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Increased HPA axis response to psychosocial stress in remitted depression is influenced by coping style

- Nina Höhne^{a,*}, Max Poidinger^a, Franziska Merz^a, Hildegard Pfister^a, Tanja Brückl^a,
 Petra Zimmermann^a, Manfred Uhr^a, Florian Holsboer^{a,b}, Marcus Ising^a
- ^a Max Planck Institute of Psychiatry, Kraepelinstr. 2–10, 80804 Munich, Germany
- b HolsboerMaschmeyer NeuroChemie, Munich, Germany

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ABSTRACT

The aim of the study was to examine the modulating effects of coping style on the response to psychosocial stress in remitted major depression (MD) and healthy controls. Thirty-three participants with a lifetime history of MD, who were in remission, and 32 age- and gender-matched healthy controls were recruited from a longitudinal-epidemiological study, in which the presence or absence of mental disorders was prospectively ascertained. Participants (aged 30–41 years) underwent two consecutive Trier Social Stress Tests (TSSTs). Subjects with a lifetime history of MD showed larger plasma ACTH and cortisol concentrations in response to both TSSTs, confirming a disturbed hypothalamic-pituitary-adrenal axis (HPA) axis regulation. Moreover, the MD group reported less positive, adaptive coping strategies and more negative, maladaptive strategies than the control group. The amount of negative coping predicted the size of the plasma cortisol response in the combined group. Our results demonstrate the importance of psychological coping strategies for the investigation of HPA axis response in depression.

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1. Introduction

In stress-related disorders such as major depression (MD), the regulation of the HPA axis is frequently disturbed (Holsboer, 2000; Ising et al., 2005; Raison & Miller, 2003). An elevated plasma cortisol response to neuroendocrine stimulation tests of the hypothalamicpituitary-adrenal (HPA) axis, like the combined dexamethasonesuppression/corticotrophin-releasing hormone stimulation test (dex/CRH test), has been consistently demonstrated in acute depression. In addition, the persistence of elevated cortisol in such tests is associated with a higher relapse risk and, thus, with a negative outcome prognosis (Appelhof et al., 2006; Aubry et al., 2007; Zobel, Yassouridis, Frieboes, & Holsboer, 1999; Zobel et al., 2001). Studies investigating the HPA axis response, during and following experimental psychosocial stress exposure such as the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993), reveal more inconsistent results when patients with MD and healthy controls are compared. A meta-analysis on the effects of seven laboratory stress studies concluded that patients with acute MD and healthy controls present similar baseline and stress cortisol, but MD patients had elevated cortisol during the recovery period

ACTH response, compared with depressed patients with a comorbid

(Burke, Davis, Otte, & Mohr, 2005). However, there were mixed results depending on the sample of depressed patients being inves-

tigated. Young, Lopez, Murphy-Weinberg, Watson, and Akil (2000)

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found elevated baseline plasma cortisol levels but normal cortisol reactivity to psychosocial stress exposure in acutely depressed patients, whereas, women with chronic MD had greater overall cortisol secretion, unlike male patients who showed a blunted peak response to psychosocial stress. In remitted depression, however, there are few studies with laboratory stress designs. A recent study found impaired habituation in subjects with remitted depression compared with healthy controls who reacted with lower cortisol response after subsequent stress exposure (Morris & Rao, 2014). Blunted HPA axis response has been described in remitted depression (Ahrens et al., 2008; Morris, Rao, Wang, & Garber, 2014), while another study reported diverging results depending on the gender of the subjects (Bagley, Weaver, & Buchanan, 2011). One further study could not find any alterations in HPA axis regulation in remitted depressed patients, compared with healthy controls (Lange et al., 2013). In addition to the distinction between acute, remitted or chronic MD, various comorbidities may underlie the conflicting results in these studies. Young, Abelson, and Cameron (2004) investigated depressed patients with and without comorbid anxiety disorders during an acute episode. They showed that patients with depression or anxiety disorder without comorbidities had lower

^{*} Corresponding author. Tel.: +49 8930622 567; fax: +49 8930622 544. E-mail address: nina_hoehne@mpipsykl.mpg.de (N. Höhne).

