# 3. Glucocorticoid Receptor Polymorphisms in Major Depression: Focus on glucocorticoid sensitivity and neurocognitive functioning



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## Abstract:

Previously, it has been suggested that hypothalamic pituitary adrenal (HPA) axis dysregulation and as a consequence increased cortisol levels, is not only a state phenomenon, but may also be a trait phenomenon in mood disorders. Cortisol exerts its effects mainly by binding to the glucocorticoid receptor (GR) and, in particular of interest in certain brain regions, the mineralocorticoid receptor (MR). Several GR polymorphisms have been shown to be associated with altered sensitivity of the HPA axis. Recently, the GR polymorphisms *Bcl*I and ER22/23EK have been associated with unipolar depression in several studies. In addition, the ER22/23EK polymorphism seems to be associated with a decreased risk of dementia in healthy individuals. Also during a depressive episode carriers of this ER22/23EK variant demonstrated a tendency towards better cognition, as measured by divided attention tests.

In this overview, currently known clinically relevant GR and MR polymorphisms are discussed in relation to mood disorders (both unipolar depression and bipolar disorder) and cognitive functioning.

## 1. Introduction: Glucocorticoids and Depression

Stressful life events often precede a major depressive episode. In the past decades a strong association between dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis and depression has been found (1-6). This association is even stronger in patients with either severe unipolar depressive disorder with psychotic symptoms or with bipolar disorder (BD) (4, 5). In recent literature this association has been cautiously considered to be a trait phenomenon of depressive episodes, rather than simply a state phenomenon (2, 7, 8). This was supported by Holsboer et al. who demonstrated that first degree family members of patients with unipolar depression display a similar, although quantitatively more modest, pattern of dysregulation then that observed during a major depressive episode (9). Also Ellenbogen et al found higher cortisol levels in the morning and afternoon in offspring of patients with BD compared to offspring of patients with MDD and healthy controls (10). In the past years, data concerning the associations between mood disorders and HPA-axis have been reviewed extensively (11, 12). The most consistent finding is hyperactivity of the HPA-axis. The combined dexamethasone-suppression/ corticotropin-releasing hormone-stimulation (CRH) test (DEX/CRH test) has been reported to be the most sensitive test for detecting HPA-axis dysregulation, with approximately 80% of patients with a major depressive episode (uni- or bipolar) found to be non-suppressors (13). The test is not very specific for depression, as in all psychiatric patients cortisol levels were elevated in comparison with age-matched controls. Previous studies showed that the DEX/CRH test may also be useful as a predictor of relapse (14, 15).

In the brain, the dysregulation of the HPA-axis in major depressive disorder (MDD) and BD is associated with neuro-endocrine and anatomical changes. The neuro-endocrine changes mainly occur in catecholaminergic systems, like dopamine and adrenalin, influencing heart rate and blood pressure (16), and serotonergic systems influencing behavior, mood and cognitive functioning (17). Animal studies have shown that glucocorticoids (GCs) enhance the effects of dopamine in the reward system of the brain, the mesolimbic region, thus influencing goal directed behavior in stressful situations (18). Sustained overdrive of GCs is negatively associated with activity of serotonergic neurons, reduced expression of 5-HT-1A receptors and reduced 5-HT-1A receptor binding, thus believed to influence mood (7).

Another regulatory hormone in the brain which can be affected in depression through diminished negative feedback action of GCs, is CRH. Overproduction of CRH (1) leads to a series of stress-like physiological and behavioral phenomena (7). The behavioral features indicate increased anxiety, while some phenomena are also observed in animal models of depression (7, 19). In the review of Van Praag, a role is suggested for CRH in the

pathophysiology of states of anxiety and depression, conditions that in humans often occur simultaneously. However, this overdrive is not sufficiently understood yet. It could be the result of a primacy of CRH overdrive, or a consequence of a down regulation of centrally localized glucocorticoid receptors (GRs).

Anatomical changes in the brain in patients with depression are found mainly in the prefrontal cortex (PFC), the amygdala and the hippocampal area consisting of smaller volumes and reduced metabolic activity (20, 21). These brain areas regulate executive function and memory. Sassi et al (22) found a significantly smaller pituitary volume in patients with BD compared with patients with unipolar depressive disorder and healthy controls. No differences between the latter two groups were found. Recently, Aihara et al (23) studied 24 patients with MDD and found 75% non-suppressors on the DEX/CRH test. In positron emission tomography (PET) scans with a radiotracer, these patients also showed a hypo metabolism in various frontal regions and hyper metabolism in the right hippocampus and parahippocampal gyrus, both normalizing after successful antidepressant treatment.



