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Cortisol predicts psychotherapy response

Cortisol as a predictor of psychological therapy response in anxiety disorders – systematic review and meta-analysis

Susanne Fischer, PhD & Anthony J. Cleare, MBBS, PhD

King's College London, Institute of Psychiatry, Psychology & Neuroscience, Department of Psychological Medicine, Centre for Affective Disorders, London, United Kingdom

Corresponding author: Susanne Fischer, PhD, King's College London, Institute of Psychiatry, Psychology & Neuroscience, Department of Psychological Medicine, Centre for Affective Disorders, PO 74, 103 Denmark Hill, London SE5 8AF, United Kingdom

E-mail: susanne.fischer@kcl.ac.uk

Telephone: +44 20 7848 5305

Abstract

Background

Although psychotherapy generally is effective in anxiety disorders, many patients are treatment-resistant. At the same time, some patients with anxiety disorders show alterations in the hypothalamic-pituitary-adrenal (HPA) axis, one of the major stress-responsive systems. Since raised levels of the end product of the HPA axis, cortisol, adversely affect cognition, we hypothesised that more pronounced alterations in cortisol levels would be associated with a less favourable response to psychotherapy. More specifically, the higher patients' basal levels and the lower their levels during exposure, the less likely we expected them to profit from treatment.

Methods

We systematically searched the Cochrane Library, EMBASE, MEDLINE, and PsycINFO to review the literature and perform a meta-analysis on the relationship between pre-treatment cortisol and psychotherapy response. Records were included if they studied patients with any anxiety disorder undergoing psychotherapy, with a pre-treatment cortisol and a post-treatment symptom measure. Correlation coefficients were extracted for meta-analyses.

Results

We identified six studies ($N = 274$). No relationship between patients' basal cortisol and post-treatment symptoms was found ($p = .981$). The systematic review showed higher cortisol during exposure sessions to predict better outcomes. Meta-analysis did not confirm this ($p = .603$).

Conclusions

Basal cortisol did not seem to predict psychological therapy responses in patients with anxiety disorders. By contrast, the current state of research is equivocal in terms of whether higher cortisol concentrations during exposure sessions are linked with better treatment outcomes, and more research is needed to investigate this.

Keywords: agoraphobia; hypothalamo-hypophyseal system; panic disorder; phobic disorders; pituitary-adrenal system; psychotherapy

1. Introduction

Psychological therapies are among the most effective treatments for anxiety disorders, with most evidence focusing on cognitive-behavioural therapy (CBT; Hofmann & Smits, 2008). Within CBT, exposure to threat cues is a key therapeutic element (e.g., Simos & Hofmann, 2013). The goal of such sessions is for patients to give up their avoidance behaviour and reduce fear and anxiety by means of habituation to phobic stimuli. Unfortunately, around a third of patients do not respond to such interventions, and, upon repeated non-response to a variety of treatments, are sometimes referred to as “treatment-resistant” patients (Durham, Higgins, Chambers, Swan, & Dow, 2012).

One possibility to minimise non-responses is to find pre-treatment features that are able to distinguish between those that are subsequently likely to respond and those who are not. This could facilitate better identification of patients that are currently being offered inappropriate treatment, and eventually guide the development of alternative interventions. Currently, the most reliable predictors of non-response include the severity of anxiety disorders and their comorbidity with other mental disorders, especially personality disorders (Bystritsky, 2006). However, these factors are limited in their ability to explain *why* some patients respond to psychological therapy and others do not. Clearly, researchers and clinicians would benefit from predictors that are more reflective of the mechanisms underlying the non-response phenomenon.

It is a frequent pathophysiological finding in anxiety disorders for there to be alterations in the hypothalamic-pituitary-adrenal (HPA) axis, one of the major stress-responsive systems. The HPA end product cortisol, a glucocorticoid, has a distinct basal diurnal rhythm, with a sharp increase upon awakening (the so-called “cortisol awakening response”, CAR) and a steady decline over the course of the day (Clow, Thorn, Evans, & Hucklebridge, 2004). Importantly, cortisol not only reacts to awakening, but it is equally responsive to stressful situations (e.g., Skoluda et al., 2015); its concentrations in blood and saliva peak at approximately 20 to 30 minutes after stressor onset. In terms of measurement, an important distinction is therefore made between *basal*, that is, resting cortisol concentrations and *stimulated* cortisol concentrations, as obtained after awakening or exposure to stressful situations. While very few studies have looked at cortisol in specific phobia and social anxiety disorder and compared them to those of healthy controls, there is accumulating evidence for basal levels to be elevated in patients with panic disorder and agoraphobia, although opposite and null-findings have been reported as well (Elnazer & Baldwin, 2014). Of note, almost all

studies to date used short-term cortisol markers, such as 24 h urinary cortisol or salivary/plasma cortisol, and it is not clear whether the observed alterations represent trait or state characteristics of the illness.

