ 50 %; age: 8–16 yrs.; no medication)	CBT (10 child sessions and 4 separate parent sessions)	Salivary CAR and daytime cortisol before, 3 months and 1 year after treatment MASC	Compared to baseline, one-year follow-up high daytime cortisol production was associated with persistence of symptoms, high CAR with remission	++	-
Tiller et al. (1988)	GAD	N = 15 patients (8 men; age: M=38, 25–65 yrs.; 8 DST suppressors, 7 matched non suppressors), N = 13 matched HC (5 suppressors, 8 non suppressors)	BT (5 weeks)	DST 1 week before and 1 week after treatment HAMA, STAI	After treatment all patients were DST suppressors, but dexamethasone concentrations remained significantly lower in initial non-suppressors	+	Non-suppressors DST 1 × 2: r = 0.964
Faucher et al. (2016)	SAD	N = 13 CBT (38.5 % women; age: M=39.31 ± 10.40 yrs.) N = 14 MBSR (35.7 % women; age: M=36.64 ± 16.15 yrs.) N = 30 HC (36.7 % women; age: M=29.77 ± 12.77 yrs.)	Group CBT and MBSR (12 weeks)	6 saliva cortisol samples and HRV during a speech task before and after treatment (HC only baseline) LSAS-T, SIS, SPS, VAS	No change in physiological measurers	++	-
Asbrand et a. (2019)	SAD	N = 65 children (WL: N = 26; female=63,6 %; age: M=11.3, 9–13 yrs.) N = 55 HC (female=60 %; age: M=11.7, 9–13 yrs.)	Group CBT (12 weeks) and waitlist	6 saliva samples during the TSST (cortisol and alpha amylase) before and after CBT or no treatment SPAI-C	Children with SAD in the waitlist group showed stronger cortisol reactivity and a higher cortisol response rate compared to children in the CBT group after treatment	+++	d= 0.71–0.74

AD = anxiety disorders; PD±AG = panic disorder with or without agoraphobia; GAD = generalized anxiety disorder; SAD = social anxiety disorder; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; HC = healthy controls; CBT = cognitive behavioural therapy; ET = exposure therapy; CT = cognitive therapy; BT = behavioural therapy; MBSR = mindfulness-based stress reduction; SSRI = selective serotonin reuptake inhibitor; ACTH = adrenocorticotropic hormone; BP = blood pressure; CAR = cortisol awakening response; ECG = electrocardiography; EDA = electrodermal activity; HR = heart rate; HRV = heart rate variability; MHPG = 3-Methoxy-4-Hydroxyphenylglycol; SCL = skin conductance level; BAT = behavioral avoidance test; SUD = subjective units of distress; VAS = visual analog scale ranging from 0 (no fear) to 10; CGI = Clinical Global Impressions-Improvement; GAS = Goal Attainment Scale; SCL-90 = Symptom Checklist–90; ASI = Anxiety Sensitivity Index; BAI = Beck Anxiety Inventory; HAMA = Hamilton Anxiety Rating Scale; STAI = State-Trait Anxiety Inventory; MASC = Multidimensional Anxiety Scale for Children; ACS = Anxiety Control Scale; FQ = Fear Questionnaire; FRQ = Fear of Rat Questionnaire; FSQ = Fear of Spiders Questionnaire; SAS = Spider Anxiety Screening; SPQ = Spider Phobia Questionnaire; SNAQ = Snake Questionnaire; LSAS = Liebowitz Social Anxiety Scale; SIS = Social Interaction Scale, SPAI-C = Social Phobia and Anxiety Inventory for Children; SPS = Social Phobia Scale; TSST = Trier Social Stress Test; ACQ = Agoraphobic Cognitions Questionnaire; BSQ = Body Sensations Questionnaire; MI = Mobility Inventory; PAS = Panic and Agoraphobia Scale; PASS = Panic Attack Symptom Scale; PDSS = Panic Disorder Severity Scale; GAD = Generalized Anxiety Disorder Scale; PASA = Primary Appraisal and Secondary Appraisal Questionnaire; BDI = Beck Depression Inventory; HAMD = Hamilton Depression Scale; CDI = Children's Depression Inventory; CTQ = Childhood Trauma Questionnaire; PHQ = Patient Health Questionnaire; DPSS-R = Disgust Propensity and Sensitivity Scale-Revised; EAST = Extrinsic Affective Simon Task; PSQI = Pittsburgh Sleep Quality Index; rMEQ = reduced Morningness-Eveningness-Questionnaire; PVT = Psychomotor Vigilance Task; r = Pearson's correlation; d = Cohen's D; AUC = area under the time curve; f^2 = multivariate f^2: small = 0.02, moderate = 0.15, large = 0.35; η^2: small ~.01, medium ~.06, large .> .14.