In depressed patients almost all abnormalities returned to a normal pattern after response to medication, indicating the influence of altered GC regulation in these brain regions. These findings are in line with results from animal studies showing the negative effects of stress on neuroplasticity, mainly in the hippocampal area (where the effects are largely reversible after stress has ended), the PFC and the amygdale (24, 25). MacMaster et al found in a pediatric population that children with a family history of MDD had significantly smaller hippocampal volumes compared to healthy controls (26), indicating that this could be a risk factor for developing MDD. In addition, patients with Cushing's disease, characterized by hypercortisolism, can also develop psychiatric syndromes like MDD, anxiety disorders and cognitive dysfunction, as well as a reduction of hippocampal volume (27). It has been shown that the decrease of hippocampal volume in these patients can be reversed after successful treatment of the Cushing's disease and the co morbid psychiatric symptoms (28). It is still under discussion whether these structural changes in depression are reversible and what their exact relationship is with elevated cortisol levels (26, 29).

In summary, these findings are indicating that in the pathophysiology of MDD, GCs play an important role, affecting mood, executive function and memory through different neuronal networks in the brain as well as affecting several neuroendocrine systems.

## 2. Glucocorticoid sensitivity during a depressive episode

The functioning of the HPA axis is characterized by negative feedback at the pituitary level on the production of ACTH, and consequently on the production of cortisol in the adrenal glands. A strong indication of this feedback functioning is obtained through an HPA axis challenge test. The dexamethasone suppression test (DST) was for years the most frequently used challenge test. Due to its simple procedure, it is widely used in psychiatry by researchers and clinicians. Cortisol levels are measured after administration of 0.25 mg or 1-2 mg of the exogenous GC dexamethasone, providing an indication of adrenal negative feedback at the pituitary level. Sensitivity to exogenous GCs is highly variable between normal individuals (30), but within individuals it is rather stable, suggesting a set point of the HPA axis with respect to feedback action, which is possibly genetically determined. One of the main problems with the DST is its limited sensitivity in major depression (about 44%). In bipolar depression and psychotic depression the sensitivity is higher (67%-78%)(31). Also in manic states, non-suppression was found after a DST (32), as well as after a DEX/CRH test (4).

Heuser et al developed the combined DEX/CRH test as a refinement of the DST (13). This challenge test consists of administration of 1.5 mg dexamethasone at 11:00 pm followed by administration of 100 microgram CRH at 3:00 pm on the next day. Cortisol and ACTH levels are sampled every 15 minutes from 2:00 pm until 6:00 pm. This test is more sensitive for major depression (about 80%), and even more sensitive when clustering patients according to age groups. Zobel et al showed that the DEX/CRH test also may be used to predict relapse of depression within six months (15). Despite the observation that cortisol and ACTH responses to the DEX/CRH test did not differ between the patients with major depression on admission, the responses were found to be significantly different just before discharge. The relapse rate in this study was found to be 4 to 6-fold increased in patients with an elevated cortisol response in the DEX/CRH test just before discharge as compared to patients with a normal cortisol response. In accordance, Appelhof et al recently showed that in a sample of 45 outpatients with major depression in remission, higher cortisol levels in the DEX/CRH test were associated with relapse (14). In a group of patients with BD the cortisol response to a DEX/CRH test was significantly higher than in a group of unipolar MDD patients (5). This difference was not only found during a depressive episode, but persisted after remission. Watson et al confirmed that in BD patients cortisol levels in response to the DEX/CRH test are increased, both during a depressive episode and in remission (33).

## 3. The role of Glucocorticoid Receptors and Mineralocorticoid Receptors in Depression

GCs exert their effects by binding to the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). In the brain the MR is predominantly localized in the hippocampus, the amygdala and the prefrontal cortex. The GR is widespread throughout the brain, but is expressed in high density in the hippocampus, the prefrontal cortex and the paraventricular nucleus of the hypothalamus, the dentate gyrus and amygdale (34). The affinity of the MR for cortisol is ten times higher than that for GR (35). Under normal non-stress circumstances, cortisol binds to the MR in the mentioned brain areas, whereas in stress situations it also binds to the GR. In the limbic system both MR and GR are co-expressed, thereby fine tuning the central effects of GCs (36, 37). The MR seems to be involved in the onset of the stress response, while the GR terminates the stress reactions and promotes memory storage preparing for future events (38). In situations of chronic stress, this balancing system is disturbed, with damaging consequences for brain functions like mood and cognition. Matsubara et al found a reduced expression of GR mRNA in peripheral blood cells in a population of bipolar as well as unipolar depressed patients. This finding seems to be, at least partially, a trait phenomenon, as they found the same results in remitted patients (bipolar and unipolar) and in first degree family members of bipolar patients (39). Pariante stresses the importance of the dysfunction of the GR and the decreased expression of this receptor in the brain in patients with MDD [see chapter in this volume]. As a compensation for this GR dysfunction, cortisol levels increase to overcome the relative resistance (12, 40). Holsboer summarizes in his review the preclinical and clinical data supporting the hypothesis that GR signaling is impaired in MDD, yielding increased CRH levels in various brain regions, which in turn may lead to MDD (11) [see chapter in this volume].

