Diplomarbeit

Genetic links of the Big Five personality traits in bipolar disorder

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Graz, am 03.03.2021 *Tanja Kirchschlager eh.*

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Abkürzungen und deren Erklärung

ANCOVA – Analysis of covariance

BD – Bipolar affective disorder

BDNF – Brain-derived neurotrophic factor

BMI – Body mass index

CLOCK – Circadian locomotor output cycles kaput

COMT – Catechol-o-methyltransferase

DNA – Deoxyribonucleic acid

DSM-IV – Diagnostic and statistical manual of mental disorders

DZ – Dizygotic

EDTA – Ethylene-diamine-tetra-acetic acid

GWAS – Genome wide association studies

ICD-10 – International classification of diseases

ICH – International conference on harmonization

MAO – Monoamine oxidase

mRNA – Messenger RNA

MZ – Monozygotic

NEO-FFI – Neuroticism, extraversion, openness for experience five factor inventory

NEO-PI – Neuroticism, extraversion, openness for experience personality inventory

PER3 – Period circadian protein homolog 3 protein

RNA – Ribonucleic acid

SKID – Structural clinical interview for DSM-IV

SNP – Single nucleotide polymorphism

tRNA – Transfer RNA

UD – Unipolar depression

WHO – World health organisation

5-HT – 5-hydroxytryptamin/serotonin

5-HTR2A – 5-hydroxytryptamine receptor 2A

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Zusammenfassung

Einleitung: Genetische Faktoren spielen eine wichtige Rolle in der Entwicklung und dem Beginn der bipolaren Störung in Abhängigkeit von auslösenden Faktoren, wie frühe Belastungen, Coping-Strategien und Sozialgefüge im Sinne des Stress-Vulnerabilitäts-Models. Ebenso wirken sich Persönlichkeitsmerkmale, welche zum Teil ebenso genetisch vermittelt werden, auf den Verlauf der bipolaren Störung aus. In dieser Studie untersuchten wir genetische Einflüsse auf die Persönlichkeitsmerkmale bei bipolaren Patient*innen

Methoden: DNA wurde aus Nüchternblut von 40 männlichen und 43 weiblichen bipolaren Patient*Innen mittels Aussalzmethode am Institut für Humangenetik Graz isoliert. Die Genotypisierung wurde mittels Omniexpress1.1 von Illumina am Life & Brain Center Bonn durchgeführt. Hypothesengeleitet erfolgte die Isolierung von Genotypen folgender Gene: COMT (rs4680), BDNF (rs6265), 5-HTR2A (rs6311, rs6313) und die Uhrengene CLOCK (rs534654, rs1801260, rs12649507), sowie PER3 (rs10462021, rs10864315, rs228682, rs228642). Die Persönlichkeitsmerkmale der ‚Big Five' wurden mittels NEO-FFI, einem Fragebogen mit 60 verschiedenen Statements, durchgeführt, um eine quantitative Analyse der Persönlichkeit der Proband*innen zu erhalten. Für die statistische Analyse wurde IBM SPSS Version 25 verwendet. Untersucht wurden die unterschiedlichen Ausprägungen der Persönlichkeitsmerkmale zwischen den Genotypträger*innen. Hier wurde das Alter der Proband*innen als Co-Variable für die Persönlichkeitsmerkmale ‚Offenheit für Erfahrungen' und ‚Extraversion' eingefügt.

Ergebnisse: Zwei der untersuchten Genvarianten für PER3 zeigten einen signifikanten Unterschied bezüglich des Persönlichkeitsmerkmals Neurotizismus der bipolaren Patient*innen. PER3 rs228682 zeigte höhere Werte bei den Genotypenträger*innen AG und AA im Vergleich mit dem GG Genotyp ($F(2/78) = .03$, $p = .003$, $Eta = .140$), während PER3 rs228642 höhere Werte für die Gruppe AG+GG als AA zeigte ($F(1/79) = .01$, $p = .008$, $Eta = .085$).

Die Analyse zeigte zusätzlich einen Trend ($p < 0.1$) der Assoziation von Persönlichkeitsmerkmalen mit den Genotypen der Gene COMT (rs4680), 5-HTR2A (rs6311, rs6313) und PER3 (rs228642).

Conclusio: Die PER3 Polymorphismen rs228682 und rs228642 zeigten einen signifikanten Unterschied für das Persönlichkeitsmerkmal Neurotizismus. Zusätzlich wurden weitere

Trends bezüglich Persönlichkeitsunterschieden bei den Genen COMT (rs4680), 5-HTR2A (rs6311, rs6313) und PER3 (rs228642) festgestellt. Es werden definitiv weitere Studien mit einer viel größeren Fallzahl benötigt, um stichhaltige Antworten zu erarbeiten und ein noch größeres Wissen über Pathomechanismen, sowie Persönlichkeitsentwicklung und -varietät von bipolar Erkrankten zu erlangen.

Abstract

Introduction: Genetic factors play an important role in BD development and onset in dependency of provoking triggers, like early life stress, coping mechanisms and social stability as described by the stress-vulnerability model. Furthermore, specific personality traits that are genetically transmitted to some extent have an impact on the course of BD. Now, in this thesis we observed the genetic influences on personality differences in BD patients.

Methods: Blood samples were taken from 40 male and 43 female BD patients and sent to the Institute of Human Genetics Graz for DNA-isolation with the salting out technique. Genotyping was performed with the Omniexpress1.1 bead chip from Illumina at the Life & Brain Center Bonn. Guided by hypotheses, the isolation of the following gene variants took place: COMT (rs4680), BDNF (rs6265), 5-HTR2A (rs6311, rs6313) and the CLOCK genes CLOCK (rs534654, rs1801260, rs12649507) and PER3 (rs10462021, rs10864315, rs228682, rs228642).

The 'Big Five' personality traits were assessed by the NEO-FFI, a questionnaire with 60 different statements, in order to receive a quantitative analysis of our participants' personality.

IBM SPSS version 25 was used for the analysis of this thesis' data. We examined the differences of personality traits in genotype carriers. Age was inserted as covariate in our model for openness for experience and extraversion.

