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Glucocorticoid and mineralocorticoid receptor polymorphisms and recurrence of major depressive disorder

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Summary
Objective: Previous research found that variants of the glucocorticoid receptor (GR) (9β, ER22/23EK, *Bcl*I, *Tth*III*l*, NR3C1-1 and N363S) and mineralocorticoid receptor (MR) gene polymorphism (−2 C/G and I180V) are associated with both glucocorticoid (GC) sensitivity and major depressive disorder (MDD). There are no data which investigated prospectively whether these variants are associated with recurrence of MDD.
Methods: Data were derived from the Netherlands Study of Depression and Anxiety (NESDA) which used the Composite International Diagnostic Interview (CIDI) to determine MDD. Polymorphisms in the GR and MR gene were determined and haplotypes were characterized. We analyzed in retrospect whether recurrent MDD ($n = 951$) in comparison with first onset MDD ($n = 919$) was associated with polymorphisms in the GR and MR gene. Furthermore, we analyzed prospectively for 4 years the time to recurrence among 683 subjects with a remitted MDD diagnosis. Time to recurrence of MDD was assessed using the CIDI and a life chart interview. Additionally, we analyzed interactions of the investigated polymorphisms with childhood trauma and recent negative life events.

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Results: GR and MR gene polymorphisms and derived haplotypes were not associated with recurrence of depression in both retrospective and prospective analyses. In addition, no consistent interactions between GR and MR polymorphisms and childhood trauma or life events were found.
Conclusion: This study did not find consistent associations between GR and MR gene polymorphisms, interactions between GR and MR haplotypes and stressful conditions and recurrence of MDD.

1. Introduction

Major depressive disorder (MDD) is one of the disorders with the highest morbidity worldwide (World Health Organisation, 2008) and long term strategies aimed at reducing recurrence could be an effective way to reduce the population burden of MDD (Vos et al., 2004). However, knowledge of the predictors of recurrence is still sparse. MDD is a complex disorder that does not result from either genetic or environmental influences alone but rather from both.

A possible link between environmental influences, e.g. stressful conditions, genetic risk factors and the risk for a recurrence of MDD could be an altered function of the hypothalamic—pituitary—adrenal (HPA) axis. In reaction to stressful conditions, glucocorticoids coordinate metabolic, endocrine, immune and nervous system responses. Recurrences of MDD are associated with childhood trauma (Hardeveld et al., 2013), recent life events (Monroe et al., 2014) and HPA-axis alterations (Ribeiro et al., 1993; Zobel et al., 1999, 2001; Harris et al., 2000; Hatzinger et al., 2002; Bhagwagar et al., 2003; 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). It has been postulated that childhood trauma can induce persistent changes in the response of the HPA axis, which can become apparent when persons are exposed to psychosocial stressors in adulthood (Von Werne Baes et al., 2012; Juruena, 2014). A recent study (Hardeveld et al., 2014) published in this journal concluded that the cortisol awakening response was associated with time to recurrence of MDD and it was postulated that an increased cortisol awakening response could also be a genetic vulnerability trait. The effects of glucocorticoids are mediated by the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) and altered sensitivity to glucocorticoids of both receptors could lead to reduced negative feedback of cortisol, an increased production of corticotrophin releasing factor and consequently hypercortisolism which has been associated with the pathophysiology of MDD (glucocorticoid cascade hypothesis) (Nemeroff, 1996; Holsboer, 2000; Pariante, 2009). Sensitivity to glucocorticoids varies between individuals (Stevens et al., 2004) and various common single nucleotide polymorphisms (SNPs) are associated with glucocorticoid sensitivity (Spijker and van Rossum, 2012). For the MR gene these are: −2 G/C and I180V (De Rijk et al., 2006; Van Leeuwen et al., 2011) and for the GR gene these are: 22/23 EK, 9β, N363S, *TthIII*l, NR3C1-1, and *Bcl*I (Huizenga et al., 1998; Van Rossum et al., 2002, 2003; Wüst et al., 2004; Spijker and van Rossum, 2012). Studies also found that these polymorphisms were associated with onset and presence of major depression (Van Rossum et al., 2006; Van West et al., 2006; Kuningas et al., 2007; Zobel et al., 2008; Krishnamurthy et al., 2008; Bet et al., 2009; Otte et al., 2009; Klok et al., 2011; Spijker and van Rossum, 2012; Szczepankiewicz et al., 2011; Gałecka et al., 2013). Three studies examined recurrent MDD versus controls in retrospect (Van West et al., 2006; Zobel et al., 2008; Gałecka et al., 2013) and found that N363s, *Bcl*I and 22/23 EK were associated with recurrent MDD. Only one study (Bet et al., 2009) investigated interactions and found that an interaction between the GR polymorphisms 22/23 EK and 9β and childhood trauma resulted in an increased risk for developing depressive symptoms at old age. To the best of our knowledge, there is no research which investigated prospectively whether these variants are associated with recurrence of MDD.

We aimed to investigate retrospectively as well as prospectively whether the SNPs located on the GR and MR which are associated with glucocorticoid sensitivity and MDD are also associated with recurrence of MDD. Furthermore, we investigated whether these SNPs interact with stressful conditions (childhood trauma, life events). Our hypothesis was that polymorphisms of the GR and MR gene associated with glucocorticoid sensitivity and depression increase the risk of a recurrent course of depression or a faster time to recurrence. Moreover, we hypothesized that these polymorphisms interact with stressful conditions (childhood trauma, recent life events), increasing the risk for a recurrence.

2. Methods

2.1. Study sample

Data were from the Netherlands Study of Depression and Anxiety (NESDA), a prospective cohort study investigating the long-term course of depressive and anxiety disorders. At baseline, 2981 subjects (18—65 years) were recruited in primary care, in specialized mental health care and in the community. The study protocol was approved by the Ethical Committee of participating universities. All subjects provided written informed consent. The rationale, objectives, and methods of NESDA have been described in detail elsewhere (Penninx et al., 2008). In brief, the NESDA cohort ($n = 2981$) consists of subjects (18—65 years) with (i) a current anxiety and/or depressive disorder, (ii) a prior history of a depressive and/or anxiety disorder and (iii) healthy controls. Subjects were recruited in primary care through a screening procedure, in specialized mental health care upon registration and in the community. All 2981 subjects were administered a baseline assessment,