In line with this model are the effects of GR antagonists and agonists on the one hand and the effects of (other) antidepressants on the GR on the other hand. The GR antagonist RU-486, the well known abortifacient mifepristone, has antidepressant effects in patients with BD (41) or MDD with psychotic features (42, 43). In a study with chronically stressed rats, it has been shown that a 4-day treatment with mifepristone normalized the stress-induced reductions in neurogenesis (44), possibly indicating the mechanism of action through blocking the GR. Interestingly, not only GR antagonists, but also GR agonists like hydrocortisone have been shown to exert antidepressant effects (45).

GR function is also positively stimulated by antidepressants. Pepin et al found *in vitro* that addition of tricyclic antidepressants (desipramine, amitriptyline, imipramine and maprotiline) or lithium to primary cultures of rat hypothalamic, hippocampal or amygdaloid neurons, GR mRNA was stimulated (46, 47). However, it is interesting that in

rats the selective serotonin reuptake inhibitors (SSRIs) such as citalopram and fluoxetine had no effect on GR mRNA (48, 49), whereas MR mRNA was stimulated by citalopram, desipramine and amitriptyline (48). It is unclear to what extent these animal data can be extrapolated to the human brain.

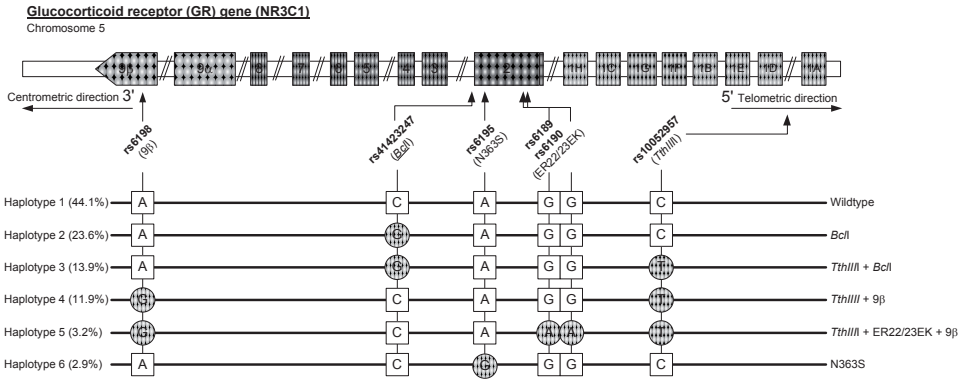
Thus, summarizing these data, although GR is more extensively studied than MR, it seems that both GR and MR are important in balancing GC levels in the brain. Imbalance in this system through dysfunction of GR and/or MR, could lead to a compensatory elevation of cortisol levels. Although still under discussion, the GR is thought to be an etiological factor in developing MDD. Studies with GR antagonists, GR agonists, and tricylic antidepressants seem to confirm this hypothesis (50). The clues suggestive of a genetic trait contributing to the development of MDD and the alterations in GR expression, as well as the dysregulation of the HPA axis during a depressive episode make the *GR* gene an important candidate gene for associations with susceptibility to MDD and response to antidepressant treatment. This article provides an overview of polymorphisms of corticosteroid receptors (both GR and MR), which in previous studies have been shown to be functionally relevant, and their associations with unipolar and bipolar depression, as well as with cognitive functioning during a depressive episode.

## 4. The relationship between GR polymorphisms and GC sensitivity

Previously, a few rare mutations of the *GR* gene in humans have been described, which lead to a generalized cortisol resistance. Patients present with hypertension and hypokalemic alkalosis (signs of adrenal overproduction of mineralocorticoids) and, in females, hirsutism, male pattern baldness and menstrual irregularities, as a consequence of overproduction of adrenal androgens. As a result of defects in the GR, the central negative feedback of GCs is reduced, GC production by the adrenal gland is increased, and cortisol binds with high affinity to the MR. The consequence is a hyperactivity of the HPA axis (51). These mutations, known to lead to the classical syndrome of GC resistance, are predominantly located in the ligand-binding and DNA-binding domains of the *GR* gene. Importantly, however, also in normal individuals, GC sensitivity, as measured with a low dose DST, varies considerably. Polymorphisms of the *GR* gene have shown to, at least partially, explain this variability in GC sensitivity (52).