+ = weak

++ = moderate

+++ = strong

[a] according to Quality Assessment Tool for Quantitative Studies (Armijo-Olivo et al., 2012; Thomas et al., 2004).

limited by concomitant psychopharmacological treatment of some patients, especially intake of benzodiazepines, different time schedules for exposure sessions and cortisol measurements, not considering the circadian related cortisol secretion variability. Interestingly, another study compared the effects of one-session exposure in the morning (high endogenous cortisol) to exposure in the evening (low endogenous cortisol) in 60 spider phobic patients (Lass-Hennemann and Michael, 2014). Assessment of anxiety symptoms before the therapy, one week as well as three months after CBT showed that treatment in the morning was significantly more effective than in the evening. A recent study in 71 patients with snake phobia did not replicate these findings despite higher cortisol levels in the morning group, but found that rather vigilance and sleep quality play a role as moderators of pre-post changes in fear reduction (Sopp et al., 2024), which points to more complex diurnal effects on exposure therapy. In the above mentioned study with 10 animal phobic women, response to an exposure session in the morning also showed an overall higher cortisol level than in the evening, though increase from naturally lower levels was much higher in the evening; but blunted cortisol responses might be anticipated when levels are already elevated (Nesse et al., 1985). Consistently, in a study with 24 PD/AG patients receiving 72 exposure sessions (3 per week), earlier sessions were associated with higher pre-exposure cortisol levels, which mediated the effect of time of day on greater clinical improvement (Meuret et al., 2016). Similarly, in a study with 20 PD/AG patients and 20 matched healthy controls, a higher symptom severity before and unfavorable therapeutic outcome after CBT, were associated with a significantly lower cortisol response under interoceptive exposure (Wintermann et al., 2022). Whether higher cortisol concentrations during exposure sessions in AD patients are associated with better treatment outcomes remained unclear in the beforementioned meta-analysis by Fischer and Cleare (2017). In a study of Kuhlman et al. (2020) with SAD patients, elevated endogenous in-session cortisol during ET predicted attenuated symptom improvement. The authors state that their cortisol indices represent rather chronically elevated cortisol with little variation during ET since less than one third of the samples exhibited at least a 20 % increase in cortisol during exposure sessions and no significant change across the trial (Kuhlman et al., 2020). Taken together, these findings emphasize the probable detrimental effect of sustained elevations in cortisol levels for treatment outcome, compared to acute increase and thus, beneficial responsiveness.

3.3. CBT effects on cortisol levels

The studies assessing the relationship between CBT effects and HPA system function in AD before, during and after intervention are summarized in Table 1. A few studies investigated changes in cortisol levels and response after CBT treatment in AD: Brand et al. (2011) investigated army recruits with protective mask phobia. They found heightened basal morning salivary cortisol levels compared to controls as well as the association of a significant reduction in afternoon cortisol levels during exposure to the phobic stimulus with symptom reduction after a two-day intensive treatment course of CBT. Similar, a study investigating responses to one- and multi-session exposure-based therapy in rat phobia, showed a reduction in cortisol levels during a behavioral avoidance test conducted pre and after successful treatment (Hemyari et al., 2020). Tafet et al. (2005) showed that a significant decrease in symptom severity after CBT in 17 GAD patients was associated with a significant reduction in elevated afternoon plasma cortisol levels, while plasma cortisol in an untreated group remained high. Comparable, in a study of Wang et al. (2013) 19 GAD patients treated with attribution retraining group therapy for 8 weeks had significantly lower morning plasma cortisol concentrations compared to baseline and in contrast to a medicated group (SSRI; N = 55). Further, a prospective study showed that remission of children with AD one year after CBT was associated with lower daytime cortisol and that low CAR levels were associated with a poorer outcome at one year follow up (Dierckx et al., 2012). Additionally, Tiller et al. (1988) found in a sample of 15 non-medicated GAD patients that non suppressors in the DST compared to suppressors at baseline had an expected normalized suppression after 5 weeks of behavioral therapy. Regarding SAD, a study investigating effects of CBT versus MBSR treatment on stress reaction to the TSST found no changes in cortisol levels after treatment (Faucher et al., 2016). Another study in children with SAD comparing a CBT group to waitlist controls showed that in children who had not received treatment a repeated social stress task led to a sensitization and stronger cortisol reactivity, concluding that a potential vulnerability to stress-related diseases, possibly leading to an enhanced cortisol stress response, might be improved with CBT (Asbrand et al., 2019). Taken together, some evidence suggests that successful CBT induces normalization of an aberrant HPA system.