Cortisol modulates cognitive processes. Upon its release from the adrenal cortex and entering the brain, it binds to both glucocorticoid and mineralocorticoid receptors that are abundantly expressed in brain memory-related networks, such as the prefrontal cortex, hippocampus, and amygdala (de Kloet, Oitzl, & Joels, 1999). In the brain, cortisol facilitates the consolidation of new information, while hampering memory retrieval (Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2012). If psychological therapy is understood at least partly as a learning process that results in an adaptive reorganisation of neuronal networks (Grawe, 2006), this may have substantial implications regarding treatment success. In fact, there is increasing evidence for a role of cortisol in fear extinction, a cognitive process that is crucial in the treatment of anxiety disorders (Bentz, Michael, de Quervain, & Wilhelm, 2010). Fear extinction comprises the consolidation of an extinction memory while the retrieval of the fear memory is impeded. A series of elegant studies in patients with different kinds of phobia has shown that exogenous administration of glucocorticoids can enhance the efficacy of exposure therapy (de Quervain et al., 2011; Soravia et al., 2006; Soravia et al., 2014). These findings raise the question of whether patients suffering from pre-treatment HPA alterations may do less well in psychological therapy.

Taken together, it is conceivable that pre-treatment cortisol levels predict psychological therapy response in patients with anxiety disorders. More specifically, it can be hypothesised that to the degree patients demonstrate pre-treatment HPA axis alterations, they profit less from the corrective learning experiences that are made during therapy. Based on the finding that patients with panic disorder and agoraphobia seem to exhibit elevated basal cortisol concentration (see above), this would mean that the higher a patient's *basal* cortisol levels, the higher their level of anxiety and/or avoidance behaviour upon completing therapy. Similarly, the extent to which a patient demonstrates HPA alterations during *stimulation* would be associated with the degree of treatment failure. Seeing that it is adaptive for cortisol to be elevated during stress to facilitate energy metabolism, in this case, this would mean that the lower the cortisol levels when facing a stressor, the more symptoms a patient would retain. Our aim was to systematically review for the first time the literature on cortisol as a

predictor of psychological therapy response in patients with anxiety disorders and to quantify the strength of this relationship.

2. Methods

2.1 Search strategy

Relevant records were identified by one of the study investigators (SF) by systematically searching the Cochrane Library, EMBASE, MEDLINE, and PsycINFO databases from the first available year until March 2015. We combined key words and subject headings in accordance with the thesaurus of each database and applied exploded subject headings. Our search string consisted of three components: 1) “cortisol” and synonyms, 2) “anxiety disorder”, including synonyms and related terms, and 3) “psychological therapy” and synonyms. The searches were part of a larger systematic search including terms related to depression, but these records were ignored for the present research question. All searches were confined to studies conducted in humans. No language restrictions were applied.

2.2 Screening and selection procedure

Identified records were discussed between the two study investigators and screened regarding the following inclusionary criteria: 1) children, adolescent or adult outpatients or inpatients primarily suffering from any anxiety disorder (i.e., separation anxiety disorder, specific phobia, social anxiety disorder, panic disorder and agoraphobia, generalised anxiety disorder, or adjustment disorder with anxiety) diagnosed according to DSM or ICD criteria, 2) any kind of pre-treatment cortisol assessment, and 3) psychological therapy (i.e., any treatment including at least one session of behavioural therapy, cognitive therapy, CBT, interpersonal therapy, psychodynamic therapy, or psychoanalysis delivered by a trained clinician) including a standardised post-treatment symptom measure. Studies looking at patients with obsessive-compulsive disorder and post-traumatic stress disorder were excluded. Comorbidity with these disorders, on the other hand, was not exclusionary, and neither was comorbidity with medical diseases or previous or current intake of medication, but this was recorded. Studies delivering a combination of psychological and pharmacotherapy were excluded. Full-text articles were retrieved and checked for relevant analyses. The reference sections of all articles were searched for additional records.