Several important *GR* gene polymorphisms have been reported to yield altered GC sensitivity, and as a consequence, result in specific clinical features (see figure 1) (52):

*Figure 1: Overview of the GR gene showing the single nucleotide polymorphisms (SNPs) and haplotypes*




- Haplotype 2 (*TthIII*I + 9β). The 9β polymorphism is a single nucleotide polymorphism (SNP) in exon 9β of the *GR* gene. An ATTTA sequence in the 3' UTR is changed into GTTTA. This polymorphism is associated with an increased stability of the mRNA of the inactive GR-β isoform and may lead to a relative glucocorticoid resistance by increased inhibition of the active GR-α isoform (53). An *in vitro* study demonstrated that this polymorphism results in reduced transrepressional effects (by which, for example, genes important in the immune system are regulated), whereas the transactivational effects appeared to be normal (54). The 9β polymorphism has also been reported to be associated with rheumatoid arthritis (53), and a 68% reduced risk of carriage of nasal *Staphylococcus aureus* in carriers of this polymorphism (55), consistent with this variant's possible effect on activity of the immune system. It is known that IL-6 and IL-1β have activating effects on the HPA-axis. Interestingly, non-lithium treated bipolar patients have a low IL-1β and a high IL-6 production, which returns to normal after lithium treatment, suggesting an association of dysregulation in the immune system and the HPA-axis in these BD patients (56), *TthIII*I is a restriction fragment length polymorphism (RFLP) in the promoter region of the *GR* gene, which has not been found to be associated with changes in cortisol sensitivity. However, a previous report showed an association with elevated basal cortisol levels (57).

- Haplotype 3 (*TthIII*I + 9β + ER22/23EK) is also associated with a relative resistance to GCs, but in contrast to haplotype 2, this resistance is linked to the transactivational effects of the GR, by which most of the adverse effects of GCs are being mediated. The ER22/23EK polymorphism is located in the transactivation domain of the GR gene, and involves two nucleotide changes in codons 22 and 23 (GAG AGG -> GAA

AAG), which have been shown to be linked. This variant has been found to be associated with a healthy metabolic profile (lower C-reactive protein (CRP) levels, lower cholesterol levels and increased insulin sensitivity), longevity in the elderly and a beneficial body composition in young adults (52, 58). After a DST, carriers of this polymorphism showed a significantly smaller cortisol suppression, indicative of a relative GC resistance (58, 59). In addition, these ER22/23EK carriers displayed lower fasting insulin levels and lower total and LDL cholesterol levels than noncarriers (58, 59). In a recent study, this polymorphism has also been associated with an increased risk of recurrent depression, and a faster response to antidepressant medication, as we will discuss later in more detail (60,83). A relationship with cognitive performance has also been demonstrated. Carriers of the ER22/23EK polymorphism in a healthy elderly population were found to have a lower risk of developing dementia, and performed better on psychomotor speed tasks (61). No differences were observed in memory tasks. The ER22/23EK polymorphism was also studied in patients with multiple sclerosis and seemed to be associated with a more aggressive course of disease (as was observed clinically, as well as radiographically) (62). This might be due to an imbalance of the immune system and uncontrolled immune response against structural components of the central nervous system, since GCs are important factors in the pro-inflammatory signal transduction system.

- Haplotype 4 (*TthIII*I+ *Bcl*I) and haplotype 6 (*Bcl*I), both involving a C to G single nucleotide polymorphism at a polymorphic *Bcl*I restriction site, were associated with hypersensitivity to GCs (63). After both a 1 mg DST and a 0.25 mg DST both heterozygous (C/G) and homozygous (G/G) G-allele carriers had lower cortisol levels than CC-carriers, indicating increased sensitivity to the effects of GCs. This was confirmed in another study investigating GR haplotypes in relation to GC sensitivity (64). One GR haplotype, a G-A-T haplotype consisting of the G allele of the *Bcl*I polymorphism, the A allele of the intron B 33389, and the T allele of the intron B 33388, was found to be associated with increased sensitivity to GCs as well (64).

  Several previous studies reported associations with unfavorable metabolic characteristics, such as increased body mass index (BMI), (65) increased abdominal visceral fat (66, 67), hypertension (68), and lower amount of lean mass in the elderly (63). Recently, Syed et al reported another polymorphism in intron 2 (rs2918419), which was associated with hyperinsulinaemia and insulin resistance in males, but not in females. The authors suggest that previous articles reporting an association of *Bcl*I polymorphism with obesity-related characteristics may reflect linkage to rs2918419, since they found that carriage of *Bcl*I variant alleles without the rs2918419 variant appeared not to be related to insulin resistance (69).