4. Discussion

We reviewed studies investigating the potential use of hormones related to the endogenic stress system as biological marker for the outcome of CBT in anxiety disorders. We focused on studies assessing basal levels and specifically before, during and after exposures sessions as well as changes in cortisol levels over the course of CBT and beyond. In summary, despite the methodological weaknesses, heterogeneity of study protocols, and mostly preliminary results, findings indicate on the one hand a detrimental effect of insufficient HPA system responsiveness regarding basal and stress-exposure related cortisol as predictor of CBT outcome as well as a beneficial effect of acute cortisol elevation, with most indicative parameters of morning cortisol response and increase before and during exposure. On the other hand, monitoring cortisol levels may function as biomarker for CBT effects, since effective treatment seems to normalize HPA system abnormalities. Moreover, findings imply that cognitive processes which are an essential part of CBT may play an important role in modulating the HPA system.

First, chronic dysregulation of the HPA system function, persistently elevated cortisol concentrations and hyporeactivity to phobic situations, possibly due to neuroendocrine adaptation processes in response to prolonged stress or due to the disorder itself, indicates a less favorable outcome of CBT in patients with AD and thus, represents a possible causal and maintaining factor. A blunted response to acute stress is associated with poorer outcome across studies in AD using CBT (Meuret et al., 2014; Siegmund et al., 2011), except for SAD, where elevated levels during exposure may be detrimental or less beneficial to outcome than in other AD (Asbrand et al., 2019; Kuhlman et al., 2020), but studies are small and conclusions are preliminary. Also, this may represent chronically elevated cortisol levels and is contradicted by a recent study with psychodynamic psychotherapy (Schmalbach et al., 2024). Following this, heightened cortisol might be beneficial by weakening the originally learned fear memory and consolidating a newly formed fear-inhibitory memory. The *memory reconsolidation hypothesis* proposes that every time the original fear memory is retrieved by a brief memory reactivation it becomes unstable through induced plasticity that opens up a transient period during which a memory becomes susceptible to disruption and can be modified (impaired, enhanced, or updated), which allows for transition into a fear-inhibitory memory (Dudai, 2006; Meir Drexler et al., 2015; Monfils et al., 2009). Investigations showed that reminding of a task ahead and encouraging anticipation or presenting a fear activating stimulus before, successful exposure can lead to persistent attenuation of conditioned fear (Johnson and Casey, 2015; Maples-Keller et al., 2017). Moreover, the impairing effect of glucocorticoids on reconsolidation is supported by animal extinction studies (Cai et al., 2006; Yang et al., 2006; Zohar et al., 2011). However, the occurrence of spontaneous recovery, renewal, rapid acquisition, and reinstatement after extinction, suggests that it does not seem to change the original fear memory (Bouton and Todd, 2014; Myers and Davis, 2002; Todd et al., 2014), which is corroborated by the inhibitory learning approach (Craske et al., 2014). Concurring, Fischer and Zilcha-Mano (2022) review that in phobias low cortisol during