N. Höhne et al. / Biological Psychology xxx (2014) xxx-xxx

anxiety disorder. Such studies demonstrate the major importance of collecting diagnostic information about medical history precisely and, in addition, controlling for comorbid anxiety disorders when investigating depression-specific alterations of HPA axis regulation after experimental psychosocial stress exposure.

A further explanation for differences in HPA axis regulation in depression may be a varying availability of appropriate coping strategies in the stress situation. There is evidence that the ability to cope with daily stress affects the neuroendocrine stress response. For instance, healthy individuals who reacted with enhanced cortisol suppression in the dex/CRH test showed a more frequent use of avoidant coping strategies, compared with individuals in whom there was incomplete or moderate cortisol suppression (Hori et al., 2010). Biondi and Picardi (1999) observed avoidant coping strategies and denial in subjects with increased HPA activity, while reduced HPA axis reactivity was associated with active, goal-directed and problem-focused coping strategies. A longitudinal study revealed that factors related to coping styles, such as higher levels of dysfunctional attitudes or avoidant ways of dealing with stress, could predict the recurrence of major depression (Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006; ten Doesschate, Bockting, Koeter, Schene, & DELTA Study Group, 2010). Taken together, coping styles appear to modulate the HPA axis reaction to laboratory and real life stressors, and are associated with the outcome prognosis of major depression, presumably, by helping individuals to manage stressful situations and reduce distress.

The first aim of the present study was to identify alterations of HPA axis regulation in response to psychosocial stress in remitted depression. In order to evaluate the stress response at the level of the pituitary and the adrenal cortex, we measured ACTH and cortisol repeatedly, before and after the two TSSTs. Second, we determined habituation effects after repeated psychosocial stress as several studies describe a significant decrease of cortisol after repeated stress exposure (Gerra et al., 2001; Kirschbaum et al., 1995; Petrowski, Wintermann, & Siepmann, 2012; Schommer, Hellhammer, & Kirschbaum, 2003; Wüst, Federenko, van Rossum, Koper, & Hellhammer, 2005). All of these studies, however, were conducted with healthy subjects. Since MD patients are known to have a disturbed HPA axis regulation and a lack of appropriate coping strategies, we investigated if participants with a history of MD have an impaired stress habituation. Finally, we examined whether a specific way of coping with stress is associated with the HPA axis response to psychosocial stress. For example, while goaldirected, positive coping strategies might help the individual to handle the stressful situation and effect a positive impact on stresshormone regulation, negative, and potentially stress-increasing coping strategies might impair appropriate adaption, both during the stress test and in the recovery period.

To address these aims, we selected participants of a prospective epidemiological study with a lifetime history of MD, as well as healthy controls. To avoid confounding effects of acute depression and comorbidities, we included only depressed subjects who were in clinical remission for at least 6 months, who all had a negative lifetime history of anxiety disorders. Both groups underwent two consecutive laboratory psychosocial stress tests.

2. Method

2.1. Sample

A total of 65 subjects, aged 30–41 years (M = 34.31, SD = 3.42), recruited from participants of the Early Developmental Stages of Psychopathology (EDSP) study were available for the current analysis. The EDSP study is a longitudinal epidemiological study designed to investigate the prevalence, incidence, risk factors, comorbidity and course of mental disorders in a community sample of adolescents and young adults. The original EDSP sample was randomly drawn from the 1994 government registries of all residents aged 14–24 years in metropolitan Munich (Germany) and surrounding counties. At baseline, 3021 participants were interviewed (TO: 1995;

response rate: 71%). Since then, three follow-up investigations have been conducted covering an overall period of 10 years. Details of study design and objectives are presented elsewhere (Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonigg, Lachner, & Nelson, 1998; Zimmermann et al., 2011). The present study sample was selected on the basis of the EDSP diagnostic assessment, from which we aggregated diagnostic information on all four assessment points.