- Haplotype 5 (N363S). This polymorphism is located in codon 363 of exon 2 of the *GR* gene. The nucleotide change (AAT -> AGT) results in an asparagine to serine amino acid. It is associated with lower cortisol levels and higher insulin levels after DST, suggesting increased GC sensitivity (70). Several reports demonstrated an association between the N363S polymorphism and obesity as could be expected if sensitivity to GCs is increased. (70) (71-74) However, in some other studies no associations were found with BMI (75, 76).

In conclusion, these GR genotypes seem to have consequences for cortisol sensitivity, both at the level of the feedback regulation at the pituitary gland and numerous target tissues. Therefore, they may be expected to induce subtle alterations in the set point of the HPA axis and may be involved in a genetic profile related to a hereditary susceptibility for depression. In the next sections the relationship between these GR polymorphisms, depression and cognition are discussed. Some relevant MR polymorphisms will also be briefly addressed.



## 5. GR polymorphisms and depression

A summary of data and an overview of studies concerning the associations between GR polymorphisms and depression are provided in Table 1. Research involving GR polymorphisms has only recently been focused on psychopathology and psychological stress (60, 77). Data are preliminary yet, but seem promising for future research. So far, several findings appear to be relevant in understanding the physiopathology of depression and will be discussed.

### *BclI polymorphism*

In 2006 the *Bcl*I polymorphism was shown to be significantly associated with major depression (60). In this study in a large Caucasian study population the frequency of homozygous carriers of the minor *Bcl*I allele were significantly higher in the depressed group compared to the healthy control group (15.5% versus 9.9% homozygotes, respectively). Recently, this finding was confirmed in two other studies (78, 79). Zobel et al found similar frequencies: respectively 15.5% and 12.2% homozygotes *Bcl*I minor allele carriers in depressive patients and controls (79). No differences in hippocampal or amygdala volumes were observed for carriers of the *Bcl*I polymorphism in this study. In addition, in a recent study in premenopausal women a significantly higher number of homozygous carriers of the minor allele of the *Bcl*I polymorphism was observed in

*Table 1: Overview of studies and summary of data concerning associations of GR polymorphisms and depression.*

| Author, year | Characterization participants | Associations | HPA axis parameters |
|---|---|---|---|
| Van Rossum *et al*, 2006(60) | 490 inpatients with MDD (86% unipolar depression and 14% BD)<br>496 Healthy controls | Association between *Bcl*I polymorphism and depression<br>Association between ER22/23EK and recurrent depression<br>Association between ER22/23EK and faster response to antidepressants, as well as a slightly better cognition with respect to the divided attention test | No associations between SNPs and DEX/CRH test |
| Van West *et al*, 2006(84) | 180 Belgian patients with MDD, uni- and bipolar<br>134 Swedish patients with MDD, unipolar<br>354 Healthy controls | Association between promoter region (NR3C1-1) SNP and MDD (Belgian sample)<br>Association between ER22/23EK polymorphism (Swedish sample) and MDD | Not tested |
| Brouwer *et al*, 2006 (82) | 98 outpatients with unipolar MDD | Trend of *Bcl*I SNP towards reduced response rate to antidepressants. In particular in a subpopulation of patients with the highest ACTH levels in the DEX/CRH test | *Bcl*I variant carriers have increased ACTH responses in the DEX/CRH test |
| Krishnamurthy *et al*, 2008(78) | 53 premenopausal women with unipolar MDD, aged 21-45<br>29 healthy controls | Association between *Bcl*I SNP and depression<br>Association between *Bcl*I SNP and higher WHR in depressive women | No differences in plasma and urinary cortisol. |
| Zobel *et al*, 2008(79) | 322 patients with unipolar MDD<br>298 healthy controls | *TthIII*I and rs1866388 SNPs less frequent in patient group, and associated with larger hippocampal volumes. | Not tested |
| Spijker *et al*, 2008(85) | 241 patients with BD<br>532 healthy controls | *TthIII*I SNP less frequent in patient group, and a trend for a lower frequency of the 9β polymorphism in BD patients.<br>Association between the 9β polymorphism and less manic episodes. | Not tested |
| Moutsatsou *et al*, 2000(86) | 15 patients with BD<br>12 healthy controls | No associations were found | Not tested |
| Feng *et al*, 2000(117) | 100 patients with schizophrenia<br>40 patients with puerperal psychosis | No associations were found | Not tested |
| Bet *et al*, 2008(81) | 221 elderly subjects (aged > 65 years) with depressive symptoms<br>685 healthy controls (aged >65 years) | ER22/23EK and 9β: in combination with childhood adversity associated with an increased risk of clinically relevant depressive symptoms. | *Bcl*I heterozygotes have lower serum cortisol binding globulin levels. ER22/23EK carriers with childhood adversity have a lower free cortisol index |

*Abbreviations; ACTH adrenocorticotrophic hormone; BD bipolar disorder; DEX/CRH test dexamethasone/ corticotrophin releasing hormone test; HRSD Hamilton Rating Scale for Depression; MDD major depressive disorder; SNP single nucleotide polymorphism; WHR waist hip ratio.*

women with unipolar MDD (78). Furthermore, in the study of Krishnamurthy a positive association between this polymorphism and abdominal fat, as measured by a higher WHR, was reported. This is of particular interest, since it has been well recognized that a relationship exists between MDD and obesity (80). Bet et al recently observed lower levels of cortisol binding globulin in heterozygous *Bcl*I carriers (aged older than 65), but in this study no association between the *Bcl*I polymorphism and depressive symptoms was found (81).