initial exposure sessions seem to facilitate retrieval of fear memories and to impede the formation of extinction memories, resulting in suboptimal treatment outcomes. Some studies have already investigated the potential use for pharmacological enhancement of exposure effects with glucocorticoids and various other substances (Singewald et al., 2014). Investigations augmenting exposure by cortisol administration found a significantly greater reduction in fear until follow up applying glucocorticoids prior to, but not post, ET (de Quervain et al., 2011; Fitzgerald et al., 2014; For a review see Hofmann et al., 2015; Nakataki et al., 2017; Raeder et al., 2019; For a review see Singewald et al., 2014; Soravia et al., 2006; Soravia et al., 2014; Steudte-Schmiedgen et al., 2021). Two recent studies with spider phobia patients showed a fear reducing effect of cortisol administration due to improving an aberrant functional connectivity of the amygdala (Nakataki et al., 2017) and restoration of the salience network activity (Soravia et al., 2018) when exposed to phobia-related stimuli. Results are encouraging but have to be further evaluated. Furthermore, an enhancing effect of cortisol on reconsolidation of the reactivated original fear memory was shown if this former memory is updated (Meir Drexler et al., 2015). This would explain the reinforcement of anxiety through fear confirming actions like avoidance and safety behavior of anxiety patients, ineffective exposure and lacking disprove of fears, respectively. Additionally, in a situation of high stress, cortisol may impair the retrieval of the new acquired extinction memory and to promote relapses and the return of fear after successful extinction learning by increasing activation of the fear network (Hagedorn et al., 2021). In Summary, not only discordant experience by the use of CBT may play a role in overcoming fear, but, despite the known impairing effect of a chronically elevated cortisol level on memory, acute stress before and during ET sessions, an activated HPA system respectively, interpreted as a flexible and adaptive response to fear-related situations, seems to be favorable for the extinction learning during fear disconfirming ET (Meuret et al., 2016), and hence a decreased cortisol response after.

Second, effective treatment seems to normalize HPA system abnormalities in AD patients which was found on different levels. First, a decrease in an elevated cortisol response over recurrent exposure sessions or repeated BATs was found in several studies (Brand et al., 2011; Gaab et al., 2005; Hemyari et al., 2020; Lass-Hennemann and Michael, 2014). Second, a few studies showed a decrease in elevated basal cortisol levels after treatment (Dierckx et al., 2012; Tafet et al., 2005; Wang et al., 2013). In this, the cortisol awakening response also plays a role with inconsistent findings whether it should be high (Dierckx et al., 2012) or low (Brand et al., 2011; Meuret et al., 2014) for beneficial therapy response, and which is probably depending on the upcoming day's demands and anticipation of it. Third, one study showed a normalization of cortisol hyporesponsiveness after CBT in the DST (Tiller et al., 1988). Taken together, cortisol appears to be one possible indicator of CBT effects on anxiety symptoms, specifically heightened basal and daytime cortisol levels before treatment as well as its dynamics in response to fear related stimuli and dexamethasone stimulation.

Moreover, the reviewed studies imply that cognitive processes, e.g. appraisal, attribution, perceived controllability, and coping, seem to have a beneficial influence on adaptive HPA system functioning and related cortisol changes (Abelson et al., 2005; Gaab et al., 2005; Tafet et al., 2005; Wang et al., 2013). Cortisol seems to be heightened during anticipating of a demanding task (Coplan et al., 1998; Meuret et al., 2014), e.g. exposure to a feared situation, whereas a more positive anticipatory cognitive stress appraisal and regulation seems to decrease the cortisol response to stress stimuli (Pulopulos et al., 2019). Further, distracting GAD patients from their anxious thoughts by refocusing the attention was demonstrated to reduce acute cortisol levels (Rosnick et al., 2013). Mayer et al., (2017) showed in a phobic fear exposure model that actual and perceived control was the determining factor for lower cortisol levels. In line with the inhibitory learning model (Craske et al., 2014), flexible responses, e.g. metacognitions, to environmental stimuli may facilitate extinction by inhibiting a conditioned reaction (Arch and Abramowitz, 2015). However, as explained above, an adaptive response of the HPA system to demands seems to be required. An investigation of the association of momentary emotion regulation and diurnal cortisol in depression and anxiety showed that current internalizing disorders seem to be associated with downregulated HPA axis functioning, while engaging in problem solving was associated with elevated cortisol reactivity (Gilbert et al., 2017). Similar, a recent longitudinal study showed that higher physiological symptoms in children with anxiety symptoms were related to hypercortisolism during the day and in contrast, that chronic worry and social concerns predicted hypocortisolism with a blunted diurnal cortisol pattern (Ma et al., 2019). Comparable, an increase in cortisol activity in older patients in remission of GAD, but not with PD and phobias, and a decrease in cortisol activity in those with persistent anxiety was found, which may be linked to symptoms of constant worry (Bakouni et al., 2020). This fits with findings in GAD with lower hair cortisol concentrations compared with healthy controls (Steudte et al., 2011). Thus, dysfunctional cognitive coping strategies might explain reduced cortisol response in chronic anxiety states, compared to acute exposure to a fear-related stimulus and adaptive HPA response. These results underscore the importance of cognitive factors in explaining HPA functioning and improvement of anxiety symptomatology, which are an essential part of CBT.