2.3 Data extraction

For each identified study one of the study investigators (SF) collected information about the first author, its year of publication, the number of treated patients, their sex and age, their primary diagnosis, eligibility criteria (e.g., comorbidity and medication), study design, type and intensity of psychological therapy, measurement of pre-treatment levels of cortisol, measurement of post-treatment symptoms of anxiety/fear and avoidance behaviour, and adjustment for covariates. For meta-analysis, either correlations between cortisol values and symptoms of anxiety/fear and avoidance behaviour upon completion of treatment (controlled for pre-treatment levels of the same symptoms), or correlations between cortisol values and change in symptoms (i.e., delta values) were extracted. When multiple cortisol measures were reported, we favoured hair, urinary and salivary cortisol over plasma cortisol. This was to obtain a measure of free (i.e., unbound cortisol, as found in these media) rather than total cortisol (Kirschbaum & Hellhammer, 1989). Moreover, we were interested in obtaining stable measures, which is why long-term (e.g. 3 cm hair cortisol) or aggregate indices (e.g. areas under the curve) were preferred over single time point assessments. Evening or afternoon measurements were to be extracted in preference to morning levels, as due to the diurnal rhythmicity of cortisol inter-individual variability is lower later in the day (Kirschbaum & Hellhammer, 1989). When multiple methods to stimulate cortisol secretion were used in the same study, results of the most frequently used method across studies were extracted to optimise comparability. When psychological therapy response was assessed at multiple time points, the assessment closest to the last therapy session was selected. Whenever studies used multiple post-treatment symptom measures (e.g., different questionnaires assessing anxiety), an average effect size was calculated and extracted. Risk of bias was assessed by means of an adapted version of a quality tool that was used in an earlier meta-analysis on the role of cortisol in functional somatic syndromes (Tak et al., 2011). We used eight of the original nine items (item two was excluded due to non-applicability) and scored them using the same three-point scale (0-2). An additional item regarding the duration (weeks) and frequency of psychological therapy (number of sessions) was added; if both were stated, the study obtained a score of 2, if duration or intensity was stated, it was given a score of 1, and a score of 0 was given to those not giving any information about either of these characteristics. The complete checklist can be found in Table 1. The maximum attainable quality score was 18.

Table 1 Quality tool to assess risk bias in studies investigating the relationship between pre-treatment cortisol levels and psychological therapy response in patients with anxiety disorders (modified from Tak et al., 2011)

1) Has the anxiety disorder been reliably assessed and validated?	<p>According to ICD-10, DSM-IV, or DSM-5 by a trained clinician (2)</p> <p>Not according to ICD-10, DSM-IV, or DSM-5 or assessor not clearly established (1)</p> <p>Self-report or not clearly stated (0)</p>
2) Is the psychological treatment sufficiently described?	<p>Both treatment duration and session frequency are reported (2)</p> <p>Only treatment duration or session frequency is reported (1)</p> <p>No information about treatment duration or session frequency are given (0)</p>
3) Are the patients defined with in- and exclusion criteria?	<p>Medication use, comorbidity with medical diseases, comorbidity with other mental disorders, 3 stated (2)</p> <p>Medication use, comorbidity with medical diseases, comorbidity with other mental disorders, 1-2 stated (1)</p> <p>None stated or not clearly stated (0)</p>
4) Are disorder characteristics presented (duration and severity)?	<p>Duration and severity of disorder are stated (2)</p> <p>Only duration or only severity is stated (1)</p> <p>None stated (0)</p>
5) Have the treating clinician and the person assessing treatment response been blind regarding pre-treatment cortisol levels?	<p>Yes (2)</p> <p>Not clearly stated (0)</p>
6) Are methods for measuring cortisol clearly stated?	<p>Time of day, behaviour shortly prior to assessment, storage conditions, type of assay performed, repeated measurements, assessing compliance, 5-6 stated (2)</p> <p>Time of day, behaviour shortly prior to assessment, storage conditions, type of assay performed, repeated measurements, assessing compliance, 3-4 stated (1)</p> <p>Time of day, behaviour shortly prior to assessment, storage conditions, type of assay performed, repeated measurements, assessing compliance, 1-2 or none stated (0)</p>
7) Are the relevant statistics clearly described and presented?	<p>Both correlation coefficient and sample size available, frequency table available, or mean value and standard deviation available (2)</p> <p>Only sample size available or only mean value available (1)</p>