Results: Two of the investigated genotypes of PER3 showed a significant difference for the personality trait neuroticism in BD patients. PER3 rs228682 showed higher scores in AG and AA genotype carriers in comparison to the GG genotype ($F(2/78) = .03$, $p = .003$, $Eta = .140$), whilst PER3 rs228642 showed higher scores for the group AG+GG than AA ($F(1/79) = .01$, $p = .008$, $Eta = .085$).

The analysis identified trends ($p < 0.1$) concerning the association between personality traits and genotypes of COMT (rs4680), 5-HTR2A (rs6311, rs6313) and PER3 (rs228642).

Conclusion: The PER3 polymorphisms rs228682 and rs228642 showed a significant difference for the personality trait neuroticism. Additional trends toward statistical significance concerning personality differences were determined for the genes COMT (rs4680), 5-HTR2A (rs6311, 6313) and PER3 (rs228642).

Further analyses with larger sample sizes are definitely needed to receive valid answers and to gain more knowledge about BD pathomechanisms and personality development/variety in BD patients.

1 Introduction

1.1 Bipolar affective disorder

Bipolar affective disorder (BD) is a psychiatric disease, which belongs to the affective disorders. BD is characterized by alternating episodes of depression and mania/hypomania. The intervals between each episode are mainly symptomless, which is called euthymia (Gallinat and Heinz 2017).

1.1.1 Classification

Different classification systems assist clinicians and researchers with the complicated task of classifying complex diseases such as BD. The two mainly used classification systems are:

- The 'Diagnostic and Statistical Manual of Mental Disorders' (DSM-IV), published by the 'American Psychatric Association' (APA).
- The 'International Classification of Diseases' (ICD-10), produced by the World Health Organization (WHO).

Both manuals place their main focus on the manifestation of psychiatric conditions and their symptoms rather than their mechanism of development (Vahia 2013).
According to the classification systems ICD-10 and DSM-IV, BD can be categorized as followed:

Table 1 BD Classification (Own table, based on American Psychiatric Association 2000; Rothenhäusler and Täschner 2013)

Bipolar I
• Depressive and manic episodes occur in a circulating manner • Euthymic periods of 'normal' moods and usual functioning in between these episodes can occur • BD I is diagnosed when the patient has at least one manic episode and one other affective episode
Bipolar II
• Depressive and hypomanic episodes occur without manic episodes • Euthymic periods of 'normal' moods and usual functioning in between these episodes can occur • BD II is diagnosed when the patient has at least one hypomanic episode and one other affective episode
Cyclothymic disorder
• Hypomanic and dysthymic symptoms for at least 2 years without pausing for more than two months • Hypomanic and dysthymic symptoms do not meet the criteria for a depressive or hypomanic episode
BD not otherwise specified
• Bipolar features that do not meet criteria for any specific BD as seen above

1.1.2 Symptoms

1.1.2.1 Manic Episodes

Criteria for a manic episode include a period of abnormally elevated or irritated mood, which lasts for at least 1 week. Additional, three out of the following symptoms must occur to diagnose a manic episode according to ICD10 or DSM-5.

- Increased self-esteem
- Less need for sleep
- Talking more, louder and quicker than usual, pressure to talk
- Easily distracted
- Racing thoughts or flight of ideas
- Increased risky behaviour
- Psychomotoric agitation, trying to do many things at once

(Rothenhäusler and Täschner 2013; American Psychiatric Association 2000).

During manic episodes, patients' judgment ability can be reduced, leading to impulse buying, debt and problems at work. Up to 30% of manic patients show psychotic symptoms.
Manic episodes are followed by euthymic periods with normal levels of energy and functioning or by depressive episodes (Rothenhäusler and Täschner 2013; Fleischhacker and Hinterhuber 2012).

1.1.2.2 Hypomanic Episodes

Hypomanic episodes are less severe and brief, because the symptoms only need to last for four days in a row. Hypomanic patients are capable of controlling their actions and adapting their behaviour to the rules and norms of their environment. About 5-15% of BD II patients develop a manic episode over time (Rothenhäusler and Täschner 2013; American Psychiatric Association 2000).

1.1.2.3 Mixed Episodes

Mixed episodes show a combination of symptoms of depressive and manic episodes and are associated with a rather dysphoric and irritated mood, anxieties, aggression and feelings of guilt. These episodes can be seen within 5% of all patients undergoing their very first episode during bipolar disorder and in up to 40% of manic episodes in long-time bipolar disorder patients (Rothenhäusler and Täschner 2012).

1.1.2.4 Depressive Episodes

Depressive episodes are not only characterized by a depressed mood for at least 2 weeks of time, but are also associated with loss of interest and enjoyment as the main characteristics. Additionally, five out of the following symptoms must be seen within the 2 weeks:

- Feelings of despair and worthlessness
- Insomnia/hypersomnia
- Change of appetite
- Fatigue/decreased energy
- Feeling restless or agitated
- Concentration problems, problems making decisions
- Thoughts about death or suicide

The above-mentioned feeling of agitation is an important risk factor to take into account when suicidal thoughts exist at the same time.
Also, a so-called morning blues with improved wellbeing in the evening can be seen in some patients. Headaches, back pain, dizziness and other physical symptoms can indicate a depression as well (Fleischhacker and Hinterhuber 2012; Gallinat and Heinz 2017; American Psychiatric Association 2000).