Interestingly, Brouwer et al demonstrated a reduced response rate to antidepressants in depressive outpatients carrying the *Bcl*I variant (82). This finding applied in particular to a subpopulation of patients with the highest ACTH concentrations in the DEX/CRH test. It was suggested that the combination of both increased ACTH levels after administration of DEX/CRH, and carriage of the minor allele of the *Bcl*I polymorphism may be a more sensitive predictor of poor response to antidepressant treatment than these factors separately.



It should be noted that the single nucleotide change at the polymorphic *Bcl*I restriction site in intron 2 is referred to as a C (major allele) to G (minor allele) alteration in some articles (63, 78, 82), while in other reports a G (major allele) to C (minor allele) change is described (79, 83). This variability in the presentation can be explained by the direction in which the sequence of the *GR* gene is read (starting from the p-telomere to the q-telomere or vice-versa). To avoid confusion and to enable comparison of several studies we also used the term “minor allele”.

### *ER22/23EK polymorphism*

The combined ER22/23EK variant was found to be associated with recurrent depression (60). The frequency of this polymorphism was 5.7% when all patients, unipolar and bipolar, were included, and did not differ statistically from the control group. However, comparison of the control group to patients with a recurrent unipolar MDD yielded a significant difference. In the healthy control group 4.2% was found to be carrier of the ER22/23EK polymorphism, whereas a carriage frequency of 7.7% in the patient group with a recurrent unipolar MDD was observed. In accordance, Van West et al showed a significant relationship between the ER22/23EK variant and recurrent MDD (84). In a Swedish population 11% of the unipolar MDD patients were found to be carriers of the ER22/23EK polymorphism, while in their control group this was only 4%. In a Belgian population, which was studied by the same authors, no association was found with the ER22/23EK variant. Recently, Bet et al found in presence of childhood adversity an association between the ER22/23EK and 9β polymorphisms and an increased risk of

clinically relevant depressive symptoms in a Dutch population of subjects aged 65 years and over (81). In absence of childhood adversity there was no association between these polymorphisms and depressive symptoms. This study demonstrates clearly the importance of gene-environment interactions.

## *Other GR polymorphisms*

In several recent studies associations between other GR polymorphisms and unipolar or bipolar depression have been found. However, until now they have not been replicated. In this paragraph we will describe them briefly. In our recent study involving 241 patients with BD, we found a significantly lower frequency of the *TthIII*I polymorphism and a trend towards a lower frequency of a polymorphism in exon 9β (85). In addition, presence of the exon 9β polymorphism was significantly associated with less frequent manic episodes in this study, but no differences were found in frequencies of the other polymorphisms. Moutsatsou et al studied two *GR* gene isoforms (GR-a and GR-b) for the presence of mutations in 15 patients with BD and 12 normal subjects (86). They did not detect any mutations in the *GR* gene, which might have been due to the small number of patients in that study. Van West et al also found a negative association with another polymorphism (NR3C1-1) in the promoter region of the *GR* gene in a Belgian sample (84). This finding is not confirmed yet in other studies. In a Swedish sample, which was investigated in the same study, no association with this SNP was observed. Recent studies reported no associations between depression and the N363S polymorphism (60, 78, 85).

## *GR polymorphisms and response to antidepressant treatment*

In several of the earlier mentioned studies there is some evidence of an association between GR polymorphisms and prediction of response. In the study of Brouwer et al, response rate was defined as more than 50% reduction of Hamilton Rating Scale for Depression (HRSD) scores after 8 weeks treatment with paroxetine (82). In this population, carriers of the minor allele of the *Bcl*I polymorphism had significantly higher ACTH levels measured in a DEX/CRH test, which was additionally correlated with a lower response rate. In a large German group of depressive patients, an association between the ER22/23EK polymorphism and a faster clinical response to antidepressant treatment was observed (60). Clinical response was defined as a reduction of the HRSD in 5 weeks of antidepressant treatment with tricyclic antidepressant or SSRIs, whereas remission was defined as a score below 10 on the HRSD. A significant effect on the HRSD score was found and carriers of the ER22/23EK polymorphism were found to be in remission on average 5 days earlier. At admission and at discharge, however, the Hamilton scores did

not differ significantly between carriers and non-carriers. Unexpectedly, DEX/CRH tests yielded no differences between carriers of the polymorphisms. This may be explained by an overriding effect of the state-dependent increased activity of CRH and arginine vasopressin and GR resistance, yielding increased HPA axis activity, which is presumed to be present in all genotypes (11).