	Relevant statistics not clearly stated (0)
8) Are potential confounders assessed? ^a	<p>Age, sex, body mass index, smoking, pre-treatment severity of anxiety/fear and avoidance behaviour, medication, physical exercise, 5-7 stated (2)</p> <p>Age, sex, body mass index, smoking, pre-treatment severity of anxiety/fear and avoidance behaviour, medication, physical exercise, 3-4 stated (1)</p> <p>Age, sex, body mass index, smoking, pre-treatment severity of anxiety/fear and avoidance behaviour, medication, physical exercise, 1-2 or none stated (0)</p>
9) Are the analyses adjusted for potential confounders? ^b	<p>Age, sex, body mass index, smoking, pre-treatment severity of anxiety/fear and avoidance behaviour, medication, physical exercise, 5-7 stated (2)</p> <p>Age, sex, body mass index, smoking, pre-treatment severity of anxiety/fear and avoidance behaviour, medication, physical exercise, 3-4 stated (1)</p> <p>Age, sex, body mass index, smoking, pre-treatment severity of anxiety/fear and avoidance behaviour, medication, physical exercise, 1-2 or none stated (0)</p>

^aIn case of exclusion at item 3, consider confounder as assessed

^bIn case of exclusion at item 3 or no significant impact on statistical analyses, consider confounder as adjusted for

2.4 Effect size calculation

To quantify the relationship between cortisol levels at baseline and psychological therapy response, correlation coefficients (r) were directly extracted by one of the study investigators (SF) or, if not available, calculated based on summary statistics. This was done in accordance with the procedures outlined by Lipsey and Wilson (Lipsey & Wilson, 2001). Whenever correlation coefficients (r) were directly extracted, we used either correlations between cortisol values and symptoms of anxiety/fear and avoidance behaviour upon completion of treatment (controlled for pre-treatment levels of the same symptoms), or correlations between cortisol values and change in symptoms (i.e., delta values). We extracted data that were adjusted for relevant covariates rather than unadjusted data whenever possible. In cases where no or insufficient statistical parameters were reported regarding our research question, the authors were contacted.

2.5 Statistical analysis

We calculated Fisher's Zr and 95% confidence intervals (CI) for each study and weighed studies based on their sample size (Lipsey & Wilson, 2001). Studies with an extreme ES (below or above two standard deviations) were to be excluded. Separate analyses for basal and stimulated cortisol measures were conducted. An aggregated ES including a 95% CI was calculated for each analysis, using SPSS 21 and the macros developed by David B. Wilson (<http://mason.gmu.edu/~dwilsonb/ma.html>). As significant statistical heterogeneity according to the Q and I^2 statistics was predicted in all analyses, random rather than fixed effects models were considered appropriate (DerSimonian & Laird, 1986). Sensitivity analyses were applied for studies with unclear eligibility. Publication bias was planned to be examined by visual inspection of funnel plots. In addition, Egger's test (Egger, Smith, Schneider, & Minder, 1997) and a trim and fill procedure (Duval & Tweedie, 2000) were to be used for quantification of publication bias.

3. Results

3.1 Search results

Our overall search yielded 25,991 records, of which 32 were considered potentially relevant for the present research question based on their title or abstract. Of these, 26 were excluded because they were not conducted in patients with anxiety disorders, did not assess cortisol levels, did not include any treatment, administered drugs as part of the treatment package, used specific interventions that did not meet our definition of psychological therapy (e.g., prayer), or did not report predictor analyses. With one study, patients and healthy controls or patients receiving different kinds of treatments had been collapsed for statistical analyses (Wedekind et al., 2008). As the data set of this study was not available, it was excluded. We undertook previously unreported analyses with one raw data set (Gaab, Jucker, Staub, & Ehlert, 2005) and obtained additional results from the authors of another study (Meuret et al., 2015). In total, six studies were eligible for data extraction.

3.2 Study characteristics

Table 2 shows the characteristics of all included studies, comprising 274 cases in total. One study focused on children and adolescents (Dierckx et al., 2012). The same study included patients with any kind of anxiety disorder, whereas the remaining studies either investigated panic disorder and agoraphobia (Meuret et al., 2015; Siegmund et al., 2011) or specific phobia (Brand, Annen, Holsboer-

Trachsler, & Blaser, 2011; Gaab et al., 2005; Lass-Hennemann & Michael, 2014). None of the studies pre-selected patients based on the severity of their illness. Comorbidity with other mental disorders was generally avoided, as was comorbidity with severe physical diseases. Patients on psychotropic medication were generally excluded; some underwent a washout period before treatment while others ensured that patients kept their intake stable over the course of psychological therapy. Diurnal salivary cortisol levels on non-treatment days were used as an indicator of basal HPA activity. Lass-Hennemann and Michael (2014), however, used the naturally occurring fluctuations of cortisol over the course of a day to study the impact of cortisol levels on therapeutic success. They split patients into two groups: the first group received treatment in the morning (higher cortisol) and the second group received treatment in the evening (lower cortisol). Studies obtained stimulated cortisol concentrations by means of repeated sampling during the first exposure session or the CAR. Of note, none of the studies found that exposure led to an overall increase in mean cortisol levels in the patient group as a whole. All patients were treated in an outpatient setting and received CBT and/or exposure therapy. Outcome measures were specific to each anxiety disorder, but usually covered both symptoms of anxiety/fear and avoidance behaviour.