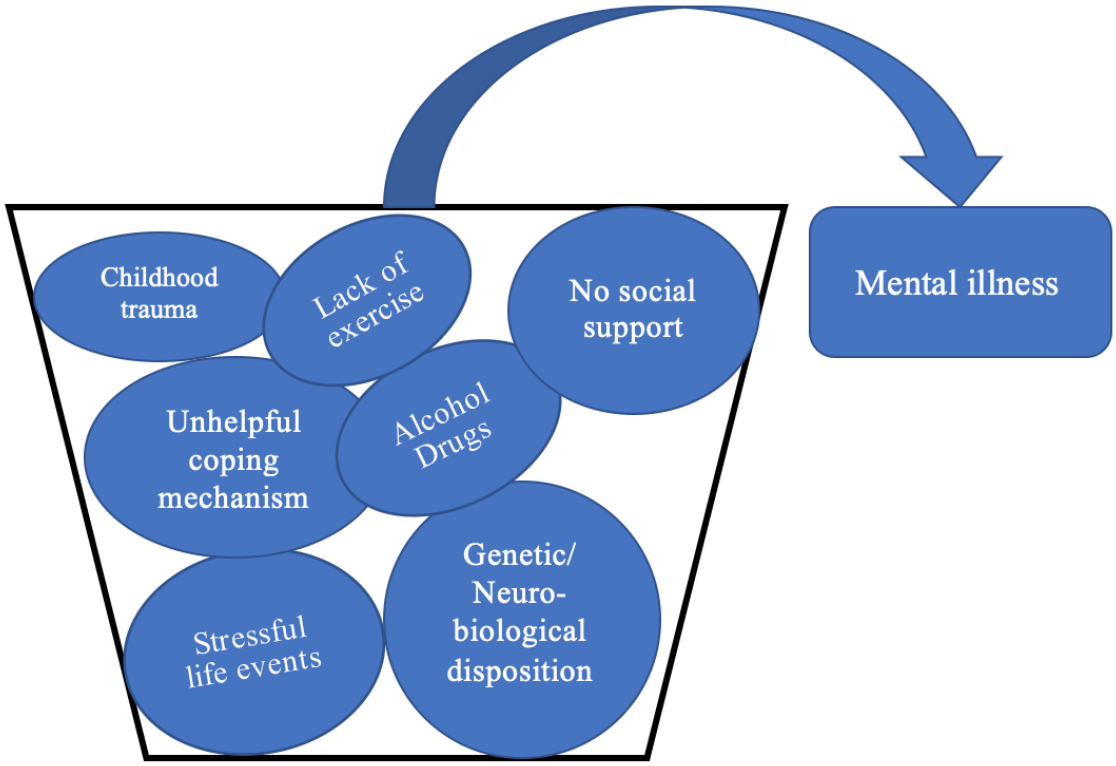
1.1.3 Epidemiology

The different types of BD can be found within 5% of the adult population, whilst BD I accounts for approximately 1-2%. The average age of onset is between 20 and 30 years. However, about 20-30% of all patients develop the psychiatric disease before the age of 20. BD shows the same prevalence in men and women (Rothenhäusler und Täschner, 2013; Gallinat and Heinz 2017; Bebbington and Ramana 1995).
Patients with BD are not only at risk for developing psychiatric and somatic comorbidities (such as substance abuse, anxiety disorders, borderline personality disorder, attention deficit hyperactive disorder or medical conditions like hypertension, asthma, diabetes, obesity and hypothyroidism), but have a rather high suicide rate with up to 20% (Gallinat and Heinz 2017; Sasson et al. 2003; Hossain et al. 2019).

1.1.4 Aetiology

BD is seen as a multifactorial disease described through the stress-vulnerability model, concerning the interaction between individual genetic disposition and critical life events triggering the disease. Genetic, neurobiological and psychosocial factors are taken into account as relevant components for an individual disposition (Möller et al. 2017; Gallinat and Heinz 2017).
The following figure portrays a simplified version of the stress-vulnerability model.

Figure 1 Interaction of individual disposition and critical life events triggering mental diseases – the stress-vulnerability model (own figure, based on Möller et al. 2017; Gallinat and Heinz 2017)



1.1.4.1 Monoamine Hypothesis

The imbalance of different neurotransmitters and alterations of the number and effectiveness of their receptors play an important role in BD (Möller et al. 2017).

Serotonin, a neurotransmitter occurring highly concentrated in the raphe nuclei of the brain stem and in the gastrointestinal tract, has an inhibitory effect in the central nervous system, dampening the stress response and controlling alertness, memory performance and how we experience pain. Furthermore, serotonin has an effect on other complex physiological systems, like respiration, cardiovascular regulation, thermoregulation and human sexual behaviour. Low concentrations of serotonin, measured through liquor concentration of 5-HIES (5-Hydroxyindoleacetic acid), a degradation product of serotonin, are associated with aggression, impulsiveness and suicidal tendencies. Not only affective disorders are associated with disturbances in the serotonergic system, but also schizophrenia, anorexia nervosa, anxiety disorders and impulse-related disorders (Lucki 1998; Fleischhacker and Hinterhuber 2012).

The catecholamines noradrenaline, adrenaline and dopamine have an excitatory effect on us. High noradrenaline concentrations are found in the central nervous system, while adrenaline, a product of the adrenal medulla, is released into blood vessels during mental and physical stress and is metabolised within mere minutes. Both catecholamines improve motivation, alertness and concentration. The central noradrenergic system seems to be overactive during manic episodes, while lacking activity during depressive ones. (Fleischhacker and Hinterhuber 2012).

The dopaminergic system has an effect on our concentration, psychomotoric speed and our ability to feel pleasure. Dopamine producing neurons can be found in the nuclei of the brainstem, retro-rubro area, substantia nigra (pars compacta) and the ventral tegmental area. Patients within a depressive episode and reduced motor activity have a dysfunctional dopaminergic system. Additionally, changes within the glutamatergic and GABAergic system as well as in different neuropeptides can be found (Dunlop and Nemeroff 2007; Möller et al. 2017).

The monoamine hypothesis has been supported by the fact that amitriptyline, as a tricyclic antidepressant, and MAO inhibitors demonstrably ease the symptoms of depression by their pharmacological effect of increasing the monoamine transmitter concentration in the synaptic gap of nerves within the central nervous system. However, other drugs, that treat depressive disorders, show the same effect on symptoms without increasing the neurotransmitter concentration, whereas other substances, cocaine for example, have no antidepressant effect, while increasing the monoamine concentration in the synaptic gap (Barchas and Altemus 1999).

This leads us again to the multifactorial model with changes within the monoamine system functioning as individual disposition for BD (Möller et al. 2017; Gallinat and Heinz 2017).

1.1.4.2 Genetic Factors

Through family, twin and adoption studies, it was possible to confirm the concept of a genetic disposition for BD. However, the genetic disposition for BD should be seen as a rather polygenetic one.

Family studies show that first-degree relatives of patients with BD have a ten times higher risk of developing the same condition than the standard population. Twin studies were able to detect a concordance rate of 80% for BD (Möller et al. 2017).

