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## Summary

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## *Introduction*

Bipolar disorder (BD) is a common mood disorder, with an estimated prevalence of 2.4 % in the Netherlands. Worldwide, BD is estimated to stay in the top ten causes of Years Lived with Disability (YLDs), accounting for 2.5% of total global YLDs. BD was once considered as an episodic illness with a relatively favorable outcome, but nowadays more attention is given to the variant with a more chronic course of the disease with cognitive deficits in between episodes, residual mood symptoms and impaired functioning in daily life roles.

The core pathophysiological underpinnings of BD have to be elucidated to be able to understand the underlying processes leading to the clinical manifestations of the disease. One of the possible strategies in identifying biological underpinnings is the introduction of endophenotypes as alternative leads to find genetic vulnerability markers instead of the complex, phenotypical, disease symptoms and syndromes. Endophenotypes are known as subclinical quantifiable traits that exist in affected and unaffected relatives independent of the clinical manifestation of the disorder. The traits can be for example, neurophysiological, biochemical, endocrine, neuro-anatomical, or cognitive in nature. In this dissertation the focus will be on the role of cortisol exposure and cognitive performance as two possible endophenotypes influencing clinical course of BD.

## *Study aims*

In order to identify risk factors, that have impact on the clinical course of BD and treatment of patients suffering from BD, we started the Bipolar Stress Study (BiSS). In this study three levels and their interactions with the environment (stressful life events and social support) were distinguished: clinical functioning (phenotype), genetic variations and vulnerability (genotype) and endophenotypes, specifically cortisol exposure and cognitive functioning.

In this dissertation, part of the results of this study is presented. The emphasis was on the role of genotypes of the cortisol receptors, and the endophenotypes, cortisol exposure and cognitive functioning. The results of the BiSS may help to develop clinically relevant diagnostic and treatment interventions to improve the course of BD and subsequently the quality of life of patients with BD.

## *Patients and Methods*

The BiSS consisted of a cross sectional, and a prospective, longitudinal part. For the cross sectional study, data of 366 patients were collected with respect to genotype, phenotype

and endophenotype. In the 24 month longitudinal study, of these 366 patients, 189 patients participated. In this thesis, the cross-sectional data at baseline are analyzed. Genetic data were associated with clinical characteristics and retrospectively collected data on clinical course of BD. In a subpopulation of the 189 patients hair cortisol was analyzed in relation to clinical characteristics of BD at baseline.

In the longitudinal study, we first assessed cognitive performance of the 189 patients at the first visit of the longitudinal part. Cognitive functioning is regarded as endophenotype with trait-like characteristics. Additionally, it is known to be influenced by other, more state-like factors as well. In order to be able to properly investigate the role of cognitive performance as an endophenotype, it was necessary to first elucidate the influence of “state-factors”, like medication use on the results of the cognitive tests. In this thesis, the influence of medication use on cognitive performance was analyzed with data of the first visit of the longitudinal part.

## *Results*

### *1. Literature review (Chapter 1 and 2)*

As a first step in approaching the relation between cortisol exposure and mood, the literature has been reviewed, regarding 1) glucocorticoid sensitivity and mood (chapter 1), and, 2) genetic variations, or polymorphisms, in the Glucocorticoid Receptor (GR) and Mineralocorticoid Receptor (MR) genes in relation to glucocorticoid sensitivity, mood and cognition (chapter 2).

Our main findings are:

#### *Chapter 1:*

- Hyperactivity of the HPA-axis occurs in 80% of the acutely depressed patients (either bipolar or unipolar) as measured by the Dexamethasone/ Corticotropin Releasing Hormone (DEX/CRH)-test, with higher cortisol levels after DEX/CRH administration.
- A long-term pattern of mild resistance for negative feedback signaling of glucocorticoids has been found, worsening during depressive episodes (not exclusively bipolar depression).
- Single nucleotide polymorphisms in the genes encoding the GR as well as the MR, influence the set-point and regulation of the HPA axis, both measured through the Dexamethasone Suppression Test (DST) with the use of a very low dose

Dexamethasone of 0.25 mg. This dosage is known to detect subtle changes in feedback response to cortisol elevation.