Table 2 Characteristics of included studies on cortisol as a predictor of psychological therapy response in patients with anxiety disorders

Study	Sample	Setting and treatment	Pre-treatment cortisol measure	Post-treatment symptom measure	Findings	Quality assessment (0-18)
Gaab, 2005	<p>N = 16 (15f, 1m), mean age 26.3</p> <p>Inclusionary criteria: age 20-40, specific phobia, animal type (DSM-IV)</p> <p>Exclusionary criteria: mental disorder other than spider phobia, medical disease, cortisone medication, > 20 cigarettes/day, history of cognitive-behavioural therapy</p>	<p>Outpatient</p> <p>Non-randomised trial</p> <p>Three 90 minute exposure sessions (two days in between on average)</p>	<p>Saliva, baseline measure 30 min before exposure, subsequent measures every 15 min during exposure, non-exposure day measures at the same time points</p>	<p>Fear of Spider Questionnaire</p> <p>Mobility Inventory – modified version</p> <p>Spider Phobia Questionnaire</p>	<p>Mean non-exposure day cortisol levels were negatively associated with change in the Fear of Spider Questionnaire and in the Spider Phobia Questionnaire; there was no association with the Mobility Inventory</p> <p>Cortisol during the first exposure session did not significantly increase but cortisol output was positively associated with change in the Mobility Inventory. There was no association with either the Fear of Spider Questionnaire or the Spider Phobia Questionnaire</p>	11
Brand, 2011	<p>N = 46 (46m), mean age 19.5 (SD = 1.6)</p> <p>Inclusionary criteria: manifest anxiety about wearing a protective mask</p> <p>Exclusionary criteria: physically or mentally ill,</p>	<p>Outpatient</p> <p>Non-randomised trial</p> <p>Five to six hours of cognitive-behavioural group therapy</p>	<p>Saliva, awakening, +10, +20, +30 min, two baseline measures before exposure, subsequent measures during and immediately</p>	<p>Protective Mask Phobia</p>	<p>The cortisol awakening response was not associated with scores on the symptom measure (initial and final scores on the symptom measure were not correlated)</p> <p>It was not reported whether mean cortisol levels during the first exposure session significantly increased but they</p>	9

	intake of medication	on two consecutive days	after exposure		were not associated with scores on the symptom measure (initial and final scores on the symptom measure were not correlated)	
Siegmund, 2011	<p>N = 10 (6f, 4m), mean age 36.9 (SD = 9.7)</p> <p>Inclusionary criteria: diagnosis of panic disorder and agoraphobia (DSM-IV)</p> <p>Exclusionary criteria: severe other mental disorder, severe somatic disease, pregnancy, lactation, disturbed sleep-wake pattern, declining four weeks of washout and unstable on psychotropic medication within past eight weeks</p>	<p>Outpatient</p> <p>Non-randomised trial</p> <p>Eight 90 minute sessions of cognitive-behavioural group therapy for four weeks and three individual exposure sessions</p>	<p>Blood, two baseline measures before exposure, subsequent measures at maximum fear level and +5, +15, +30, +60 min</p>	<p>Panic and Agoraphobia Scale</p>	<p>Mean cortisol levels during the first exposure session did not significantly increase. They were negatively associated with scores on the symptom measure (controlled for pre-treatment symptom scores, excluding the 3 patients who were on antidepressants)</p>	11
Dierckx, 2012	<p>N = 116, age range: 8-16</p> <p>Inclusionary criteria: primary diagnosis of generalised anxiety disorder, separation anxiety disorder, social phobia, or specific phobia (DSM-IV)</p> <p>Exclusionary criteria:</p>	<p>Outpatient</p> <p>Non-randomised trial</p> <p>Ten child sessions of cognitive-behavioural therapy and four</p>	<p>Saliva, awakening, +30 min, 12 pm, 8 pm</p>	<p>Diagnosis according to the Anxiety Disorder Interview Schedule for DSM-IV – child version</p>	<p>Diurnal cortisol output did not differ between the 28 non-responders (phase 2), the 48 late responders (phase 2), and the 40 early responders (phase 1; groups did not differ in sex, age, or pre-treatment symptom scores)</p> <p>The cortisol awakening response did not differ between the 28 non-responders (phase 2), the 48 late</p>	12