Basically, the risk of developing BD is genetically modified, but in contrast to monogenetic diseases, which are triggered by one causal gene, specific interactions with

the environment, chronic stress and other provoking triggers (e.g. childhood trauma, financial problems) pave the way for BD (Fleischhacker and Hinterhuber, 2012).

A range of researches has focussed on the neurotransmitter system and its responsible genes in context to the monoamine hypothesis. Polymorphisms of the serotonin transporter (5-HTT), monoamine oxidase A (MAO A) and the catechol-o-methyltransferase (COMT) are well-documented for BD in prior candidate-gene approaches. Additionally COMT polymorphisms correlate with the occurrence of schizophrenia and suicidal behaviour (Craddock and Forty 2006; Möller et al. 2017; Fleischhacker and Hinterhuber, 2012).
Another well-documented gene is brain derived neurotrophic factor (BDNF). This neurotrophin is relevant for neuronal growth, differentiation and plasticity. There have been both positive and negative studies concerning the association between BDNF and BD (mostly based on ethnic differences), indicating that BDNF polymorphisms may not have a major impact on developing BD. However, genetic variants correlate with the appearance of rapid cycling and therefore seem to be associated with the clinical presentation of BD. This gene will be discussed more deeply in the following chapter.
Apart from the above-mentioned genes, many others seem to play an important role for the individual vulnerability for BD. However, we do know that the interaction of different genetic polymorphisms lay the foundation for BD development and psychiatric symptoms. These polymorphisms can be found in a wide range of different genes, like genes coding for neurotrophic factors, ion channels and their signalling pathways, CLOCK genes or cell adhesion proteins, to name but a few. Identifying further genetic factors and their interactions can extent our horizon concerning the aetiology for BD, its treatment and the identification of environmental and psychosocial factors interacting with the genetic predisposition (Craddock and Forty 2006; Mullins et al. 2020).
Further information concerning genetic polymorphisms in BD will be provided in a later chapter.

1.1.4.3 Current State of Research

Nowadays our knowledge about susceptibility genes of BD has greatly expanded. Different loci and genes have sparked interest and provide further insight concerning not only the aetiology but other topics like treatment and pharmacodynamics/pharmacokinetics of various drugs or the course and severity of BD (Qi et al. 2020; Budde et al. 2017).
Those promising genes do not belong to the monoamine or neurotransmitter systems since other fields have now come into consideration. One of them is the so-called circadian

rhythm, which is often disturbed in patients with BD. This system works as an endogen clock, regulating sleep, body temperature and the release of different hormones amongst other important functions. Impairment leads to dysregulation and encourages the appearance of disorders, in particular sleeping and other psychiatric disorders.

ARNTL (Aryl hydrocarbon receptor nuclear translocator-like), CLOCK (Circadian Locomotor Output Cycles Kaput) and PER 1-3 (Period) are examples for genes involved with this system.

Other susceptibility genes code for ion-channels. CACNA1C (calcium voltage-gated channel subunit alpha1 c), for example, is a protein coding gene for a calcium channel. It functions as an important neuronal regulator of contraction in muscular tissue in the human heart and skeleton. Several studies were capable of reporting CACNA1C gene variants as significant in the development of BD. (Ferreira et al. 2008; Sklar et al. 2008; Budde et al. 2017). The following table gives a quick overview about promising susceptibility genes and their loci that have been investigated in one or more genomewide association studies (GWAS) (Budde et al. 2017).

Table 2 Excerpt of genomewide significant findings in BD (Budde et al. 2017)

Gene	Locus	Evidence
PTGFR	1p31.1	Supported by 1 study
LMAN2L	2q11.2	Supported by 2 studies
Various genes	3p21	Supported by 2 studies
TRANK1	3p22.2	Supported by 4 studies
ADCY2	5p15.31	Supported by 1 study
MIR2113, POU3F2	6q16.1	Supported by 2 studies
SYNE1	6q25.2	Supported by 2 studies
MAD1L1	7p22.3	Supported by 1 study
ELAVL2	9p21.3	Supported by 1 study
ADD3	10q25.1	Supported by 1 study
ANK3	10q21.2	Supported by 4 studies
ODZ4	11q14.1	Supported by 3 studies
CACNA1C	12p13.33	Supported by 4 studies
RHEBL1, DHH	12q13.12	Supported by 2 studies
DGKH	13q14.11	Supported by 1 study
ERBB2	17q12	Supported by 1 study

NCAN	19p13.11	Supported by 1 study
TRPC4AP	20q11.2	Supported by 1 study

Especially the ODZ4 gene seems to be rather important for further investigation. A large GWAS with 7481 patients with BD and 9250 controls found a new variant of ODZ4, which is associated with the development of BD.

This gene codes for the tendering protein 4, a transmembrane signal transduction protein. There seems to be a connection between the regulation of neuronal and synaptic connectivity during development of the human brain and ODZ4, but researches concerning this specific gene are still in their infancy. More studies need to be conducted concerning this promising field.

TRANK1 and SYNE1 count as other promising susceptibility genes. TRANK1 encodes for tetratricopeptide repeat and ankyrin repeat-containing protein and is not only associated with BD, for murine models were capable of identifying an association with lupus erythematosus, a systemic disease that can lead to neuropsychiatric symptoms.

SYNE1 encodes the outer nuclear membrane protein Nesprin-1α. Variants of this gene are associated with BD and multiple physical disorders, like hearing loss, myopathies, arthrogryposis and cancer. Further research needs to be conducted in other to clarify the involved mechanisms and the magnitude of impact concerning disease risk and course (Ikeda et al. 2018; Orrù and Carta 2018; Qi et al. 2020; Budde et al. 2017).

Niamh et al. conducted an even larger GWAS, with 41.917 BD cases and 64 associated genomic loci. Interestingly, many of these loci are found in genes encoding for calcium channel blockers, synaptic pathways and neuronal structures, targeted by antipsychotic and antiepileptic pharmaceuticals.

This GWAS also underlines the important aspect of neuronal growth and plasticity concerning BD development. The reduced expression of the protein-coding gene FURIN, essential for neuronal development and functioning, shows a strong association with BD. An interesting fact, especially when we revive our already acquired knowledge about BDNF and BD. Niamh et al. was also capable of reproducing the significance of TRANK1 for BD, describing an incredibly strong association.

