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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,

which lasted on average 4 h and included assessment of psychopathology, demographic and personal characteristics, psychosocial functioning, and biomarkers. Based on clinical judgment and if necessary screening of the medical records, subjects with a primary diagnosis of psychotic disorder, obsessive—compulsive disorder, bipolar disorder, severe addiction disorder, and those not fluent in Dutch were excluded. All subjects were from Northern-European ancestry.

For our present study, the first 4 years were used. We selected subjects with a lifetime history of MDD ($n = 1925$). The diagnosis was assessed at baseline and based on the DSM-IV based Composite International Diagnostic Interview (CIDI), lifetime version 2.1. Of these, 55 subjects were excluded because they did not have DNA data or that the samples of these subjects did not pass basic quality control (see GR and MR variants section). Subjects with or without DNA data did not differ in age, sex or history of recurrent MDD. We applied two different analytic approaches. First, we analyzed in retrospect whether subjects with GR and MR polymorphisms associated with glucocorticoid sensitivity more often had a recurrent MDD ($n = 951$) as compared to those having a single episode ($n = 919$). Second, in a more stricter approach we selected those who were in remission of MDD for at least 6 months preceding the baseline assessment and assessed time to recurrence prospectively during 4 years using the life chart interview (LCI) (Lyketsos et al., 1994). The LCI uses age- and calendar-linked personal landmarks to describe time sequence of symptoms of MDD. In this way, it was possible to assess time to recurrence of MDD per month follow-up. Recurrence was defined as recurrence of symptoms after remission to at least mild severity level persisting for at least 1 month with the additional criterion that a CIDI-confirmed MDD diagnosis was present during follow-up. 810 subjects fulfilled the definition of a remitted MDD diagnosis. Of these, 18 subjects were excluded because these subjects did not collect DNA data or the DNA samples did not pass basic quality control. 80 subjects (10.1%) were excluded because they did not have a (complete) LCI during follow-up or were lost to follow-up. Drop-out was associated with lower educational attainment ($F = 1.99$, $p = 0.05$), but not with sex or age. Finally, 29 subjects were excluded because the diagnosis changed to bipolar disorder during follow-up. Consequently, in 683 subjects GR and MR polymorphisms could be analyzed prospectively for recurrence of MDD.

2.2. GR and MR variants

For the present study, MR and GR SNPs were selected which in previous research were associated with glucocorticoid sensitivity (Spijker and van Rossum, 2012). For the GR gene these are: 22/23 EK (rs6189/rs6190, GAGAGG > GAAAGG), 9β (rs6198, A > G), N363S (rs56149945, previously coded rs6195, AAT > AGT), *TthIII*I (rs10052957, C > T) NR3C1-1 (rs10482605, T > C) and *Bcl*I (rs41423247, C > G). For the MR gene these are: −2 G/C (rs2070951, G > C) and I180V (rs5522, A > G). Genotyping of the SNPs was performed on two platforms: OpenArray® Real time PCR System (Life Technologies, Carlsbad, USA) and Affymetrix 6.0 (Santa Clara, CA; Perfegen 5.0, Mountain View, CA, USA) which was imputed against the 1000 genomes (1KG Phase reference panel 1 release version 3 2012-03-14). Subjects were excluded based on a SNP genotype missing rate of >10%, heterozygosity $-0.1 < F < 0.1$ or when the X chromosome status did not match phenotype sex. Best guess genotype data was used based on a cut-off of 0.90. Allele frequencies lower than 1% were excluded. For the data retrieved from OpenArray® Real time PCR System, also samples with a call rate <95% were removed. The retrieved SNP data were highly correlated (Pearson square >0.95). Because the number of usable DNA samples was larger in the Affymetrix 6.0 dataset, this dataset was used. An exception was −2 G/C which could only be retrieved through OpenArray® Real time PCR System.

2.3. Stress related factors

We determined two types of stress related factors: negative life events in the last year and childhood trauma. Number of negative life events were determined with the Brugha questionnaire (Brugha et al., 1985) which included 12 specific events and one 'other' category asking about serious other negative life events. The number of life events in the past year was calculated. For childhood trauma a cumulative childhood index was constructed (Wiersma et al., 2009; Hovens et al., 2010) by asking four questions regarding the occurrence and frequency of childhood experiences of emotional neglect, or emotional, physical, or sexual abuse. A cumulative index was calculated as the sum of the number and frequency of the four types of abuse for each subject in line with earlier studies (Wiersma et al., 2009; Hovens et al., 2010).