- The GR polymorphisms ER22/23EK (rs6189/rs6190) and 9 $\beta$  (rs6198) and the MR polymorphism MRI180V (rs5522) show a relative resistance for cortisol suppression after the DST. The GR polymorphisms *BclI* (rs41423247), N363S (rs6195) and the MR polymorphism -2G/C (rs2070951) show a relative hypersensitivity for cortisol suppression after the DST.
- In utero stress and early trauma are important (dys)regulators of this set-point, probably through epigenetic changes leading to different functional gene expression and subsequent protein synthesis.

### Chapter 2:

- By looking at different polymorphisms in the GR gene and the relation with cognitive endophenotypic and phenotypic characteristics, it has been shown that the *BclI* (rs41423247) and ER22/23EK (rs6189/rs6190) polymorphisms are associated with risk on developing depression in several studies.
- The polymorphism ER22/23EK (rs6189/rs6190) associates with a decreased risk of dementia in healthy individuals.
- During a depressive episode, carriers of this ER22/23EK (rs6189/rs6190) variant demonstrated a tendency towards better cognition compared with non-carriers, as measured by divided attention tests.

Concluding, the above described polymorphisms in the GR and MR gene, are associated with phenotypic characteristics in mood and endophenotypic features in cognition, revealing a possible mediating mechanism through changing the HPA-axis set point. Mainly the *BclI* (rs41423247) and the ER22/23EK (rs6189/rs6190) are associated with higher risk for depressive episodes.

## 2. *GR/MR polymorphisms and clinical course (chapter 3 and 4)*

Due to findings in BD research that the HPA-axis is dysregulated, we investigated the GR and MR as important receptors in the regulation of the feedback loop in the HPA-axis on pituitary level. Hereby, we focused on genetic variations of the GR and MR gene in relation to clinical characteristics of BD. The results of the cross sectional study show that the GR and MR gene polymorphisms associate with clinical characteristics and retrospective course of BD, the exact findings are as follows:

### Chapter 3

- In the first analysis (n= 245) no differences in frequencies of polymorphisms were found in bipolar patients compared to healthy controls.
- The 9 $\beta$  (rs6198) polymorphism in the GR gene is less frequent in bipolar patients with a history of more than a median number of 5 (hypo)manic episodes.

### Chapter 4

- In the extended cohort (n=326, in 40 patients genotype failed), an association is found between the haplotype consisting of the 9 $\beta$  (rs6198) polymorphism in combination with the TthIII (rs10052957) polymorphism in the GR gene and a higher risk on seasonal patterns of hypomania.
- For the BclI (rs41423247) haplotype, we observed a similar trend for higher risk of seasonal hypomania.
- Carriers of the ER22/23EK (rs6189/rs6190) polymorphism have an almost 8 years earlier onset of their first (hypo)manic episode than non carriers.
- No relation between MR gene polymorphisms and characteristics of BD was found.

Our findings indicate that 9 $\beta$  (rs6198), BclI (rs41423247), and ER22/23EK (rs6189/rs6190) influence clinical features of BD. This relationship of GR-polymorphisms with the course and characteristics of BD can be added to a growing number of studies, in which the regulation and functioning of the GR has been shown to be related to clinically relevant aspects of mood disorders. However, we found a non-linear relationship between GR polymorphisms and sensitivity of the central feedback on cortisol production. The idea is that the HPA-axis has an optimum set point in a U-shaped curve with regard to cortisol exposure at pituitary level. This is illustrated by the fact that some SNPs lead to relative resistance while others are involved in relative hypersensitivity in response to GCs: both can be involved in dysregulation of mood. Moreover, with the influence of GR polymorphisms, specifically 9 $\beta$ (rs6198) or BclI (rs41423247), on HPA-axis regulation, other factors, like seasonal induced changes in cortisol sensitivity, can further deregulate the system, leading to proneness for seasonal episodes as shown in chapter 4.

### 3. *Cortisol levels in saliva and hair, and the relationship with clinical course of BD (chapter 5)*

As first in the world, we applied a new technique for assessing cortisol levels in scalp hair in patients with BD. This could give us the opportunity to get insight in the influence of e.g. life events, mood episodes and effects of treatment on the long-term functioning of the HPA-axis. In chapter 5 we showed the following results:

- Compared to healthy controls, bipolar patients have similar cortisol levels in scalp hair.
- There is no association between hair and saliva cortisol levels assessed in the BD group.
- Within the BD patients with higher cortisol levels as measured in hair, we found an association with an older age at onset (>30 years).
- In addition, a higher rate of psychiatric co-morbidity with the exception of panic disorder was found in patients with higher cortisol levels.
- Remarkably, patients with co-morbid panic disorder reveal lower cortisol levels in hair, even when compared to healthy controls, whereas saliva cortisol was non-significantly increased.