These findings, especially the involvement of neuronal pathways and calcium channel signalling, definitely lay the foundation for further scientific research in BD development and therapeutic approaches (Mullins et al. 2020).

All these findings identified a vast amount of susceptibility genes and paved the way for further investigation, however, the impact of other systems on BD, like genomic regulatory systems, has not been clarified yet.

It is a challenging task to identify such complex and delicate systems associated with the genetic mechanisms of BD and many correlations still lie in the dark (Qi et al. 2020).

1.2 The Big Five of Personality

The term ‘personality’ is a concept of the interaction of cognitive, emotional and motivational processes and describes the totality of a person’s psychological process, that determines their actions and their way of experiencing (Kuhl 2009).

After years of research within the personality psychology branch it could be shown, that personality can be described through the five factor model (FFM), which includes the basic dimensions ‘neuroticism’, ‘extraversion’, ‘openness for experience’, ‘agreeableness’ and ‘conscientiousness’ (Fehr 2006).

These five dimensions can be assessed through the NEO inventories (neuroticism, extraversion, openness for experience), which are sets of different items used to explore each dimension. The NEO-five factor inventory (FFI), for example, is a shorter version of the 180 items containing NEO-PI (Costa and McCrae 2008).

1.2.1 Historical Outline

In 1936, Gordon Allport and Henry Odbert, American psychologists, created a list with 18.000 adjectives using ‘Webster’s New International Dictionary’. Out of these 18.000, 4.504 adjectives were usable for describing individual personality factors. Thirteen years later, Catell managed to reduce this list even further, breaking it down to 16 main factors.

In the 1980s, the American psychologists Paul Costa and Robert McCrae proved that there are five basic dimensions of personality (Fehr 2006). Furthermore, Costa and McCrae published their NEO-PI-R with its 180 items in order to measure these five dimensions and their 6 facets in 1985. Each dimension with its facet scale are shown in table 3 (Costa and McCrae 1995). In 1989 the shorter version NEO-FFI with 60 items was published (Costa and McCrae 2008). Dr. Fritz Ostendorf and Dr. Alois Angleitner, psychologists and researchers from the University of Bielefeld, confirmed the structure of the five basic dimensions for the German-speaking area in 1990 (Fehr 2006).

Since then, NEO inventories have been used in clinical practice and different medical settings. Specific scales from the NEO inventories can point out a higher risk for developing different psychiatric diseases or even assist the clinician with making a diagnose (Costa and McCrae 2008). For example, patients with either BD or unipolar depression score rather high on neuroticism, a predisposition for experiencing negative emotions (Bagby et al. 1996).

Table 3 NEO-PI-R facet scales based on Costa and McCrae 1995

Dimensions	***Neuroticism***	***Extraversion***	***Openness for experience***	***Agreeableness***	***Conscientiousness***
Facet scales	-Anxiety -Angry Hostility -Depression -Self-Consciousness -Impulsiveness -Vulnerability	-Warmth -Gregariousness -Assertiveness -Activity -Excitement Seeking -Positive Emotions	-Fantasy -Aesthetics -Feelings -Actions -Ideas -Values	-Trust -Straightforward-ness -Altruism -Compliance -Modesty -Tender-Mindedness	-Competence -Order -Dutifulness -Achievement Striving -Self-Discipline -Deliberation

1.2.2 The Five Factors

The five basic factors of personality are described as follows:

- Neuroticism

Neuroticism refers to nervousness, mood swings and an anxious behaviour (Neyer and Asendorpf 2018). People with high neuroticism levels tend to be more sensitive and are more likely to suffer from stress. Problem solving and controlling of emotions can be impaired (Muck 2004). They are also capable of experiencing emotions much stronger and clearer than others (Fehr 2006). A range of studies has come to the conclusion that different psychiatric conditions, especially mood and anxiety disorders, share a high level of neuroticism, which seems to work as a vulnerability marker for these disorders (Weinstock and Whisman 2006; Malouff et al. 2005; Kendler and Myers 2010; Duggan et al. 1995).

Now concerning BD, neuroticism is highly associated with both dimensions of the condition, depression and mania. Higher neuroticism scores compared to standard population can even be seen in euthymic BD and recovered unipolar depressive (UD) patients, whereby such elevated trait levels in euthymic patients imply a depression-prone development for the future (Quilty et al. 2009; Bagby et al. 1996).

Lozano et al. (2001) describes a positive association between high neuroticism scores and severity of depressive symptoms (Lozano and Johnson 2001). Furthermore, Sariusz-

Skapska et al. (2003) conducted a study with 60 UD and BD participants and found significantly higher levels of neuroticism in the UD cohort compared to the BD cohort (Sariusz-Skapska et al. 2003).

- Extraversion

Extraversion is about sociability and talkativeness. Extraverted personalities are rather active, confident and friendly and have a passion for new or exciting situations and challenges. They tend to have a rather optimistic attitude as well (Muck 2004).
Extraversion correlates negatively with anxiety and depression in BD patients, often combined with high levels of neuroticism. A positive association can be seen with the BD dimension mania with manic patients, reaching much higher scores in this trait (Jylhä and Isometsä 2006; Quilty et al. 2009). One study was capable of identifying higher premorbid scores as risk factor for future onset of BD (Lönnqvist et al. 2009)
Low extraversion scores can also occur in anxiety disorders, such as social phobia or panic disorder (Bienvenu et al. 2004). Heerlein et al. (1996) described lower extraversion scores in schizophrenic patients, too (Heerlein et al. 1996)

- Openness for experience

Openness for experience describes a creative and curious personality. It is about being open-minded, looking for innovation and having a great diversity of interests. These personalities use their intellectual activity to its fullest and see the big picture with their way of thinking (Fehr 2006). It can be observed that obsessive compulsory disorder is associated with high openness for experience scores (Bienvenu et al. 2004). Furthermore, Babgby et al. (1996) describes an intriguing correlation of this personality trait in euthymic BD patients and recovered patients with UD. Interestingly enough, euthymic BD patients score significantly higher than recovered UD patients, indicating that euthymic BD patients are more creative and are still sensitive to finding new interests and receiving positive emotions from innovation (Bagby et al. 1996). Moreover, this personality trait functions as a distinctive marker for BD since both, bipolar and major depressive disorder, show high levels of neuroticism and low levels of extraversion, agreeableness and conscientiousness, whilst BD patients are additionally characterised by higher levels of openness for experience (Barnett et al. 2011). Quilty et al. (2013) describes the same situation, with higher scores being found in BD than UD (Quilty et al. 2013).