2.4. Covariates

Besides age and sex, pharmacological treatment was also considered a covariate based on previous studies (Brouwer et al., 2006; Anacker et al., 2011). This was assessed based on inspection of the medication boxes used in the past month and coded using the WHO Anatomical Therapeutic Chemical (ATC) classification (REF to URL). Regular use of antidepressants was categorized into selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (ATC-code N06AA) or other antidepressants (ATC-code N06AF/N06AX). Use of antidepressants was dichotomized into yes or no. Furthermore, we took into account possible genetic variation in the Dutch population. An earlier study performed in NESDA (Abdellaoui et al., 2013) identified three principal components which showed significant correlations with geography, distinguishing between: North and South, East and West, and the middle-band and the rest of the Netherlands.

2.5. Statistical analyses

SNPs were tested for Hardy—Weinberg equilibrium. Haplotypes were created with Phase (http://stephenslab.uchicago.edu/software.html) (Stephens et al., 2001). For each haplotype three genotype combinations were distinguished carrying 0, 1, or 2 copies of the haplotype allele. Power calculations for the cross sectional (logistic

regression) analyses were performed with Quanto version 1.2.4 (http://www.mybiosoftware.com/population-genetics/5931), and indicated that for the SNP with the highest minor allele frequency (rs2070951) we could detect an OR of 1.13 with 80% power, this was OR = 1.92 for the SNP with the lowest minor allele frequency (rs6189) (calculation of gene-effect only, unmatched case control ratio 1:1 and assuming a log additive model of inheritance). As recommended by Owzar et al. (2012), for the prospective (Cox proportional hazards model) analysis the software program R version 3.1.2 was used. Calculations indicated that for the SNP highest minor allele frequency (rs2070951) we could detect an HR of 1.29 with 80% power, this was HR = 3.00 for the SNP with the lowest minor allele frequency (rs6189) (event rate = 36.6%, landmark time = 24 months, probability that time to event is greater than landmark time = 19.2%, and assuming a log additive model). All other analyses were performed with SPSS version 20.0. Subsequently, associations between GR and MR polymorphisms, its haplotypes and recurrence (recurrent versus single episode, time to recurrence) were analyzed using multinomial logistic regression analyses and Cox regression analyses, adjusted for age, sex, principal components and treatment. Finally, we checked for interactions between GR and MR haplotypes and stress related factors. Interaction terms were calculated by multiplying the GR and MR haplotypes by the stress-related factors. So, nine different haplotypes were analyzed with two different stress related factors (18 tests), in retrospect as well as prospectively. Bonferoni correction for multiple testing was performed for GR/MR polymorphism analyses (16 tests, $p < 0.003$), haplotype analyses (18 tests, $p < 0.003$) and interaction terms (18 tests <0.003).

3. Results

3.1. Characteristics

As mentioned previously, we applied two different analytic approaches to assess recurrence. The characteristics are presented in Table 1. Of the subjects ($n = 1870$) which were analyzed in retrospect 68.4% were female and the mean number of episodes of MDD was 3.4 (sd = 3.9). 919 subjects (49.1%) had a first MDD and 50.9% had a recurrent MDD lifetime. As expected, the average age of the subjects was higher in those with a recurrent course (41.2 versus 42.8 years, $p < 0.01$). In the longitudinal analyses ($n = 683$) 48.8% ($n = 333$) of the included subjects had a lifetime recurrent MDD and 36.6% ($n = 250$) had a recurrence of MDD during follow-up. The mean time to recurrence was 11.8 months (sd = 12.6). Subjects with a recurrence of MDD during follow-up more often had a childhood trauma (48.3% versus 57.3%, $p = 0.03$) and used more often an antidepressant (17.3% versus 31.6%, $p < 0.001$). Age and sex distributions did not differ among the GR and MR genotypes besides SNP −2 G/C of which less females had a GG genotype in comparison with GC or CC (62.8 versus resp. 69.0 and 70.7, $p = 0.03$).

