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Increased cortisol awakening response was associated with time to recurrence of major depressive disorder

Florian Hardeveld[a,*], Jan Spijker[a,b,c], Sophie A. Vreeburg[d], Ron De Graaf[b], Sanne M. Hendriks[a], Carmilla M.M. Licht[d], Willem A. Nolen[e], Brenda W.J.H. Penninx[d], Aartjan T.F. Beekman[d]

[a] *Pro Persona, Institute for Mental Health Care, P.O. Box 70, 6710 RR Ede, The Netherlands*
[b] *Netherlands Institute of Mental Health and Addiction, P.O. Box 725, 3500 AS Utrecht, The Netherlands*
[c] *Behavioral Science Institute, Radboud University Nijmegen, P.O. Box 9104, 6500 HE Nijmegen, The Netherlands*
[d] *Department of Psychiatry/EMGO Institute for Health and Care/Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands*
[e] *Department of Psychiatry, University Medical Center Groningen, University of Groningen, P.O. Box 72, 9700 AB Groningen, The Netherlands*

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Summary
Introduction: Although HPA-axis activity has been studied extensively in relation to depression, there is no consensus whether HPA-axis parameters predicts major depressive disorder (MDD) recurrence. We investigated whether HPA-axis parameters (cortisol awakening response (CAR), the dexamethasone suppression test (DST) and evening cortisol) predict time to recurrence in remitted subjects with a history of MDD and whether childhood trauma and life events interact with HPA-axis parameters in increasing the risk for recurrence.
Method: Data were derived from 549 subjects with a lifetime diagnosis of MDD in remission for at least six months preceding the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA). Subjects were followed up with two interviews over the course of four years to assess recurrence. DSM-IV based diagnostic interviews were used to assess time to recurrence of MDD. Seven salivary cortisol samples collected at baseline with information on CAR, evening cortisol and the DST. Hazard ratios were calculated using Cox regression analysis, adjusted for covariates.

* Corresponding author at: Pro Persona, P.O. Box 70, 6710 RR Ede, The Netherlands. Tel.: +31 318433400; fax: +31 318433614.
E-mail address: f.hardeveld@propersona.nl (F. Hardeveld).

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Results: A higher CAR was associated with time to recurrence of MDD (HR = 1.03, 95%CI 1.003—1.060, $p = 0.03$) whereas evening cortisol and DST were not. No interactions between HPA-axis parameters and stress-related factors were found.
Conclusions: Our data support previous studies reporting that subjects with a higher CAR are more vulnerable to recurrence of MDD.

1. Introduction

Major depressive disorder (MDD) is often a chronic or recurrent disorder (Judd, 1997) and is one of the most disabling disorders worldwide (World Health Organization, 2008). Prevention of recurrence is therefore an important goal in the management of major depression. To that end, further knowledge on pathogenic mechanisms underlying recurrence of major depression is needed. The hypothalamic pituitary adrenal (HPA) axis is one of the main neuroendocrine systems activated under stress. Hyperactivity of the HPA-axis among depressed patients is a rather consistent research finding (Stetler and Miller, 2011) and alterations of the HPA-axis generally normalizes after full remission of depressive symptoms (Holsboer, 2000; Kaestner et al., 2005; Aihara et al., 2007; Pariante, 2009; McKay and Zakzanis, 2010). However, inconsistent findings have been observed (Bhagwagar et al., 2003; Mannie et al., 2007; Vreeburg et al., 2009b; Lok et al., 2012). Hyperactivity of the HPA-axis often results in hypercortisolism, which is associated with the pathophysiological pathway leading to MDD known as the glucocorticoid cascade hypothesis (Holsboer, 2000). A number of alterations in the HPA-axis found in major depression indicate hyperactivity of the HPA-axis. These are (i) hypercortisolism, resulting in a high evening cortisol (Kirschbaum and Hellhammer, 1989), (ii) an impaired circadian rhythm in terms of cortisol secretion in the first hour after awakening as reflected by an elevated cortisol awakening response (CAR) (Pruessner et al., 1997; Clow et al., 2010), (iii) a reduced negative feedback response to a dexamethasone suppression test (DST) (Ribeiro et al., 1993) and (iv) increased release of adrenocorticotrophic hormone (ACTH) and cortisol in response to corticotrophin-releasing hormone (CRH) after administration of 1.5 mg of dexamethasone, known as the combined dexamethasone/corticotrophin releasing hormone test (DEX/CRH test; Nemeroff, 1996; Holsboer, 2000).

Although HPA-axis activity has been studied extensively in relation to depression (Stetler and Miller, 2011), there is no consensus on whether HPA-axis parameters have predictive value for recurrence of MDD. HPA-axis alterations may represent an underlying active disease process in depression and may predict risk for recurrence. Although a number of studies have examined this issue (Ribeiro et al., 1993; Zobel et al., 1999; Harris et al., 2000; Zobel et al., 2001; Hatzinger et al., 2002; Appelhof et al., 2006; Aubry et al., 2007; Bhagwagar and Cowen, 2008; Pintor et al., 2009; Rao et al., 2010; Bockting et al., 2012; Vrshek-Schallhorn et al., 2013), different HPA-axis measurements were used. Of the above mentioned studies, one study found that higher evening cortisol levels predicted recurrence (Rao et al., 2010), a literature review suggested that non suppression on the DST was related to relapse/recurrence (Ribeiro et al., 1993), and five studies found an association between non-response on the DEX/CRH test and recurrence (Zobel et al., 1999, 2001; Hatzinger et al., 2002; Appelhof et al., 2006; Pintor et al., 2009). However, also inconsistent findings have been reported, e.g. a higher CAR predicted MDD recurrence in two studies (Harris et al., 2000; Vrshek-Schallhorn et al., 2013) whereas a lower CAR was found to do so in another study (Bockting et al., 2012).

It has also been suggested that early-life stress can induce persistent changes in the response of the HPA axis, which becomes especially visible when persons are exposed to psychosocial stressors in adulthood (Baes et al., 2012). A possible mechanism is reduction of glucocorticoid receptor function leading to a decrease in inhibitory feedback resulting in hypercortisolism. Rao et al. (2010) observed that the risk for recurrence was higher among those with elevated cortisol levels and recent life events. Therefore, when investigating the predictive value of HPA-axis parameters on recurrence of MDD, it is important to take a potential interaction effect of recent stressors and childhood trauma into account (Adam et al., 2010). However, the literature is inconsistent, e.g. two other studies did not find any interactions (Bockting et al., 2012; Vrshek-Schallhorn et al., 2013).

Since results are inconsistent and different HPA-axis parameters were measured, which makes previous studies difficult to compare, there is a need for further research. To our knowledge, large-scale prospective studies that examine different HPA-axis parameters simultaneously along with the interaction of HPA axis parameters with childhood trauma and life events are scarce and some of these studies only targeted adolescents (Rao et al., 2010; Vrshek-Schallhorn et al., 2013). We assessed whether HPA axis parameters predict recurrence in remitted adult MDD subjects and whether stress-related factors (childhood trauma, life events) interact with HPA-axis parameters in predicting recurrence. Since hyperactivity as well as hypo-activity have been found to be associated with recurrence of MDD, we will examine potential non-linear associations with recurrence.

2. Methods

2.1. Study sample

Data were drawn from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study on the long-term course of depressive and anxiety disorders in different health care settings and illness phases. For the present study, we used the baseline assessment and follow-up assessments at two and four years. The study protocol was approved by the Ethical Review