	comorbid substance use, obsessive-compulsive disorder, post-traumatic stress disorder, pervasive development disorder, IQ < 85, current medication for any anxiety disorder, current corticoid medication	separate parent sessions (phase 1), ten supplementary sessions for children and parents together (phase 2)			responders (phase 2), and the 40 early responders (phase 1; groups did not differ in sex, age, or pre-treatment symptom scores)	
Lass-Hennemann, 2014	<p>N = 60 (60f)</p> <p>Inclusionary criteria: female, age 18-50, 25 ≥ BMI ≥ 20, using oral contraceptives, spider phobia (DSM-IV)</p> <p>Exclusionary criteria: any other axis I disorder, severe acute or chronic disease, allergic reaction to insect bites, recent history of cortisone therapy, smoking, pregnancy or lactation, current pharmacotherapy or psychological therapy</p>	<p>Outpatient</p> <p>Randomised trial</p> <p>One exposure session until all intervention steps were completed or up to three hours</p>	<p>Saliva, baseline measure immediately before exposure, subsequent measures every 30 min during exposure and immediately after exposure, 30 patients treated at 8 am and 30 patients treated at 6 pm</p>	<p>Behavioral Approach Test</p> <p>Fear of Spider Questionnaire</p>	<p>Cortisol did not significantly rise in response to exposure. The 30 morning patients had greater change in the Behavioral Approach Test when compared to the 30 evening patients; there were no between-group differences in the Fear of Spider Questionnaire (the groups did not differ in age, pre-treatment symptom scores or pre-treatment cortisol levels)</p>	13
Meuret, 2015	<p>N = 26 (23f, 3m), age 33.1 (SD = 9.1)</p> <p>Inclusionary criteria: age 18-65, principal diagnosis of panic disorder and</p>	<p>Outpatient</p> <p>Non-randomised trial</p> <p>Three weekly exposure</p>	<p>Saliva, awakening, +30 min, 60 min before exposure, immediately before entering the feared</p>	<p>Anxiety Control Scale</p> <p>Anxiety Sensitivity Index</p> <p>Body Sensations</p>	<p>The cortisol awakening response before the first exposure session was positively associated with change in the Anxiety Sensitivity Index, the Body Sensations Questionnaire, and the Anxiety Control Scale; there was no association with the Mobility Inventory</p>	9

agoraphobia (DSM-IV)	sessions plus one session after eight weeks	situation, +30 min, immediately after exposure, +30 min	Questionnaire Mobility Inventory for Agoraphobia	for Agoraphobia Cortisol did not significantly increase in response to exposure. Mean cortisol levels on exposure days were positively associated with change in the Anxiety Sensitivity Index and the Mobility Inventory for Agoraphobia; there was no association with the Anxiety Control Scale or the Body Sensations Questionnaire
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3.3 Risk assessment

Quality scores ranged from 9 to 13 out of 18 maximum points. In general, patient inclusionary and exclusionary criteria and the therapeutic interventions were described comprehensively. The reporting of the diagnostic procedures, duration of the illness, and blindness of the study personnel towards patients' cortisol levels, on the other hand, was often lacking detail or missing altogether. Studies varied in their extent of describing sampling procedures and biochemical analysis of cortisol, and in their handling of confounding variables, such as age or sex.