3.2. MR- and GR genotypes and haplotypes

Genotype distributions for all polymorphisms were in Hardy Weinberg equilibrium (Pearson square >0.05). The frequencies of the GR and MR SNPs are described in Table 2. Notable, there were no individuals in our study sample carrying homozygote SNPs of rs6189/6190 TT and rs56149945 CC. Concordant with previous studies (Van Winsen et al., 2009; Spijker et al., 2011; Klok et al., 2011), six main haplotypes were found for GR and three for MR. Frequencies are displayed in Table 3. Both haplotypes of GR and MR (haplotypes 1) with the highest frequencies consisted of the major alleles of the measured SNPs. After post hoc Bonferroni correction for multiple testing ($p < 0.003$), no associations between the GR and MR SNPs, its haplotypes and recurrence of depression were found (Tables 2 and 3). Also no consistent interaction terms ($p < 0.003$) between stress related factor and GR/MR haplotypes were found (Table 4). Although non-significant after Bonferoni correction, there are results worth mentioning. Two copies of the haplotype characterized by the minor allele of −2 C/G of the MR were associated with time to recurrence (HR = 0.53, 95% CI = 0.29—0.94, $p = 0.03$) indicating a protective effect (Table 3). Subjects with two copies of the haplotype TCTCCAA (*Bcl*I, *Tth*III*l*) of the GR had more often a recurrent course in comparison with those with one or zero copies (OR = 2.75, 95% CI 1.07—7.03, $p = 0.04$) (Table 3). Two copies of this haplotype was, on the other hand, also associated with a longer time to recurrence (33.5 months versus 11.9 and 11.3, $p = 0.002$). It should be noted that in this later analyses the number of subjects who had two copies of the haplotype 4 was only four. Also two interactions need to be addressed, GR haplotype CGTCCGA (9β, NR3C1-1, *Tth*III*l*) with childhood trauma (HR = 0.74, 95% CI = 0.60—0.92, $p = 0.01$) and GR haplotype TGCCCAG (N363S) with recent life events (HR = 7.75, 95% CI, 1.07—56.10, $p = 0.04$) because of the low p-values (see Table 4). However, considering the number of tests conducted and the inconsistency of the findings with contrasting findings in the retrospective and prospective analyses, we consider these chance findings.

Our 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 (CAR) could also be a genetic vulnerability trait. Therefore, we also investigated whether the CAR was associated with GR and MR polymorphisms in our study sample. The methods of the HPA-axis parameters measurements were described in our recent study (Hardeveld et al., 2014). For this analyses we used the baseline sample ($n = 2981$). Eventually, 1211 subjects were included, after excluding invalid CAR data or DNA data. Using ANOVA, no associations between CAR and the investigated haplotypes were found. We also analyzed a possible interaction of CAR by haplotype on time to recurrence ($n = 490$). However, no interactions were found.

4. Discussion

This study did not find consistent associations between GR and MR polymorphisms, interactions with childhood trauma or recent life events and recurrence of MDD. So, our results suggest that these polymorphisms may be associated with onset and presence of MDD (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.,

Table 1 Characteristics of the subjects in the retrospective and prospective cohort.

	Life time MDD ($n = 1870$)			Recurrence during follow-up ($n = 683$)		
	First ($n = 919$)	Recurrent ($n = 951$)	p	No recurrence ($n = 433$)	Recurrence ($n = 250$)	p
Socio-demographic factors						
Female, *n* (%)	616 (67.0)	664 (69.8)	0.19	300 (69.3)	190 (76.0)	0.06
Age, mean years (sd)	41.2 (12.9)	42.8 (11.8)	<0.01	44.4 (12.8)	42.6 (12.0)	0.07
Stress related factors						
Childhood trauma, *n* (%)	513 (55.9)	558 (59.0)	0.18	210 (48.6)	142 (57.3)	0.03
Childhood trauma, mean (sd)	1.12 (1.23)	1.11 (1.17)	0.87	0.85 (1.07)	1.11 (1.22)	0.003
Life events in past year present, *n* (%)	403 (43.9)	379 (39.9)	0.08	144 (33.3)	96 (38.4)	0.18
Life events in past year, mean (sd)	0.75 (1.09)	0.64 (0.94)	0.02	0.50 (0.83)	0.54 (0.80)	0.50
Treatment						
Use of antidepressants, *n* (%)	336 (36.3)	309 (32.5)	0.08	75 (17.3)	79 (31.6)	<0.001

2009; Klok et al., 2011; Spijker and van Rossum, 2012; Szczepankiewicz et al., 2011; Gałecka et al., 2013) but not with recurrence of MDD. Three studies examined recurrent MDD versus healthy controls in retrospect (Van West et al., 2006; Zobel et al., 2008; Gałecka et al., 2013). So, these studies found that the investigated SNPs were associated with presence of recurrent MDD but these studies did not investigate recurrence of MDD versus first onset which makes a comparison with our study difficult. It should be noted that also negative results were found and none of the investigated SNPs were consistently confirmed in previous studies.

