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Salivary cortisol levels and the 2-year course of depressive and anxiety disorders

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Summary
Introduction: Depression and anxiety disorders have been associated with hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis. However, lower cortisol levels have also been observed in depressed patients. Whether cortisol level predicts the course of these disorders has not been examined in detail. We examined whether salivary cortisol indicators predict the 2-year course of depression and anxiety disorders.
Methods: Longitudinal data are obtained from 837 participants of the Netherlands Study of Depression and Anxiety, with a DSM-IV based depressive and/or anxiety disorder at baseline. At baseline, seven saliva samples were obtained, including the 1-h cortisol awakening response, evening cortisol level and a 0.5 mg dexamethasone suppression test. At follow-up, DSM-IV based diagnostic interviews and Life Chart Interview integrating diagnostic and symptom trajectories over 2 years were administered to determine an unfavorable course.
Results: 41.5% of the respondents had a 2-year unfavorable course trajectory without remission longer than 3 months. Adjusted analyses showed that a lower awakening response was associated with an unfavorable course (RR = 0.83, $p = 0.03$). No associations were found between evening cortisol or cortisol suppression after dexamethasone ingestion and an unfavorable course trajectory.
Conclusions: Among patients with depressive or anxiety disorders, a lower cortisol awakening response — which may be indicative of underlying exhaustion of the HPA axis — predicted an unfavorable course trajectory.

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1. Introduction

Depressive and anxiety disorders are prevalent and disabling disorders. The burden is partly due to their course, often chronic or recurrent. In addition, comorbidity of depression and anxiety disorder frequently occurs (Kessler et al., 1996) and is related to an even poorer outcome (Merikangas et al., 2003; Penninx et al., 2011). However, little is known about predictors of the course of these disorders, while such knowledge would greatly improve our understanding of these diseases or could lead to identification of risk groups. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation is believed to play an important role in the pathophysiology of depressive and — to a lesser extent — anxiety disorders. Mostly, hyperactivity of the HPA axis has been observed, as reflected by elevated cortisol levels, in addition to less suppression of cortisol after a dexamethasone suppression test (DST) or Dexamethasone/Corticotropin Releasing Hormone (Dex/CRH) test for depression (Modell et al., 1997; Bhagwagar et al., 2005; Vreeburg et al., 2009a) or panic disorder (Abelson et al., 2007). However, there also appears to be a group of patients showing hypocortisolism (Oldehinkel et al., 2001; Bremmer et al., 2007; Penninx et al., 2007), possibly a sign of exhaustion of the HPA axis, after chronic and recurrent depressive episodes (Oldehinkel et al., 2001; Bremmer et al., 2007). Salivary cortisol measures are increasingly used, since they reflect unbound, active cortisol, and their collection is minimally intrusive (Kirschbaum and Hellhammer, 1989). The cortisol awakening response reflects the natural response of the HPA axis on awakening (Fries et al., 2009), which represents a distinct feature of the HPA axis and has received increasing interest as a promising biomarker in the previous years (Clow et al., 2010). Evening levels reflect basal activity, and the DST provides information on the negative feedback system (Carroll et al., 1981). Using these measures, we observed that persons with a remitted or current Major Depressive Disorder (MDD) showed a higher cortisol awakening curve (Vreeburg et al., 2009a), as did persons with a current Panic Disorder with agoraphobia (Vreeburg et al., 2010b). Persons with other anxiety disorders e.g. social phobia, generalized anxiety disorder and panic disorder without agoraphobia did not show different cortisol levels as compared to controls.

Although cross-sectional associations have been established, it remains largely unclear whether HPA-axis dysregulation predicts the course of depression and anxiety disorders. Longitudinal studies investigating such temporal associations are important, since they learn us more about the underlying interaction of HPA-axis dysregulation and depression and anxiety disorders. In addition, they provide insights into the clinical implications of HPA-axis dysregulation as they may point out whether hypo- and or hyperactivity of the HPA-axis does identify patients with a more unfavorable course trajectory e.g. due to HPA-axis dysregulation negatively impacting mood recovery processes or limiting treatment efficacy. There is some evidence that increased cortisol responses to the Dex/CRH test or DST predict relapse in remitted outpatients with depressive disorder (Ribeiro et al., 1993; Appelhof et al., 2006; Aubry et al., 2007; Pintor et al., 2009), panic disorder (Coryell et al., 1989), or in depressed inpatients (Zobel et al., 1999; Ising et al., 2007). Baseline salivary cortisol, cortisol responses on the DST or Dex/CRH test, however, were not related to the treatment response or outcome of depression or panic disorder (Coryell and Noyes, 1988; Ribeiro et al., 1993; Hatzinger et al., 2002; Schule et al., 2003; Brouwer et al., 2006; Papakostas et al., 2010). However, for panic disorder, abnormal DST results (Coryell et al., 1991) or elevated 24-h cortisol levels (Abelson and Curtis, 1996) were also associated with more anxiety, phobias and disability 2—4 years later.

Overall, the above described studies do provide some inconsistent indications that HPA-axis activity may predict the course trajectory of depression and anxiety disorders. Several of these studies were rather small-scaled and not always checked whether the predicting value of HPA-axis indicators is due to or independent of correlated clinical characteristics, such as baseline symptom severity. Large-scale longitudinal studies examining the role of HPA-axis indicators in the naturalistic course trajectory of patients with a current depressive or anxiety disorder remain to be conducted. This study examines whether various salivary cortisol measures (cortisol awakening response, evening level and suppression after dexamethasone ingestion) predict the 2-year course trajectory in 837 subjects with baseline depression or anxiety disorders, correcting for detailed demographic and clinical covariates.

2. Methods

2.1. Study sample

Data are from the Netherlands Study of Depression and Anxiety (NESDA), a large cohort study on the course of depressive and anxiety disorders among 2981 adults (18—65 years). Respondents were recruited from the community, in primary care through a screening procedure conducted among 65 general practitioners, and in specialized mental health care when newly enrolled at one of the 17 participating mental health organization locations. The overall study sample included persons with psychopathology as well as controls without a psychiatric diagnosis. General exclusion criteria — determined through physicians' records as well as through screening questions to the respondents during the screening phone interview — were: a primary diagnosis of psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder and not being fluent in Dutch. For objectives and methods of NESDA see Penninx et al. (2008) The research protocol was approved by the Ethical Committee of participating universities and all respondents provided written informed consent.

Baseline data were obtained from September 2004 to February 2007. After 2 years (October 2006 to April 2009), a face-to-face follow-up assessment was conducted with a response of 87.1% (2596 of the 2981 respondents participated). Non-response was significantly higher among those with younger age, lower educational level, non-North European ancestry and those with major depressive disorder, but was not associated with sex or the presence of anxiety disorder (Lamers et al., 2012).

The presence of depressive (Major Depressive Disorder, Dysthymia) or anxiety (Panic Disorder, Social Phobia, Generalized Anxiety Disorder, Agoraphobia) disorders was