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The remitted MD group included participants with a lifetime diagnosis of MD, according to DSM-IV. They had to be in remission, that is, they had not fulfilled the diagnostic criteria for a major depression during the last 6 months. The exclusion criteria were a DSM-IV lifetime diagnosis of dysthymia, schizophrenia, substance use disorder, social phobia or blood injection phobia. As a control sample we recruited age- and gender-matched healthy controls with a negative history of any affective disorder, generalised anxiety disorder (GAD) or any other mental disorder mentioned within the exclusion criteria of the MD sample. In the analysis, we focused on depression-specific alterations of HPA axis regulation. Therefore, we selected only individuals without a lifetime history of anxiety disorders, including agoraphobia. panic disorder, obsessive compulsive disorder, post-traumatic stress disorder or any specific phobia, to avoid the possibility that comorbid anxiety disorders might confound the results of the stress tests (Veen et al., 2009; Young et al., 2004). We did not exclude GAD in the MD group due to the substantial diagnostic overlap between both disorders (Hettema, 2008; Zbozinek et al., 2012), Medical conditions known to influence the HPA axis activity were also excluded. Finally, 65 participants (33 MD, 32 controls) were enrolled. More detailed information on the selection of the study participants is provided in Supplementary material.

The study was approved by the local Ethics Committee of the Ludwig Maximilians University, Munich. All participants gave oral and written consent after being informed about the study procedure.

2.2. Measures

2.2.1. Diagnostic assessment

Eligible EDSP participants were invited by letter and contacted by telephone. If respondents gave their consent to participate and fulfilled inclusion criteria then they were invited for a diagnostic assessment with the computerised Munich version of the Composite International Diagnostic Interview (M-CIDI). The CIDI allows for the standardised assessment of symptoms, syndromes and diagnoses of DSM-IV disorders, as well as their onset, duration and severity (Wittchen & Pfister, 1997). The same interview was used in the EDSP study at all assessments. Trained interviewers conducted the interval version of the M-CIDI covering the period between the previous assessment and the current evaluation.

The presence of acute depression symptoms within the last 14 days was evaluated using the Beck Depression Inventory II (BDI) (Hautzinger, Keller, & Kühner, 2009). Participants were invited for the experimental part of the study if they did not exceed a BDI score of 14. Furthermore, they were asked to fill out self-rating questionnaires at home before the experimental study took place. The mean time between the diagnostic assessment and the experimental session was 13.92 days (SD 18.51).

2.2.2. Psychological assessment

Stress coping was evaluated using the 78 items version of the German Stress Coping Inventory (Stressverarbeitungsfragebogen, SVF78, Erdmann & Janke, 2008). The SVF78 defines coping as a dispositional construct measuring the individual reaction in response to the following general condition: "When I am disturbed, irritated or upset by something or someone...". The 78 items can be grouped into 13 subscales, each consisting of six statements. According to the results of factor analyses, subscales can be clustered into four categories. Three categories (POS1-POS3) can be assigned to "positive", goal-directed and/or potentially stress-reducing coping strategies, while one category (NEG) comprises "negative" $potentially\ stress-increasing\ strategies.\ The\ first\ positive\ category\ (POS1)\ is\ labelled$ devaluation/defence, including subscales of minimisation and denial of guilt. The second category (POS2) can be described as distraction from stressful situations and comprises the subscales of distraction and substitute gratification. The third category (POS3) labelled control comprises the subscales of situation control, response control and positive self-instructions. The category of negative strategies (NEG) contains the subscale escape, rumination, resignation and self-blame. The SVF78 shows excellent reliability (Cronbach α/split-half coefficients: POS1, .88/.91; POS2, .86/.85; POS3, .89/.92; NEG, .94/.96) for all subscales and categories (Ising, Weyers, Janke, & Erdmann, 2001).

2.2.3. Experimental procedure

The experimental part of the study included a test session with two consecutive TSSTs. Investigators and participants were blinded for the actual group assignment as to MD or healthy control subject, according to the M-CIDI diagnoses. The test session was scheduled in the afternoon from 1:15 p.m. to 5:15 p.m., when plasma cortisol concentrations are assumed to decrease due to circadian rhythmicity (Lightman et al., 2002). After arriving at the laboratory, subjects were asked for an urine sample to test for use of drugs known to interfere with stress hormone activity (e.g. benzodiazepines, amphetamines or cannabinoids) and they were each given a pulse watch (Polar® RS400) to wear, to record heart rates. A venous catheter was placed into the forearm vein (non-dominant side), at least 30 min prior to collection

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