What could be explanations for our negative results? El Hage et al. (2009) postulated that gene environmental interactions in depression involves complex participation of serotonergic genes modulating responses to stress through the HPA-axis. Also modulating genes involved in the HPA-axis, for example FKPB5, may be associated with MDD risk (Spijker and van Rossum, 2012; Szczepankiewicz et al., 2014). El Hage et al. (2009) hypothesized that subjects with a low activity of 5-HTTLPR have elevated activity in the amygdala. A hyperactive amygdala enhances HPA-axis functioning which could lead to sustained hypercortisolism which is associated with recurrence of MDD (Hardeveld et al., 2014). Whether sustained hypercortisolism will be present is also dependent on MR and GR expression which is modulated by FKPB5, among others. In our study the CAR was not associated with GR and MR haplotypes. So, it could be that in our sample GR and MR haplotypes did not, or only slightly, contribute to hypercortisolism and hereby did not increase the risk for a recurrence of MDD. Alternatively, interactions of GR and MR haplotypes with serotonergic or modulating genes of the HPA-axis may increase the risk for a recurrence.

Although an earlier study using NESDA data (Holleman et al., 2012) did not convincingly find an association of HPA-axis parameters and childhood trauma, substantial evidence reviewed by Juruena (2014) indicates that childhood trauma can induce changes in the ability of the HPA-axis to respond to stress in adulthood by reducing the ability of cortisol to bind to GR and MR. It was postulated that an imbalance in MR and GR functioning may be a risk factor for depression. This mechanism could also lead to an increased awakening response which we found to be associated with recurrence of MDD (Hardeveld et al., 2014). The contribution of the GR and MR polymorphisms in epigenetic modification may be minor.

To the best of our knowledge, this is the first study that investigated GR and MR polymorphisms and recurrence of MDD prospectively. We examined multiple GR and MR gene polymorphisms in a large sample and used standardized instruments to determine diagnosis and recurrence. However, there are a number of limitations. First, we did investigate candidate genes which were associated with glucocorticoid sensitivity and MDD but other SNPs located on the GR or MR gene could be involved in recurrence. We did not perform a whole gene-based association analysis of SNPs on the GR and MR. However, if we would have tested more SNPs, requirements for significance would have been more stringent with accompanying power issues. On the other hand, because we tested several SNPs Bonferonni correction had to be performed. If we would have tested less SNPs a significant result would have been found. Also, for some polymorphisms the sample size was small or absent limiting our power to detect small to medium effect sizes, given that we had 80% power to detect an odds ratio 1.92 for the SNP with the lowest minor allele frequency in the retrospective analyses, this was HR = 3.00 for the prospective analyses.

Another concern relates to the retrospective collection of data. The assessment of a single episode MDD in retrospect may not be accurate. Though, our prospective data were not showing associations either.

In conclusion, although there is considerable evidence that these polymorphisms are associated with onset and presence of MDD no consistent associations of the GR and MR candidate gene polymorphisms with recurrence of MDD were found. To draw firmer conclusions, replication is needed preferably using a whole gene-based association analysis

Table 2 Association of GR and MR gene polymorphisms with recurrence of MDD.[a]

