



# Evidence for a normal HPA axis response to psychosocial stress in patients remitted from depression



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**Summary** The purpose of this study was to investigate subjective mood and the effect of a psychosocial stress challenge on cortisol response in patients remitted from depression in comparison to healthy controls. Only few studies on small samples have been conducted on the influence of psychosocial stress on HPA system responsivity in this group. Results regarding patients who have achieved clinical remission from depression remain inconclusive so far. In comparison to healthy controls, some studies found blunted cortisol responses to a psychological stressor in patients with remitted depression. However, others found no differences. This discrepancy may be due to use of heterogeneous stress measures or dissimilar sample sizes and characteristics, e.g. including patients with comorbid generalized anxiety or patients with an unknown duration of remission. The present study included 77 healthy controls and 70 unipolar depressed patients who had achieved stable, full remission for at least 6 months (average 31 months) with no further Axis I disorder. Participants underwent the Trier Social Stress Test and salivary cortisol levels and mood were assessed repeatedly during the experimental procedure. For both groups, we observed a marked cortisol response and worsening of mood after the stress challenge. However, no differences between formerly depressed patients and healthy participants were observed. Assuming a disturbed HPA system regulation in acute depression, we interpret these findings as evidence for a restored HPA axis function in fully remitted patients.

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## 1. Objective

A decisive part of our existence is to cope with stressful situations. Stress is the individual's physiological and psychological response to all possible kinds of demands (Selye, 1984). In response to stress, various adaptive responses are activated, including the hypothalamic-pituitary-adrenal axis (HPA axis) which is commonly studied as a physiological system that reacts to stress.

Preclinical and clinical data suggest that stress exposure plays a causal role in the etiology of depression (Nestler et al., 2002; de Kloet et al., 2005). Significantly elevated basal cortisol levels in the morning and evening have been found in clinically depressed patients compared to healthy controls (Knorr et al., 2010). In stress provocation tests, acutely depressed patients showed an increased pre-stressor plasma cortisol level (Young et al., 2000, 2004) and increased cortisol levels during the stress recovery period (i.e. the time following the stress exposure) (Burke et al., 2005). Corresponding to these altered cortisol responses to stress, acutely depressed patients' subjective reports and ratings revealed more intense and persisting negative emotional reactions to stress. Indeed, depressed patients are reported to describe life events in general as more stressful and more unpleasant than healthy controls (Bylsma et al., 2011). Negative feelings toward aversive events have also been found to persist for longer in acutely depressed patients, and correlate positively with the duration of the depressive episode (Peeters et al., 2003).

While studies in acutely depressed patients indicate alterations in stress responses, it is not clear whether these alterations persist after remission. Behavioral studies focusing on the subjective experience of participants point toward the endurance of these alterations: remitted patients performing the Trier Social Stress Test (TSST) have been reported to describe more negative affect both before and after an exposure to stress compared to healthy controls (Bagley et al., 2011). In line with this, Dettenborn et al. (2012) found evidence of elevated hair cortisol concentrations at the onset of an acute episode suggesting that HPA dysregulation may be present for months prior to the onset of an episode (Dettenborn et al., 2012). HPA axis dysregulation seems to be also associated with an increased risk of relapse, even if patients have reached clinical remission (Zobel et al., 1999, 2001), which suggests a link between neuroendocrine abnormalities and the recurrence of depressive episodes.

A question arises as to whether HPA axis dysregulation can generally be found in patients in remission or whether such dysregulation might be present in remitted patients only immediately prior to or after acute episodes. Relatively few studies have investigated HPA axis function in remission using stress provocation tests, and thus far, the findings are inconsistent: Some found reduced cortisol responses in remitted patients during social stress tests (Trestman et al., 1991; Brown, 2001; Ahrens et al., 2008; Morris et al., 2013), while others observed no difference between remitted patients and healthy controls in general in this respect but a reduced cortisol response in previously depressed women compared to men with a history of MDD (Bagley et al., 2011). Inconsistencies between the described studies may be due to design and sampling factors such as heterogeneous sample characteristics, small sample size,

varying durations of patient remission, and the use of different measures of stress.

In the present study, we therefore investigated stress responsivity in formerly depressed individuals using a psychosocial stress test – the TSST. Using the TSST, stress responsivity was tested both at a behavioral (subjective reports on current mood) and hormonal (cortisol responses) level. In order to avoid confounding effects of recent acute depressive episodes, only outpatients who were fully remitted from unipolar depression for at least 6 months (average of 31 months) were included. Patients did not have any comorbid Axis I diagnoses, including anxiety disorders. The aforementioned criteria allowed us to address whether both subjectively reported negative emotional responses and abnormal cortisol responses (indicating persistent HPA system dysfunction) would occur in response to the TSST for those patients in stable remission from depression.

## 2. Methods and materials

70 patients remitted from depression (37 females, 33 males) and 79 group-matched healthy volunteers (38 females, 39 males) participated in the present case–control study (Table 1). Participants were recruited by advertisements in the community via local newspapers and the Internet. The remitted patients had a history of a previous major depressive episode diagnosed by the patients' clinical psychiatrist (according to DSM-IV) and had to be in full remission for at least 6 months. A Hamilton Depression Score (HAMD-17) less than 7 and a Becks Depression Inventory (BDI) score less than 10 at the time of the experiment was mandatory for all participants. Patients were excluded if suffering from endocrine, cardiovascular, or other chronic diseases, thyroid disease, those having an intake of benzodiazepines on the test day, and those with Axis I disorders other than major depression.

The TSST was consistently conducted between 14 h and 17 h in order to avoid circadian effects on baseline cortisol levels (Kudielka et al., 2004).

Prior to the experimental session, we performed a detailed telephone interview to screen about the diagnostic history of major depression of the participants, which was in a 2nd step followed by an analysis of clinical records (where possible) and the evaluation of the patient's self-report. After arrival at the laboratory at 14 h on the testing day, all participants provided their written informed consent.

A member of the research staff with formal training in the administration of diagnostic interviews then conducted the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) to confirm the diagnosis of unipolar depression and to exclude patients with comorbid diagnoses. Additionally, the member of the research staff performed the HAMD-17 (Hamilton 1960) and collected further socio-demographic information (such as marital status, number of children, and occupation).

Then, participants rested for another 20 min. At approx. 1520 h participants were taken to a separate room where a two-person evaluating panel was awaiting them behind a desk (Kirschbaum et al., 1993b). The TSST is generally a public speaking task followed by a mental arithmetic task in front of an evaluating panel of judges (Kirschbaum et al.,

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