

# The Munich vulnerability study on affective disorders: premorbid neuroendocrine profile of affected high-risk probands

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Received 29 September 2003; received in revised form 2 March 2004; accepted 19 April 2004

## Abstract

One of the most characteristic alterations in depression is a disturbed regulation of the hypothalamic-pituitary-adrenocortical (HPA) system. A function test combining the pre-treatment of 1.5 mg dexamethasone (DEX) with a challenge of 100 µg corticotropin-releasing hormone (CRH) reveals a pathological increase in the adrenocorticotropin and cortisol release in patients with major depression. These changes partially persist after successful treatment with remission and therefore, might represent trait or vulnerability markers. To further address this question, we were investigating the premorbid neuroendocrine profile of 74 healthy high-risk probands (HRPs) with a positive family history for affective disorders. The aim was to identify premorbid vulnerability factors. During the observation period, 19 HRPs developed an affective disorder. Their premorbid DEX/CRH test results were compared with 19 age- and sex matched controls. No significant differences could be observed between these two groups. Our results suggest that a dysregulated HPA system indicated by this function test can rather be regarded as a neurobiological scar developing during the course of affective disorders.

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**Keywords:** Affective disorders; Vulnerability; Dexamethasone/CRH test; Neuroendocrinology

## 1. Introduction

During a depressive episode a dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis is one of the most prominent neurobiological findings. Cortisol and adrenocorticotropin (ACTH) secretion are increased, corticotropin-releasing hormone (CRH) is elevated in the cerebrospinal fluid, and the cortisol secretion after dexamethasone (DEX) is insufficiently suppressed (for review, see Holsboer, 2000), a fact that has been widely used in the DEX-suppression test (DST). To increase sensitivity the DST has been combined with a CRH challenge (Heuser et al., 1994). In this DEX/CRH test patients with major depression show a dose-dependent increased cortisol and ACTH release, suggesting an impaired negative feed-back mechanism

by a decreased corticosteroid receptor function (Modell et al., 1997).

After a successful treatment with antidepressants a blunting of ACTH-response and a normalisation of elevated CRH in the cerebrospinal fluid have been reported (De Bellis et al., 1993; Heuser et al., 1996). However, not all patients show this normalisation. Therefore, the DEX/CRH test has also been used to monitor the antidepressant therapy, and patients that show an elevated cortisol response at discharge from hospital have a 4- to 6-fold higher risk for relapse than individuals with a normal response (Zobel et al., 2001) at that time point.

This leads to the assumption that the dysregulation of the HPA-system found in depression might also represent a neurobiological vulnerability marker for these disorders. Since all the above mentioned studies have been performed after the onset of the disorder, it cannot be ruled out that these changes represent only state markers or biological scars due to neuroadaptive mechanisms.

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Addressing this question, we initiated the so-called “Munich vulnerability study on affective disorders” in 1988. In this study, we applied a prospective high-risk design and investigated healthy probands with a high genetic load for affective disorders due to a positive family history of the disease. The aim was to identify premorbid vulnerability factors.

At the index investigation, we found an increased cortisol secretion in the DEX/CRH test in high-risk probands (HRPs) compared to controls. The ACTH response did not differ between HRPs and controls. Thirty-two percent of these HRPs had a hormonal pattern that was indistinguishable from those of depressed patients (Holsboer et al., 1995). In a follow-up investigation about 4 years later, these DEX/CRH test results remained surprisingly stable over time, at the group level as well as at the individual level, (Modell et al., 1998) so that one of the criteria for a neurobiological vulnerability marker is fulfilled.

The most important requirement is, however, whether a premorbidly dysregulated HPA-axis indeed predicts the onset of the disorder. In the present analysis, we were able to test this hypothesis since 19 subjects out of our initial sample of 74 HRPs have developed an affective disorder during the follow-up period until now.

## 2. Methods

### 2.1. Subjects

During the first (1988–1992) and second recruitment period (1994–1998), a total number of 740 consecutively admitted inpatients with a diagnosis of major depression, bipolar disorder, or “bipolar II” disorder (bipolar disorder not otherwise specified) were screened to identify those patients who had (1) at least one first-degree relative with an affective disorder or schizophrenia, and (2) at least one first-degree relative who did not have any current or lifetime DSM-III-R diagnosis of a psychiatric disorder including alcoholism and substance abuse. The latter relative was determined as our HRP. All diagnoses were verified by the Structured Clinical Interview for DSM-III-R (German version, Wittchen et al., 1990). Serious medical illness was ruled out by a thorough medical examination and laboratory tests (including electrocardiogram, blood analysis and urinary screening for drugs, e.g. amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates). The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study protocol had been approved by the local ethics committee and probands gave a written informed consent after the nature of the procedures had been fully explained. More details of the general selection procedure are given elsewhere (Holsboer et al., 1995).

Out of the 740 screened patients 136 fulfilled the inclusion criteria; 50 of them agreed to participate and allowed contact with relatives. Out of this group of 101 HRPs, 82 subjects took part in the investigation (see Fig. 1). Three families provided four HRPs each, four families three HRPs, 15 families two HRPs, and 28 families one HRP. The respective diagnoses of the index patients and of the second affected family members were bipolar disorder (index patients:  $n = 17$ ; second affected family members:  $n = 4$ ), major depression, recurrent episode ( $n = 23$ ;  $n = 27$ ), and major depression, single episode ( $n = 10$ ;  $n = 14$ ). Four second affected family members suffered from schizophrenia and a further second affected family member from schizoaffective disorder. Twenty-three HRPs had an affected mother and 22 an affected father as index patient; 11 HRPs were brothers and 26 sisters of the index patient.

Combined DEX/CRH tests were available in a total sample of 74 HRPs. Since the index investigation we stayed in contact with most of the HRPs. Until now, 19 of the initially 74 HRPs developed a psychiatric disorder between 6 months and 10 years after the initial neuroendocrine assessment. The diagnoses were confirmed by the SCID I structured clinical interview. The exact diagnoses, age at onset and elapsed time until onset of the disorder of the affected HRPs are listed in Table 1.

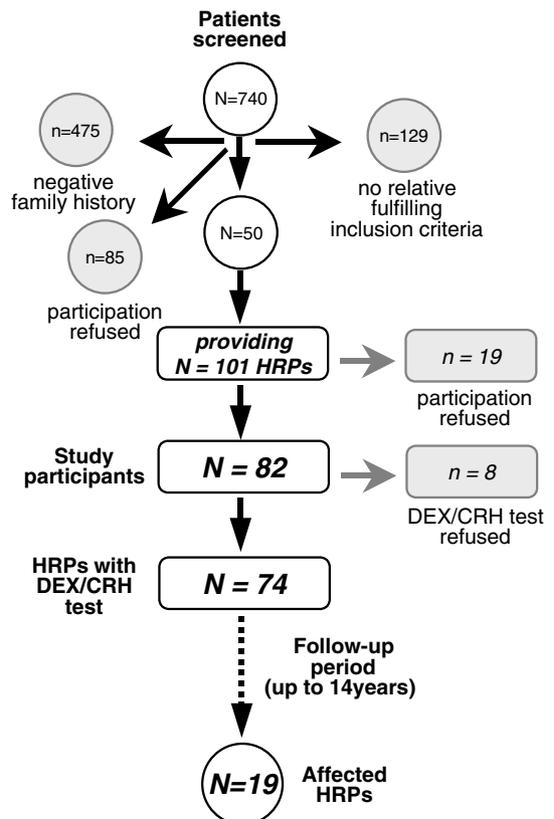


Fig. 1. Study design.

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