3.4 Systematic review and meta-analysis

A separate review and meta-analysis was conducted for basal and stimulated cortisol measures, respectively. Results regarding basal cortisol levels were mixed: One study found higher levels of cortisol to predict worse outcomes (Gaab et al., 2005), one study found the opposite (Lass-Hennemann & Michael, 2014), and one study did not find any such association at all (Dierckx et al., 2012). The first two studies looked at adult patients with arachnophobia, while the latter study used mixed anxiety disorders as present in a sample of children. The meta-analysis confirmed these conflicting findings: there was no statistically significant relationship between basal cortisol levels and response to psychological therapy as measured by either post-treatment symptom scores (controlled for pre-treatment scores) or symptom change (three independent ES, $n = 192$, mean ES = -0.003, 95% CI [-0.282, 0.289]; $Z = -0.024$, $p = .981$; see Figure 1 for forest plot). To exclude potential effects of stress anticipation on basal cortisol levels, we eliminated the Lass-Hennemann and Michael (2014) study that measured basal cortisol levels on the same day that the first exposure session took place. This did not change our results significantly (two independent ES, $n = 132$, mean ES = 0.152, 95% CI [-0.239, 0.501]; $Z = 0.757$, $p = .449$); and neither did excluding the Dierckx et al. (2012) study conducted in children (two independent ES, $n = 76$, mean ES = 0.069, 95% CI [-0.509, 0.604]; $Z = 0.215$, $p = .829$). The Q and I^2 statistics did not indicate significant heterogeneity among the basal cortisol studies ($Q = 4.81$, $p = .091$, $I^2 = 58.37\%$). However, the small study number precludes us from stating that heterogeneity was definitively absent and did not allow us to evaluate publication bias.

Figure 1 Forest plot of the three identified studies examining the association between basal cortisol levels pre-treatment and psychological therapy response in patients with anxiety disorders. Positive correlation coefficients mean that high pre-treatment levels of basal cortisol were associated with either higher scores on measures of anxiety/fear and avoidance behaviour post-treatment (controlled for pre-treatment scores) or with lower change scores (in the latter case, coefficients were inverted for illustrative purposes). The plot shows the correlation coefficients and 95% confidence intervals for each included study.

Regarding stimulated cortisol levels, two methods were used: repeated sampling over the course of the first exposure session and the CAR. Three out of four studies provided evidence for higher cortisol levels during exposure being linked to better psychological therapy responses (Gaab et al., 2005; Meuret et al., 2015; Siegmund et al., 2011). The first one was conducted in patients with arachnophobia and the latter two in patients with panic disorder and agoraphobia. The fourth study, which was the only one conducted in an exclusively male sample, did not confirm this (Brand et al., 2011). However, a positive effect of cortisol was again found in the Lass-Hennemann and Michael (2014) study that measured basal cortisol levels in arachnophobic patients on the same day the first exposure session took place. By contrast, a greater CAR was associated with worse outcomes (Meuret et al., 2015) or had no impact on treatment response at all (Brand et al., 2011; Dierckx et al., 2012). The meta-analysis showed that there was no statistically significant relationship between stimulated cortisol levels and response to psychological therapy in general (five independent ES, $n =$

203, mean ES = -0.025, 95% CI [-0.200, 0.151]; $Z = -0.277$, $p = .782$; see Figure 2 for forest plot). Findings remained insignificant when only including those studies that used exposure sessions as a means to stimulate and measure cortisol concentrations, which meant excluding the Dierckx et al. (2012) study (four independent ES, $n = 87$, mean ES = -0.074, 95% CI [-0.337, 0.201]; $Z = -0.521$, $p = .603$). Again, the Q and I^2 statistics did not indicate significant heterogeneity among the stimulated cortisol studies ($Q = 4.74$, $p = .342$; $I^2 = 11.31\%$).

Figure 2 Forest plot of the five identified studies examining the association between stimulated cortisol levels pre-treatment and psychological therapy response in patients with anxiety disorders. Positive correlation coefficients mean that high stimulated pre-treatment levels of cortisol were associated with either higher scores on measures of anxiety/fear and avoidance behaviour post-treatment (controlled for pre-treatment scores) or with lower change scores (in the latter case, coefficients were inverted for illustrative purposes). The plot shows the correlation coefficients and 95% confidence intervals for each included study.

4. Discussion

This systematic review and meta-analysis yielded two main findings. First, there was no relationship between anxious patients' basal cortisol levels and psychological therapy response. Second, there

was evidence from the systematic review for higher cortisol levels during the first exposure session to predict worse treatment outcomes. Subsequent meta-analysis did not confirm this.

The first finding is in contrast to our initial expectation that patients with anxiety disorders with higher cortisol levels would respond less favourably to psychological therapy. However, our hypothesis was based on evidence showing that panic disorder and agoraphobia (rather than anxiety disorders in general) is characterised by hypercortisolism (Elnazer & Baldwin, 2014); the studies included in this particular analysis mainly looked at phobias, which are under-researched in terms of HPA alterations. It is further noteworthy that the included patients likely presented with mild forms of their disorder. This is evident from the observation that no study used illness severity cut-offs as an eligibility criterion, the majority of patients were very young, barely suffered from any comorbidities with other mental disorders, and were exclusively treated in outpatient settings. It is conceivable that alterations in the HPA axis predict treatment response only in those patients with more severe, persistent or disabling illnesses, as has been noted in the case of major depressive disorder (Jurueña et al., 2009). Research concentrating on panic disorder and agoraphobia and on patients with protracted illness courses is warranted at this point to further test this hypothesis.