SNP genotype (%)			Female ($n = 1870$)		Age ($n = 1870$)		First ($n = 919$, 49.1%), versus recurrent ($n = 951$, 50.9%) MDD at baseline					Time to recurrence during follow-up ($n = 683$)	
			%	*p*	Mean	*p*	First[b] *n* (%)	Recurrent *n* (%)	*p*	OR[c] (95% CI)	*p*	HR[d] (95% CI)	*p*
Glucocorticoid receptor gene													
ER22/23EK	CC	84.1	68.6	0.54	42.1	0.56	792 (98.4)	826 (98.0)	0.54	–	–	–	–
	CT	1.6	63.3		42.6		13 (1.6)	17 (2.0)		1.31 (0.63–2.71)	0.54	1.36 (0.64–2.93)	0.43
N363S	TT	80.2	68.3	0.30	42.0	0.52	765 (97.2)	778 (96.6)	0.52	–	–	–	–
	TC	2.5	61.2		43.2		22 (2.8)	27 (3.4)		0.83 (0.46–1.47)	0.52	0.92 (0.34–2.50)	0.88
*Bcl*I	GG	39.5	68.5	0.94	42.2	0.96	360 (43.5)	401 (46.4)	0.31	–	–	–	–
	CG	30.6	68.0		42.1		379 (45.8)	364 (42.1)		0.87 (0.71–1.06)	0.17	0.92 (0.70–1.20)	0.52
	CC	9.8	67.2		41.9		89 (10.7)	100 (11.6)		1.02 (0.74–1.40)	0.89	1.04 (0.68–1.58)	0.86
9β	TT	61.0	67.1	0.82	42.1	0.37	579 (68.0)	596 (66.9)	0.89	–	–	–	–
	TC	26.5	68.7		42.3		246 (28.9)	265 (29.7)		1.04 (0.85–1.29)	0.68	1.07 (0.81–1.41)	0.62
	CC	3.0	71.9		39.8		27 (3.2)	30 (3.4)		1.10 (0.64–1.87)	0.74	0.71 (0.31–1.60)	0.41
*TthIII*I	CC	40.7	68.5	0.96	42.6	0.39	386 (49.2)	398 (47.6)	0.70	–	–	–	–
	TC	35.0	68.1		42.8		324 (41.3)	350 (41.9)		1.04 (0.84–1.27)	0.74	0.85 (0.64–1.23)	0.27
	TT	8.4	67.6		41.9		74 (9.4)	88 (10.5)		1.14 (0.82–1.63)	0.40	0.92 (0.60–1.42	0.72
NRC3C1-1	AA	54.7	68.4	0.85	42.4	0.51	512 (67.3)	541 (66.5)	0.93	–	–	–	–
	AG	24.2	67.7		42.4		223 (29.3)	242 (29.8)		1.03 (0.83–1.28)	0.78	1.14 (0.86–1.51)	0.37
	GG	2.9	71.4		40.4		26 (3.4)	30 (3.7)		1.11 (0.65–1.91)	0.71	0.52 (0.21–1.27)	0.15
Mineralocorticoid receptor gene													
−2 G/C	CC	16.4	69.0	0.03	42.2	0.80	140 (21.3)	176 (25.7)	0.16	1.23 (0.89–1.71)	0.20	1.29 (0.80–2.06)	0.29
	GC	35.4	70.7		41.7		341 (52.0)	339 (49.6)		0.97 (0.74–1.28)	0.85	1.21 (0.79–1.85)	0.37
	GG	17.9	62.8		42.0		175 (26.7)	169 (24.7)		–	–	–	–
I180V	CC	1.5	68.3	0.38	41.0	0.56	17 (2.0)	12 (1.3)	0.30	0.67 (0.32–1.40)	0.29	1.12 (0.28–4.46)	0.87
	TC	18.9	67.1		41.5		187 (21.7)	177 (19.7)		0.89 (0.70–1.12)	0.30	1.15 (0.84–1.56)	0.39
	TT	71.2	61.9		42.2		658 (76.3)	712 (79.0)		–	–	–	–

Abbreviations: SNP = single nucleotide polymorphism, OR = odds ratio, HR = hazard ratio.

[a] GR data was completed for ER22/23EK in 1648 (85.7%) subjects, for N363S in 1592 subjects (82.7%), for *Bcl*I in 1693 subjects (87.9%), for 9β in 1743 subjects (90.5%), for *TthIII*I in 1620 (84.4%) subjects and for NRC3C1-1 in 1574 (81.8) subjects. In 1340 subjects (69.6%) MR genotyping was completed for −2 G/C and in 1763 subjects (91.6%) for I180V.

[b] Pearson chi-square.

[c] Logistic regression, adjusted for age, sex and principal components. Reference category is the major allele.

[d] Associations were tested with Cox regression analyses adjusted for age, sex, principal components and treatment with antidepressants. Reference category is the major allele.

Table 3 Associations of GR and MR haplotypes with recurrence of MDD.