Our findings raise the question whether changes in HPA-axis functioning might be limited to subgroups of patients or whether changes in HPA-axis functioning might be limited to the stress response itself and not to long-term mean cortisol levels. Additionally, the findings that saliva and hair cortisol did not correlate supports the concept that both analyses for cortisol indeed differ in what aspect of the HPA-axis functioning is assessed. Cortisol in hair reflects long-term free cortisol levels, whereas saliva reflects short-term free cortisol levels which are influenced by acute stress responses, diurnal variation, as well as pulsatility of cortisol secretion. Finally, several clinical characteristics correlate with hair cortisol levels; although results might be complex to interpret properly, our findings gives impetus to further research to the relationship of hair cortisol levels and retrospective clinical aspects of BD.

### 4. *Associations of cognitive functioning with medication use in BD (chapter 6)*

Currently, it has been convincingly found that cognitive deficits regarding attention, working memory and executive functioning, can have a negative impact on social



functioning and the clinical course of BD. Biologically seen, HPA-axis dysregulation can cause impairment of cognitive functioning. Before using cognitive functioning as endophenotype in relation to cortisol exposure and to clinical characteristics, we decided to first investigate the “state-like” effects on cognition. We started with analyzing the influence of medication use on cognitive performance, and continued with analyzing the influence of current mood on cognitive performance. Therefore, the Test for Attentional Performance (TAP) was explored in relation to medication use and clinical parameters. Our main findings in chapter 6 comprise:

- A significant association between use of multiple types of medication and poor cognitive performance regarding executive functioning.
- Attention and working memory showed a similar, however non-significant trend.
- Particularly the use of antipsychotics is associated with impaired executive functioning.
- Lithium use is *not* associated with diminished cognitive performance.

The question remains whether medication use, specifically use of multiple types of medication (polypharmacy), is causing cognitive impairments or is an expression of the severity of the disease. In other words, it might be possible that patients with a more severe form of BD need more medication. However, we adjusted the analyses with inclusion of disease severity, which did not alter the results, indicating that the medication use might be an independent factor. However, other study designs, like Randomized Controlled Trials, could investigate this important topic in more depth.

### *Conclusion*

In this dissertation, several factors are identified as risk factors influencing clinical course of BD. At the genetic level, several GR gene polymorphisms altering cortisol sensitivity, associate with seasonal patterns of mood episodes, especially hypomania. In particular the 9 $\beta$  polymorphism (rs6198) seems to associate with clinical characteristics of BD. One hypothetical explanation could be the link with increased anti-inflammatory activity. These findings give further biological background to the importance of sensitivity of cortisol feedback response in relation to mood disorders.

At the endophenotypic level, higher cortisol exposure assessed by hair analysis is associated with more psychiatric co morbidity in BD patients, and an older age at onset of the disease. However, no difference is found between the total group of BD patients and healthy controls, indicating that long-term cortisol in scalp hairs is not changed

when comparing with a broad phenotypic entity like BD. This is underlining the need of precise defined and unambiguous long-term phenotypic parameters like mood episodes, anxiety symptoms, life events, and cognition, all in preceding months. This thesis gives impetus to further research with this technique, in order to identify consequences of chronic stress and chronic stress hormone elevations.

Cognitive function is another endophenotypic marker. Before using cognitive performance as endophenotype, we first investigated the influences of medication as potential confounder. We found that cognitive performance is related to the number and types of medication used. It should be noted that while lithium had no effect on cognition, the use of antipsychotics significantly did. With this result in mind, the next phase in the analysis of the Bipolar Stress Study will be to first investigate the influence of current mood on cognitive functioning as second potential confounder. Thereafter, we will study the relationship between cognition and GR and MR polymorphisms, as well as cognition as potential endophenotypic risk factor influencing course of BD.

Summarizing, cortisol exposure and cognition are both associated with several clinically relevant phenomena defining course of BD, thereby giving ground to further investigation of the consequences on the long-term effects of differences in cortisol exposure in BD patients in the Bipolar Stress-study.