A quick overview about the personality traits in BD patients compared to standard population can be seen in Figure 2.

Furthermore, high openness for experience scores also predict better academic performance and executive functioning, indicating a natural intellectual curiosity and desire to have insight in different topics (Hazrati-Viari et al. 2012)

- Agreeableness

Agreeableness characterizes personalities that are cooperative and helpful. They do not enjoy confrontation and yield to their opposite when it comes to that. In extreme cases individuals might even appear submissive (Muck 2004). Agreeable personalities also tend to put their personal needs behind those around them (Fehr 2006).

This trait plays a more important role in personality disorders than mood disorders. High levels of agreeableness are associated with dependent personality disorders, whereas low levels can be found in antisocial and narcissistic disorders (Costa and Widiger 2002).

However, a rather interesting correlation can be seen in BD patients. The BD dimension mania is not only associated with higher levels of neuroticism and extraversion, but also shows a negative association with agreeableness. Manic patients are usually not depicted as submissive and rarely avoid confrontation, which accounts for the negative association (Quilty et al. 2009). Additionally, a Dutch cohort study identified low agreeableness scores as risk factor for developing (hypo-)manic episodes and symptoms in patients initially diagnosed with UD or anxiety disorder (Mesbah et al. 2019).

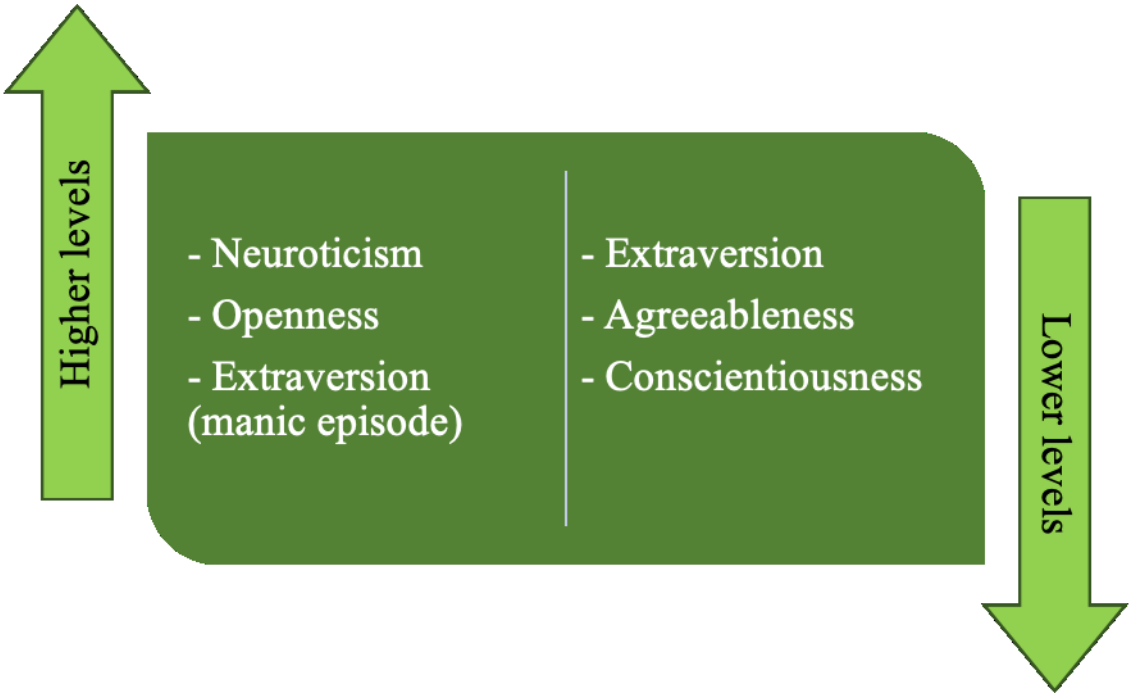
- Conscientiousness

Conscientiousness is all-about self-discipline. These personalities work hard and concentrated on their tasks (Fehr 2006). They show a strong willpower and are rather performance-orientated and get their work done dutifully (Muck 2004). Similar to agreeableness, low levels of conscientiousness can be found in individuals with an antisocial disorder, probably due to the lack of self-discipline (Costa and Widiger 2002).

Barnett et al. (2011) describes conscientiousness as one of the traits which are significantly lower in BD patients (Barnett et al. 2011). Petersen et al. (2001), suggests that patients with major depressive disorder show a similar association. Here the 76 participants with a diagnosed major depressive disorder had significant higher scores on the neuroticism scale and lower scores on the extraversion and conscientiousness scales (Petersen et al. 2001).

Furthermore, Quilty et al. (2013) identified a negative link between the symptom severity of mania and conscientiousness or its facet 'deliberation' to be more specific (Quilty et al. 2013). Lozano et al. (2001) portrayed another interesting result in a study with 39 BD I diagnosed participants. Here, high conscientiousness scores seemed to predict an increase of manic symptoms among the participants (Lozano and Johnson 2001).

Figure 2 The 'Big Five' personality scores in BD patients compared to standard population (own figure, based on Quilty et al. 2009; Bienvenu et al. 2004)



1.2.3 Limitations of the NEO inventories

The NEO inventories, that assess the basic five personality dimensions, cannot be used in order to receive a complete psychological picture of a patient. The patient's cognitive skills, for example, will not be taken into account with this assessment.

It is also up to the clinician if he puts a clinical significance on specific scores. Some scores might cause interpersonal problems without being a pathological problem in need of treatment.

The NEO inventories should also not be used on patients with dementia, deliria or within psychotic breaks. Additionally, patients can alternate their scores on different dimensions to a certain extent by lying or feigning illness (Costa and McCrae 2008).

1.2.4 Genetic and Environmental Influences

With the advances of the past in order to assess personality through five basic dimensions, not only did clinicians use this knowledge to comprehend mental illness in its origins, moreover, the genetic and environmental influences have become of particular interest (Rimoin et al. 2007).