Haplotype[a]			First ($n = 919$, 49.1%), versus recurrent ($n = 951$, 50.9%) MDD at baseline[c]			Time to recurrence during follow-up ($n = 683$)[d]			Mean time to recurrence (months)[e]	
	%	n[b]	n (%)	OR (95% CI)	p	n (%)	HR (95% CI)	p	Mean (sd)	p
Glucocorticoid receptor gene										
1. TGTCCAG	47.2	0	478 (25.6)	—	—	184 (26.9)	—	—	14.1 (13.2)	0.17
(wildtype)		1	1005 (53.7)	0.97 (0.78—1.21)	0.79	354 (51.8)	0.96 (0.71—1.29)	0.77	11.3 (12.6)	
		2	387 (20.7)	0.99 (0.76—1.30	0.95	145 (21.2)	1.13 (0.80—1.60)	0.49	10.0 (11.4)	
2. TCTCCAG	20.2	0	1189 (63.6)	—	—	428 (62.7)	—	—	11.6 (13.3)	0.60
(*Bcl*I)		1	618 (33.0)	0.87 (0.72—1.06)	0.18	229 (33.5)	1.05 (0.80—1.37)	0.75	12.5 (11.6)	
		2	63 (3.4)	0.94 (0.57—1.57)	0.82	26 (3.8)	0.90 (0.46—1.77)	0.76	8.2 (9.1)	
3. CGTCCGA (9β,	16.7	0	1324 (70.8)	—	—	484 (70.9)	—	—	11.0 (12.2)	0.29
NR3C1-1, *Tth*III*l*)		1	492 (26.3)	1.03 (0.83—1.27)	0.80	177 (25.9)	0.99 (0.74—1.31)	0.93	13.8 (13.7)	
		2	54 (2.9)	1.14 (0.66—1.97)	0.64	22 (3.2)	0.69 (0.31—1.56)	0.37	11.5 (8.8)	
4. TCTCCAA	12.8	0	1473 (78.8)	—	—	531 (77.7)	—	—	11.3 (12.0)	0.002
(*Bcl*I, *Tth*III*l*)		1	374 (20.0)	0.96 (0.76—1.21)	0.74	144 (21.1)	0.86 (0.63—1.19)	0.37	11.9 (13.4)	
		2	23 (1.2)	2.75 (1.07—7.03)	0.04	8 (1.2)	1.21 (0.45—3.27)	0.71	33.5 (17.9)	
5. TGCCCAG	1.5	0	1823(97.5%)	—	—	668 (97.8)	—	—	11.9 (12.6)	0.17
(N363S)		1	47 (2.5%)	1.18 (0.66—2.13)	0.58	15 (2.2)	0.89 (0.33—2.39)	0.81	3.25 (2.6)	
		2	0	—	—		—	—	—	
6. CGTTTGA (9β,	1.1	0	1840 (98.4)	—	—		—	—	11.9 (12.6)	0.30
ER22/23EK,		1	30 (1.6)	1.23 (0.63—2.72)	0.48	668 (97.8)	1.33 (0.62—2.86)	0.46	6.9 (10.4)	
NR3C1-1, *Tth*III*l*)		2	0	—	—	15 (2.2)	—	—		
Mineralocorticoid receptor gene										
1. GA	49.2	0	358 (19.1)	—	—	111 (16.3)	—	—	14.2 (14.8)	0.47
(wildtype)		1	1196 (64.0)	1.00 (0.78—1.28)	0.91	451 (66.0)	1.27 (0.86—1.87)	0.24	11.6 (12.1)	
		2	316 (16.9)	1.25 (0.91—1.72)	0.18	121 (17.7)	1.30 (0.82—2.07)	0.27	10.8 (12.7)	
2. CA (—2 G/C)	38.8	0	596 (31.9)	—	—	218 (31.9)	—	—	12.1 (12.9)	0.33
		1	1056 (56.5)	0.95 (0.77—1.17)	0.63	397 (58.1)	0.95 (0.73—1.24)	0.82	11.1 (12.3)	
		2	217 (11.6)	1.00 (0.72—1.41)	0.99	68 (10.0)	0.53 (0.29—0.94)	0.03	16.0 (13.0)	
3. CG (I180V)	12.0	0	1477 (79.0)	—	—	548 (80.2)	—	—	11.3 (12.0)	0.34
		1	364 (19.5)	0.89 (0.70—1.12)	0.30	130 (19.0)	1.17 (0.86—1.59)	0.32	13.8 (14.5)	
		2	29 (1.6)	0.67 (0.32—1.41)	0.29	5 (0.7)	1.30 (0.32—5.30)	0.71	5.5 (6.4)	

Abbreviations: OR = odds ratio, HR = hazard ratio, MDD = major depressive disorder.

