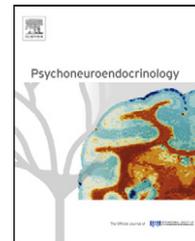




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# Longitudinal hypothalamic–pituitary–adrenal axis trait and state effects in recurrent depression

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## KEYWORDS

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Cognitive therapy

## Summary

**Background:** Hypothalamic–pituitary–adrenal (HPA)-axis hyperactivity has been observed in (recurrent) major depressive disorder (MDD), although inconsistently and mainly cross-sectional. Longitudinal studies clarifying state-trait issues are lacking. We aimed to determine whether HPA-axis (hyper)activity in recurrent MDD is: (I) reflecting a persistent trait; (II) influenced by depressive state; (III) associated with stress or previous episodes; (IV) associated with recurrence; and (V) influenced by cognitive therapy.

**Methods:** We included 187 remitted highly recurrent MDD-patients (mean number of previous episodes: 6.3), participating in a randomized-controlled-trial investigating the preventive effect of additional cognitive therapy on recurrence. In an add-on two-staged patient-control and prospective-cohort design, we first cross-sectionally compared patients' salivary morning and evening cortisol concentrations with 72 age- and sex-matched controls, and subsequently longitudinally followed-up the patients with repeated measures after three months and two years.

**Results:** Patients had higher cortisol concentrations than controls ( $p < .001$ ), which did not change by MDD-episodes during follow-up. HPA-axis activity had no relation with daily hassles or childhood life events. Cortisol concentrations were lower in patients with more previous episodes ( $p = .047$ ), but not associated with recurrence(s) during follow-up. Finally, randomly assigned cognitive therapy at study-entry enhanced cortisol declines over the day throughout the two-year follow-up ( $p = .052$ ).

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*Conclusions:* Our results indicate that remitted recurrent MDD-patients have a persistent trait of increased cortisol concentrations, irrespective of stress. In combination with our finding that patients' cortisol concentrations do not change during new MDD-episodes (and thus not represent epiphenomenal or state-effects), our results support that hypercortisolemia fulfills the state-independence criterion for an endophenotype for recurrent depression.

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## 1. Introduction

Hypothalamic–pituitary–adrenal (HPA)-axis research in major depressive disorder (MDD) has been predominantly cross-sectional in nature, comparing patients in a depressed state with healthy controls (Gold et al., 1986). Observations of hypersecretion of corticotrophin releasing hormone (Holsboer, 2000) and cortisol (Vreeburg et al., 2009a; Knorr et al., 2010), reduced feedback from glucocorticoids (Pariante and Miller, 2001), and enlarged endocrine glands (Rubin et al., 1995), resulted in a general consensus of an HPA-axis overdrive in patients with more severe forms of MDD (Stetler and Miller, 2011). However there were also conflicting data; (I) some studies observed no elevated or even lowered cortisol concentrations in MDD-patients compared with controls (Strickland et al., 2002; Ahrens et al., 2008; Carpenter et al., 2009); (II) glucocorticoid treatment and diseases with higher (e.g. Cushing's), but also lower cortisol concentrations (e.g. Addison's; posttraumatic stress disorder) are both associated with MDD (Oquendo et al., 2003; Starckmann, 2003; Wolkowitz et al., 2009); and (III) treatments with glucocorticoid receptor agonists as well as antagonists have both been proposed anti-depressogenic (Pariante, 2009).

In addition, it has been increasingly recognized that MDD is a chronic recurrent disorder. Indicatively, at least 80% of clinically recovered MDD-patients will experience a recurrence during 25-years follow-up (Bhagwagar and Cowen, 2008). With, on average, five subsequent major depressive episodes (MDEs), the recurrent nature of MDD is a severe burden to patients, families and societies (Greden, 2001; Bockting et al., 2006; Bhagwagar and Cowen, 2008). The predominant cross-sectional studies could not address the association of HPA-axis disturbances with this recurrent course of MDD. More recently, longitudinal studies investigated HPA-axis activity preceding, and subsequent to, the depressed state. For example, HPA-axis hyperactivity was also observed in remitted MDD-patients (Bhagwagar et al., 2003; Vreeburg et al., 2009a), although others found no differences or even hypoactivity (Van Den Eede et al., 2006; Ahrens et al., 2008). In addition, during transition from an acute depressive state to remission, sustained HPA-axis hyperactivity predicted recurrence during follow-up (Zobel et al., 2001; Appelhof et al., 2006). Likewise, higher cortisol concentrations in adolescents prospectively determined MDD onset during follow-up (Goodyer et al., 2000).

Taken together these findings raise the question whether abnormal HPA-axis activity in MDD-patients reflects a state only during MDEs, and/or represents a persistent trait. This question is not merely of academic importance. For example, if HPA-axis abnormalities show to be state-dependent, these abnormalities could mediate some of the MDE-symptoms and scarring effects. Proven true, treatment during a MDE directed at normalizing HPA-axis activity could reduce these

symptoms and prevent scarring. On the other hand, if HPA-axis abnormalities show to be a trait, they could be involved in the pathogenesis of a new or recurrent MDE. If so, preventive treatment directed at normalizing HPA-axis activity could be indicated (Pariante, 2009). For example, cognitive therapy could be a promising candidate as it was shown to protect against recurrences (Bockting et al., 2005) and to normalize HPA-axis activity (Hsiao et al., 2011).

Besides these clinical aspects of the state-trait discussion, it also poses pathogenetic issues. If HPA-axis abnormalities show to be state-dependent, they might be the consequence of epiphenomenal effects of depressive symptoms or accompanying daily hassles. On the contrary, if HPA-axis abnormalities show to be a trait, they might be the consequence of traumatizing childhood life-events (CLEs) (Heim et al., 2001), scarring-effects of previous MDEs (Kendler et al., 2000) and/or perinatal programming (Matthews, 2002), but could also be genetically regulated (endophenotype) (Hasler et al., 2004). This latter hypothesis is strengthened by previous research showing evidence that fulfilled the following endophenotype criteria: familial association (Mannie et al., 2007), cosegregation (Holsboer et al., 1995), and heritability (Bartels et al., 2003). However, the endophenotype state-independence criterion, i.e. "manifests in an individual whether or not illness is active" (Gottesman and Gould, 2003), has, to our knowledge, not yet been addressed for HPA-axis activity in MDD.

To further clarify these state-trait issues, we performed a longitudinal study to assess HPA-axis activity over time in highly recurrent MDD-patients. At study entry all patients were in remission, and compared with a matched control group. Subsequently, the patients were followed-up prospectively at three months and two years, while MDD-recurrence and HPA-axis activity were monitored.

We hypothesized that in patients with recurrent MDD HPA-axis hyperactivity: (I) reflects a trait, i.e. remitted patients exhibit higher cortisol concentrations compared with controls; (II) is additionally influenced by depressive state (i.e. more outspoken HPA-axis abnormalities during a recurrent MDE at follow-up); (III) is associated with (a) current daily hassles, (b) CLEs, and (c) number of previous MDEs. Furthermore, we hypothesized that: (IV) cortisol concentrations are higher in patients who experience recurrence(s), compared with patients who remain in remission during the entire follow-up period; and finally that (V) preventive cognitive therapy normalizes heightened HPA-axis activity.

## 2. Methods and materials

### 2.1. Design

The patient sample used in this study was recruited at psychiatric centers and through media announcements to

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