The second finding partly aligns with our a priori hypothesis stating that the higher patients' cortisol levels during stimulation, the better their subsequent treatment response. The systematic review indicated this to be true for values obtained during the first exposure session (three of four studies finding this) but not for the CAR. This is in concordance with studies that administered exogenous glucocorticoids one hour before exposing patients to feared situations and objects; doing so led to a significant decrease in fear symptoms in patients with social anxiety disorder, arachnophobia, and acrophobia (de Quervain et al., 2011; Soravia et al., 2006; Soravia et al., 2014). Our review complements and extends these findings by including patients with panic disorder and agoraphobia. Of note, similar to the studies by Soravia et al. (2006; 2014), in none of the studies included herein did mean cortisol levels increase significantly in response to the exposure sessions. One of the reasons for this could be that marked increases in cortisol are only evoked when an individual is confronted with social evaluation (Dickerson & Kemeny, 2004), whereas our patients were merely facing feared objects and non-evaluative social situations. Nevertheless, our review indicates that even marginally elevated cortisol levels during exposure may be beneficial in terms of achieving a good treatment response. Taken together, it is intriguing to speculate that endogenous cortisol aids

fear extinction by both suppressing the retrieval of aversive stimulus-related memories and enhancing the consolidation of extinction memories (Bentz et al., 2010). Importantly, our meta-analysis did not confirm the findings of our systematic review. Although this was possibly due to the small overall sample size in this particular sub-analysis, our reported findings need to be interpreted with caution and more independent studies with larger sample sizes are necessary before clinical implications can be discussed.

This is the first systematic review and meta-analysis on cortisol as a predictor of psychological therapy response in patients with anxiety disorders. While we believe it useful in terms of summarising the current state of research and pinpointing promising avenues for future research, several limitations need to be considered when interpreting our results. First, our extensive search yielded very few studies that matched the present research question. As a result of this, the results of the random-effects meta-analysis need to be interpreted with caution and the extent of publication bias remains unclear. Second, with several of the included studies, the information of whether the treating clinicians and assessors of treatment response were blind to the subjects' cortisol levels was missing. This aspect is of special importance in psychological therapy trials, where the therapist has substantial influence on the treatment outcome. However, as biochemical analyses are usually conducted in batches and after a study has been terminated, we believe it unlikely that this was a relevant factor in any of the included studies. Third, as with nearly every systematic review and meta-analysis, there was methodological heterogeneity across studies. For instance, the herein reviewed studies differ in the percentage of included men/women. This may have somewhat hampered their comparability, as it is well-known that cortisol levels differ between men and women (Miller et al., 2016; van Cauter, Leproult, & Kupfer, 1996). Unfortunately, the small number of studies prevented us from identifying and quantifying the study characteristics that may have been particularly relevant to the here reported findings. Meta-regression will allow investigation of this point this once further studies on the topic have been published.

5. Conclusion

In sum, our findings suggest that basal cortisol concentrations do not predict responses to psychological therapy in patients with relatively mild forms of anxiety disorders. By contrast, the current state of research is equivocal in terms of whether higher cortisol concentrations during

exposure sessions are linked with better treatment outcomes in patients with panic disorder and agoraphobia and in those with arachnophobia.

Several suggestions for future investigations into this topic can be deduced from this initial review of the literature. First, there is a need for data on the consequences of the frequently reported basal HPA alterations in panic disorder and agoraphobia in terms of psychological therapy success. Similarly, despite representing an integral part of treating generalised anxiety disorder, no studies have investigated whether cortisol concentrations during exposure are linked with outcomes in this group while this line of enquiry would clearly deserve more attention. Second, future researchers may be well-advised to use long-term measures of basal HPA axis functioning, such as hair or fingernail cortisol concentrations (Herane Vives et al., 2015), which are robust against the influence of state-like variables (e.g., time of day). Third, we believe it commendable for further studies to consider additional confounding factors, in particular illness severity and duration upon study entry and the blinding of study personnel towards individual patient cortisol values. Provided this research is affirmative of the evidence linking higher cortisol levels during exposure sessions to better outcomes, it may prove worthwhile to consider the use of naturally occurring fluctuations in cortisol levels or the administration of synthetic analogues as a means to increase therapeutic benefit in anxiety disorders.

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