Twin studies were capable of recognising an important coherence between genetics and personality. In 1997 Riemann, Strelau and Angleitner used monozygotic and dizygotic twins and described a higher correlation rate among monozygotic twins concerning their basic five personality dimensions (Riemann et al. 1997).

The results are shown in the table below.

Table 4 Interclass correlations of the NEO-FFI for monozygotic (MZ) and dizygotic (DZ) twins (Riemann et al. 1997)

Scales	**Correlation rate MZ twins (N=660)**	**Correlation rate DZ twins (N=304)**
Neuroticism	.53	.13
Extraversion	.56	.28
Openness for experience	.54	.34
Agreeableness	.42	.19
Conscientiousness	.54	.18
Mean	.52	.23

The personality of monozygotic twins does not correlate to 100%, indicating environmental influences being responsible for possible discrepancies (Rimoin et al. 2007). Studies concerning these environmental influences divide them in shared and non-shared factors. Shared environmental factors create similarities among partners, siblings or other pairs, while non-shared create variance in personality. Especially the influence of non-shared factors seems to have a vast impact on personality development (Neyer and Asendorpf 2018).

Furthermore, the genetic and environmental influences interact with each other. Parenting styles, social environment and education can either reinforce or weaken the effect of a genetic predisposition that, for example, might cause an antisocial behaviour (Kuhl 2010).

1.2.5 Utilisation

Knowledge about personality traits can be in practical use in many different aspects of life. Individualised parenting and education can lay the foundation for a successful school career for example. Marketing and counselling also use ‘personality’ as a concept for target group orientation and individualisation of their working methods (Neyer and Asendorpf 2018).

The treatment of mental health problems is another essential field of application for personality concepts. Psychotherapy is a therapy form tailored to the personality of each individual. In order to enhance treatment outcomes, therapists seek adjustment of their therapy plans and techniques concerning their patients’ personality. Moreover, studies were capable of identifying a matching therapist-patient personality as a crucial factor concerning patients’ development during treatment and symptom reduction (Werbart et al. 2018; Neyer and Asendorpf 2018).

1.3 Interrelation of genetics, bipolar disorder and personality

As seen in figure 1, genetic and neurobiological factors play an important role concerning the stress-vulnerability model of BD. Therefore, this following chapter is dedicated to provide information about the hypotheses-based, selected candidate genes and their complex correlations with BD and personality.

Genetic aspects of mood disorders have soon come into consideration after Kraepelin noted an increased appearance of these disorders in families of patients in early 20th century. Since then studies predicted a hereditary rate between 70 to 85% for BD.
In order to identify genes that are connected to BD, those that play an important role in the complex neurotransmitter system and biogenic amine modulation have mainly been taken into account (Rimoin et al. 2007).
Additionally, genetic variants of circadian genes have sparked great interest. These genes are essential for functioning circadian rhythms, such as daily sleep and wake cycle, hormone secretion, body temperature, eating behaviour and many other complex systems. Disturbances in this balanced system due to genetic polymorphisms can lead to manifestation of mood disorders (BD, unipolar depression, seasonal affective disorder), sleep problems and metabolic disorders (Kim et al. 2015; Takahashi et al. 2008; Nievergelt et al. 2006).
Another interesting cluster of genetic variants concerning mood disorders are neuronal growth, differentiation and plasticity factors (Lang et al. 2005; Frustaci et al. 2008; Numakawa et al. 2010).
The candidate genes concerning these above-mentioned systems that I used for my research are described in the following section.

1.3.1 Candidate genes

COMT

The gene coding for the COMT enzyme is located on chromosome 22 band q11.2. This gene spans over 28 kb and contains six exons. COMT appears in two isoenzymes, a membrane bound form in central nervous tissue and a soluble form in liver, kidney and lungs. Especially high concentration levels of the membrane bound form are found in the spinal cord, cerebellum, medulla, cerebral cortex and in the dorsolateral prefrontal cortex. The enzyme transfers a methyl group from s-adenosine-l-methionine to catecholamines,

inactivating them by this process. This way COMT follows its important task of regulating the central dopamine levels, especially in the prefrontal cortex.

The enzyme expression is thought to be regulated by drugs, nutritional factors and progesterone. Estrogenic factors and the tumour necrosis factor α seem to have a regulating effect as well.

However, COMT activity itself can be altered likewise by a genetic variant. The Val/Met polymorphism (rs4680), found on codon 158, is one of the most well-known polymorphisms to neuroscientists. The valine to methionine substitution is due to a single nucleotide change (G to A). The Met allele carriers catabolize dopamine about 3-4 times less effective than the Val carriers. This is the result of a better thermostability at 37° Celsius in the Val carriers (Montag et al. 2012; Tunbridge 2010).

Further investigation shows that this polymorphism is associated with the appearance of different psychiatric conditions and influences the development of personality. The Val/Met polymorphism has an effect on the prefrontal cortical function, with the Val allele being responsible for a reduction in executive cognition. This effect might be one of the mechanism responsible for the Val allele being associated with a higher vulnerability for schizophrenia (Egan et al. 2001).

Furthermore, Met allele carrier are associated with lower scores of extraversion and higher neuroticism scores. Studies were capable of linking depression and anxiety with the polymorphism as well (Craddock and Forty 2006; Hoth et al. 2006; Montag et al. 2012; Pełka-Wysiecka et al. 2012).

These findings made the COMT gene rather appealing for further investigation concerning personality and mood disorders.

BDNF

Brain derived neurotrophic factor is part of the neurotrophin superfamily. The gene coding for this specific factor lies on chromosome 11p13. Generally, neutrophins are neural products that modulate neuronal growth, development, survival and plasticity. Furthermore, BDNF plays an important role in hippocampal development, which is essential for learning and memory efficiency (Craddock and Forty 2006; Frustaci et al. 2008).