4.1. Conclusion and future directions

In summary, cortisol levels may have the potential to serve as biomarker for current anxiety severity and effectiveness of treatment. However, the interpretation of the results from currently available studies are clearly limited by small sample sizes, diverse type of cortisol assessment (e.g. salivary, plasma, hair) and methods to assess the HPA system function (e.g. cortisol awakening response, diurnal decline, stress response), different experimental conditions (e.g. time of day, natural or induced panic attacks, type of stressor), differentially performed ratings (self-ratings, therapist-ratings, specific vs. general anxiety symptoms) and treatment procedures (e.g. group, individual, virtual reality), including the combination with medication, different duration of treatment (e.g. 1–24 sessions) and follow up periods. Further variables like childhood adversity, biological (e.g. sex, genes, medication, oral contraceptives, etc.) or diurnal moderators (e.g. sleep efficiency, arousal, chronotype), duration of the disorder and comorbidity with other psychiatric disorders may contribute to inconsistencies and should be considered. For instance, smoking status, depression, especially female gender and the use of the contraceptive pill were shown to be related to a mainly blunted HPA axis reactivity (Bakouni et al., 2020; Kische et al., 2021; Wintermann et al., 2016).

In conclusion and in line with Laufer et al. (2018), the measurement of the global HPA system function, CAR, diurnal slope, acute and long-term cumulative cortisol output on consecutive days as well as before, during and after exposure in CBT might be useful to monitor the disease status, severity, and treatment effect along the CBT depending on the effect that is investigated. Moreover, differential approaches may be beneficial for the improvement in different states of the AD as well as for specific AD: reducing stress response to a fear-related stimulus or chronically elevated cortisol levels in the initial phase of an AD and activating/normalizing a downregulated, exhausted HPA system in persistent AD, like GAD and SAD, through exposure and cognitive techniques and possibly glucocorticoid augmentation. Importantly, cognitive processes and coping strategies, such as appraisal, sense of control, focus of attention, vigilance and self-monitoring, as well as avoidance behavior during the CBT may mediate the differential effects on the HPA system and should be included in future investigations. Finally, further reviews may include other forms of psychotherapy and determine common or different mechanisms of actions.

Based on the evidence available to date, we deduce the following recommendations for future studies to clarify the role of cortisol in specific AD and on CBT effects: 1) assessment of CAR, daily cortisol and

hair cortisol before and after the psychotherapeutic intervention including at minimum one follow up after 3 month to measure hair cortisol levels, 2) assessment of cortisol before and after the exposure intervention by keeping the time of measurement comparable within and between the individuals, 3) ensuring diagnostic properties and specifically the comorbidity of AD and depression, 4) applying a global and AD-specific assessment of anxiety dimensions and of the therapy-related effects, such as cognitive processes, 5) assessing first onset and duration of AD symptoms as well as childhood adversity as putative moderating factor of HPA system response, 6) correcting for medication use, sex and age, and 7) considering further putative moderating variables on exposure, such as sleep quality. As HPA system abnormalities seem not to be a general pattern of AD, within subject-analyses could help to better identify those who most profit from a priori and concomitant HPA system measurements related to clinical outcomes to improve decision making for clinicians in terms of best fitting therapy.

CRediT authorship contribution statement

Angelika Erhardt-Lehmann: Writing – review & editing, Supervision. **Jennifer Lange:** Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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