To summarize, some evidence exists that unipolar MDD is associated with the *Bcl*I and the ER22/23EK polymorphisms. Additionally, the minor allele of the SNP NR3C1-1 in the promoter region of the *GR* gene was found to have a lower frequency in a mixed population of unipolar and bipolar depressed patients. Also, in a large group of patients with bipolar disorder a lower frequency of the *TthIII*I polymorphism and a trend towards lower frequency of the 9β polymorphism was found.



## 6. GR polymorphisms and cognition

### *Mood disorders*

In both unipolar MDD and bipolar disorder, cognitive dysfunction can occur. In fact, cognitive symptoms such as reduced ability to think, lack of concentration and indecisiveness are, according to the Diagnostic Statistic Manual (DSM)-IV, some of the core symptoms in diagnosing a depressive episode. Also in the definition of a manic episode, cognitive symptoms are included. During a depressive episode, most well known cognitive deficits include diminished performance on shifting attention tasks, memory impairments, and problems with executive function (87-89).

While it is clear that cognitive impairment occurs during disturbed mood episodes, there is also growing evidence that these symptoms can persist in the euthymic phase of unipolar MDD and BD. In euthymic patients with unipolar recurrent MDD a persistent impairment of executive function was found (90). Persistent neuropsychological deficits present in BD also in the euthymic state, particularly impairment in sustained attention and working memory (91). This suggests that such deficits could be vulnerability trait markers of the illness (87). Additional evidence for this hypothesis is presented in studies of first degree family members of patients with BD, who show cognitive impairments in executive function, psychomotor speed and verbal ability, although milder than in the patient groups (90, 92). Some studies found that the deficits correlate with both the duration of illness and the number of episodes (93). However, Mur et al argue that these deficits, especially in executive function, are amongst the core symptoms of the disease, independent of course and severity of the disease (94). In BD, poor outcome is highly associated with cognitive impairment in remission, particularly executive dysfunction,

leading to impairment of psychosocial and occupational functioning (95). In a review on this topic, Glahn et al conclude that there are deficits in sustained attention, executive function and working memory in euthymic BD patients (96). These deficits are more severe in BD patients in comparison with unipolar patients, and could be trait markers of the illness. To enable interpretation of future studies on this topic, it is important to differentiate between patient groups (97), since patients with unipolar recurrent MDD seem to have different neurocognitive profiles compared to patients with BD and elderly patients with MDD (98).

Recently, some studies focused on the association between cognitive impairment, structural cerebral changes and GR polymorphisms. Zobel et al found in 64 patients with unipolar MDD, that during treatment with citalopram, the cortisol patterns in a DEX/CRH test changed and this finding was correlated with improvement of working memory. Other cognitive functions were not related to changes in HPA axis function in this study (99). In the earlier mentioned study of Zobel (see table), associations between the GR gene polymorphisms *TthIII*1 and rs1866388 and hippocampal volumes were found, possibly related to cognitive impairment, but this was not tested in this study (79).

In the German depressed patients a test for divided attention was performed (60). Impaired performance on this test in a group of depressed patients has been shown to be related to therapy resistance, as well as an elevated risk on to relapse within 6 months (100). During a depressive episode, ER22/23EK carriers showed a shorter reaction time with respect to the divided attention test than non-carriers. At discharge they also tended to perform better, although this effect was not statistically significant. This suggests that carriers of the ER22/23EK polymorphism may be relatively protected from potentially harmful consequences of increased HPA axis activity on cognitive functioning.

### *Dementia*

In elderly patients with recurrent MDD, there is an overlap between depression and Alzheimer's disease. This is mainly because these patients exhibit a generalized pattern of cognitive deficits. One diagnostic feature is the reversibility of these symptoms of depression, which is clearly not the case in Alzheimer's disease (101). Over activity of the HPA axis has been associated with neurocognitive decline and dementia (102, 103). This decline in neurocognitive functioning could possibly be explained by elevated cortisol levels, which is also associated with increased risk of cardiovascular pathology. Cortisol levels tend to increase with aging, both in healthy and demented elderly (104, 105), but to a greater extent in demented patients. Magri et al conclude in their review that, besides the harmful effects of elevated cortisol levels on cognition, hippocampal

neuronal impairment may in turn be responsible for reactive elevation of cortisol levels (106).