[a] Wildtype consisted of the major alleles of the six SNPs of GR haplotype respectively two SNPs of the MR haplotype. Haplotype were further characterized by the minor allele (in brackets) of the SNP plus the major alleles of the other SNPs.

[b] Estimated number of haplotype copies.

[c] Logistic regression, adjusted for age, sex, and principal components. Reference category is zero copies of the haplotype.

[d] Associations were tested with Cox regression analyses, adjusted for age, sex, principal components and treatment with antidepressants.

[e] Associations were tested with ANOVA.

Table 4 Interactions of stress related factors, haplotypes of the GR and MR gene on the risk for a recurrence of MDD.

Haplotype[a]	Haplotype by childhoodtrauma ($n = 1870$)[b]		Haplotype by childhood trauma ($n = 683$)[c]		Haplotype by recent life events ($n = 1870$)[b]		Haplotype by recent life events ($n = 683$)[c]	
	OR (95% CI)	*p*	HR (95% CI)	*p*	OR (95% CI)	*p*	HR (95% CI)	*p*
Glucocortocoid receptor gene								
1. TGTCCAG (wildtype)	1.04 (0.93—1.17)	0.51	1.14 (0.98—1.33)	0.10	1.06 (0.93—1.21)	0.41	1.18 (0.94—1.48)	0.16
2. TCTCCAG (*BcI*I)	0.91 (0.79—1.04)	0.16	1.07 (0.89—1.29)	0.48	0.97 (0.82—1.14)	0.68	0.86 (0.65—1.15)	0.30
3. CGTCCGA (9β, NR3C1-1, *TthIII*l)	1.07 (0.92—1.24)	0.36	0.74 (0.60—0.92)	0.01	0.90 (0.76—1.07)	0.23	0.95 (0.68—1.33)	0.76
4. TCTCCAA (*BcI*I, *TthIII*l)	1.02 (0.86—1.22)	0.80	1.02 (0.80—1.32)	0.86	1.16 (0.93—1.44)	0.19	0.82 (0.53—1.25)	0.35
5. TGCCCAG (N363S)	0.70 (0.44—1.10)	0.12	0.72 (0.27—2.00)	0.52	0.77 (0.40—1.47)	0.43	7.75 (1.07—56.10)	0.04
6. CGTTTGA (9β, ER22/23EK, NR3C1-1, *TthIII*l)	0.94 (0.52—1.69)	0.83	1.36 (0.85—2.17)	0.20	0.93 (0.41—2.08)	0.86	1.00 (0.50—2.02)	0.99
Mineralocorticoid receptor gene								
1. GA (wildtype)	0.94 (0.82—1.08)	0.40	1.00 (0.82—1.21)	0.98	0.96 (0.82—1.13)	0.65	0.96 (0.71—1.28)	0.76
2. CA (—2 G/C)	1.00 (0.87—1.13)	0.93	1.10 (0.92—1.32)	0.31	1.05 (0.91—1.21)	0.53	1.16 (0.89—1.50)	0.28
3. CG (I180V)	1.11 (0.93—1.32)	0.22	0.84 (0.65—1.09)	0.20	0.98 (0.82—1.20)	0.81	0.77 (0.49—1.22)	0.27

Abbreviations: OR = odds ratio, HR = hazard ratio, MDD = major depressive disorder.

[a] Wildtype consisted of the major alleles of the six single nucleotide polymorphisms (SNPs) of glucocorticoid gene haplotype respectively two SNPs of the mineralocorticoid gene haplotype. Haplotype were further characterized by the minor allele (in brackets) of the SNP plus the major alleles of the other SNPs representing the number of haplotype copies (0, 1, or 2).

[b] Risk for a life time recurrent course versus first episode. Logistic regression, adjusted for age, sex and principal components.

[c] Time to recurrence. Associations were tested with Cox regression analyses, adjusted for age, sex, principal components and treatment with antidepressants.

of SNPs on the GR and MR also including interactions with modulating and serotonergic genes. In this way, the complex pattern of interaction between environmental factors and genetic factors related to recurrence of MDD could be further unraveled.

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Conflict of interest

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