To our knowledge, only two studies have focused on the relationship between aging, neurocognitive decline and GR polymorphisms. First, in a Dutch population of more than 6000 elderly, carriers of the ER22/23EK polymorphism were found to have a lower risk of developing dementia (61). At baseline, dementia was less prevalent in this group (with an 86% risk reduction). In a second group of more than 1000 Dutch elderly in the same study, a cerebral MRI was also performed. ER22/23EK carriers showed significantly less cerebral white matter lesions, as well as a decreased risk of progression of these lesions. In this study, non-demented ER22/23EK carriers performed better on psychomotor speed tests. However, no differences in memory tasks between genotypes were found (61). Another study of Kuningas et al confirmed in a cohort of 563 participants of 85 years and over the association between cortisol levels and impaired global cognitive functioning, and in particular impairments in attention and psychomotor speed. No associations between these test performances and GR polymorphisms were observed (107).



## 7. MR polymorphisms

Theoretically, it seems plausible that MR polymorphisms could also affect vulnerability for mood disorders, but until now this hypothesis has not been extensively studied. Kuningas et al found an association in the afore mentioned study between the MR SNP I180V, consisting of a GTT to ATT change in exon 2 (codon 180) and the prevalence of depressive symptoms in the elderly (107). Interestingly, this SNP is also associated with increased saliva cortisol and plasma cortisol responses and higher heart rate in reaction to a psychosocial stressor (the Trier Social Stress Test) in normal subjects (108, 109).

## 8. Future perspectives

To summarize, evidence is accumulating showing that carriers of GR polymorphisms *Bcl*I and ER22/23EK may be more vulnerable to developing MDD. In addition, carriers of the ER22/23EK polymorphism appear to be protected against dementia, but these data on cognitive functioning have not yet been confirmed. Other studies focusing on GR and MR polymorphisms showed associations with uni- or bipolar depression, but these data also need replication, preferably in larger populations. Future research should therefore invest in replicating these association studies in additional and larger patient groups. Another important aspect in future studies should be the proper definition of patient groups. Bipolar depressed and unipolar depressed patients seem to differ with respect

to the severity in HPA axis dysregulation and the clinical effects of GR polymorphisms (5, 10, 22). Therefore, it could be argued that these two types of patients should be investigated separately. On the other hand, others have demonstrated that BD and MDD patients are endophenotypically rather similar and even may be considered as one disease entity with both showing increased cortisol and ACTH release after stimulation with CRH following DEX suppression (11).

Many discrepancies exist with respect to the relationship of GR polymorphisms with HPA dysregulation in various brain areas. It remains intriguing that the two GR polymorphisms (*Bcl*I and ER22/23EK) with opposite effects with respect to GC sensitivity to adrenal feedback and in peripheral tissues are both associated with depression. It is also known that increased as well as decreased levels of glucocorticoids in the brain can be associated with depression. Supporting this is the finding that GR antagonists as well as GR agonists have been shown to have antidepressant effects. These apparent contradictory findings could possibly be explained by the complex mechanism of action of the GR. GR acts like a transcription factor, and is able to both positively and negatively regulate target genes. The production of CRH in the brain is regulated by GCs through binding to GRs in different brain regions. While the GR stimulates the CRH expression in limbic regions like the amygdala, it inhibits CRH production through a negative feedback mechanism in the hypothalamus (110, 111). An important focus is the balancing system of GR as well as MR. Future research should elucidate the importance of the MR in the pathophysiology of MDD. Studies in rats have shown MR is up regulated in the brain after psychological stress, associated with inhibition of the HPA-axis (112). Blockade of the MR in the brain leads to activation of the HPA-axis, under basal and stressful conditions. This is reflected in the decrease in blood pressure, heart rate and corticosterone response in rats after administration of a MR antagonist (113, 114). Besides these autonomic responses, MR also enhances cognitive responses like spatial learning in rats (115) as well as behavioral responses, such as a dramatic decrease in aggressive behavior in rats towards an intruder after treatment with a MR antagonist (116). In humans, brain MR function has not yet been extensively studied, however, animal studies seem encouraging for future research in this field.

It is of paramount importance to obtain more insight in the pathophysiology of depression and its clinical consequences, such as cognitive impairment. Identification of genetic markers for prediction of response to treatment and relapse is important in order to develop new treatment strategies. It will also be important in future research to differentiate between patient groups, since different neurocognitive profiles have been identified in unipolar, bipolar and elderly patients with unipolar MDD. This may also have implications for treatment possibilities. Elucidating the connections between GR and MR polymorphisms and depression may provide new insights from a combined

endocrine-genetic perspective and may in the future offer possibilities to classify patients in more homogeneous groups for whom treatment and risk of relapse predictions can be made and in addition, may provide new therapeutic targets to influence this system in these illnesses.

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