Additionally, BDNF is linked with stress, depression and anxiety. Depressed and stressed (acute and chronic) patients show decreased levels of BDNF expression, however, after antidepressant therapy, these levels increase. Low BDNF expression is also linked with

higher scores of the personality trait neuroticism which is associated with depressive and anxiety disorders (Sen et al. 2003; Lang et al. 2005; Frustaci et al. 2008).
Moreover, BD and high levels of neuroticism are linked with a well-documented genetic variant within this region. The G196A polymorphism (rs6265) causes valine to be substituted by methionine on codon 66. The Val66Met substitution can be found in about 18% of Caucasian population with the Val allele being associated with the earlier mentioned BD and high neuroticism scores. This polymorphism seems to not only alter BDNF secretion and trafficking, but also hippocampal functioning and integrity (Sen et al. 2003; Lang et al. 2005; Frustaci et al. 2008; Craddock and Forty 2006).

5-HTR2A

The serotonergic system has long been a promising field concerning both the aetiology of affective disorders and the regulation of behaviour. Already in 1948, Serotonin was identified as a central transmitter for peripheral vasoconstriction. Nowadays we know about a vast amount of systems that are influenced and/or controlled through the release of serotonin. Such systems include the human cardiovascular regulation, respiration, thermoregulation, the circadian rhythm, appetite, aggression, sexual behaviour and learning. Even more interesting are the serotonergic influences on psychiatric disorders.

Affective disorders, anxiety disorders, schizophrenia, anorexia nervosa and some impulse-related disorders and personality features such as aggression, substance abuse and obsessive control are related to, among others, the alteration of the serotonergic system.
Furthermore, the serotonergic system has not only been investigated in the cause of associations with psychiatric diseases, for several studies identified an effect of functional polymorphisms on personality traits and impulsive behaviour (Nomura et al. 2006; Delvecchio et al. 2016; Lucki 1998).
Obviously, with all these different physiological functions under serotonergic influence, serotonin-binding receptors are not only located in the central nervous system, but also in the peripheral nervous system, blood vessels, gastrointestinal tract, platelets and smooth muscle. The serotonin producing neurons (5-HT neurons) of the central nervous system are mainly located in the dorsal and median raphe nuclei of the midbrain and is distributed in forebrain regions, including the hippocampus, amygdala, striatum, hypothalamus and cortex. Interestingly enough, 5-HT neurons are often found in a bifurcated manner, an ideal

structure for influencing different central nervous regions simultaneously (Ni et al. 2006; Lucki 1998).

Now, the 5-HTR2A (=5-hydroxytryptamine receptor 2A) is one of the most common expressed serotonin receptor subtypes in post-synaptic neurons of the central nervous system, especially in the cortex, hippocampus, nucleus accumbens and caudate nucleus.
The gene encoding for 5-HTR2A is located on chromosome 13q14.2. There are quite a few functional polymorphisms interacting with 5-HTR2A expression, however, two have received rather much recognition among researchers. One of them is the T102C (rs6313) polymorphism. Different studies were capable of describing an association between the C-allele carriers and lower expressions of 5-HTR2A plus lower receptor binding activity. Exactly this genetic variant has also shown to be related with higher extraversion scores in personality analyses (Raote et al. 2007; Lucki 1998; Ni et al. 2006; Gong et al. 2015).
These alterations are linked with neuropsychiatric diseases, such as affective disorders, schizophrenia, psychotic syndromes, suicide and nicotine addiction. However, studies were also capable of identifying the T-allele of the T102C polymorphism as a risk factor for myocardial infarction, stroke (or high values of platelet aggregation in general) and hypertonia (Jobim et al. 2008).
The other well-documented polymorphism, A1438G (rs6311), has found its way in a vast amount of studies with its wide-ranging effects on psychiatric disorders, rheumatologic diseases and impulsive behaviour. This polymorphism appears to correlate with the susceptibility of affective disorders, especially major depressive disorder. However, data concerning this relationship turned out to be rather inconsistent (Zhao et al. 2014).
Other genetic studies suggest interactions of A1438G with personality traits. In a mentally healthy population, A-allele carriers have shown higher extraversion scores and distinctive social behaviour (Ham et al. 2004; Saiz et al. 2010; Zhao et al. 2014; Nomura et al. 2006).

CLOCK

An immense amount of physiological processes in mammalian organisms underlies a circadian rhythm, driven by an endogenous timing system. Such processes include sleep, metabolism and the immune system. Nowadays our knowledge has come so far to understand the circadian clock's control does not stop there, for our cardiovascular and nervous system, aging, intestinal flora and cancer development are deeply influenced by this endogenous clock.

However, to make this clock 'tick', complex molecular sequences that include rhythmic gene transcription, rhythmic histone modification and circadian RNA polymerase II activation take place (Rijo-Ferreira and Takahashi 2019; Vitaterna et al. 1994).
All these processes can be seen as a circadian gene network. The centre of the circadian gene network is built up by molecular sequences of the suprachiasmatic nucleus (SCN) of the hypothalamus and their transcriptional-translational feedback loops.
The transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle arnt-like (BMAL or ARNTL) bind with the period genes (PER1, PER2, *PER3*) and cryptochrome genes (CRY1, CRY2) after heterodimerization and activate transcription.
A negative feedback loop is formed by accumulated PER and CRY proteins repressing CLOCK/BMAL activity in the nucleus and, therefore, repressing their own transcription.
The CLOCK/BMAL heterodimer also activates transcription of retinoic acid-related orphan receptor-α (REV-ERB alpha and RORa). With RORs activating and REV-ERBa inhibiting the transcription of BMAL, another feedback loop is formed.
PER and CRY gene expression can be activated outside the SCN too as neuronal PAS domain protein 2 (NPAS-2), a similar protein to CLOCK, heterodimerizes with BMAL. NPAS-2 also works as a backup protein in order to keep the circadian rhythm in the SCN upright after CLOCK impairment, as it functionally substitutes for CLOCK (Shearman et al. 2000; Vitaterna et al. 1994; Rijo-Ferreira and Takahashi 2019; Kim et al. 2015).

Obviously, with all the above-mentioned physiological processes underlying the circadian clock's control, a disruption of this system ends in numerous negative impacts, from encouraging tumour cell proliferation and migration in breast cancer to higher rates of obesity and diabetes or different forms of sleep disorders. Interestingly enough, dysfunctional circadian rhythms are strongly associated with affective disorders (Li et al. 2018; Rijo-Ferreira and Takahashi 2019).
Several studies underline that a dysfunctional circadian rhythm increases not only the susceptibility for BD, but also the occurrence of insomnia, rates of episodes and appetite disturbances in BD patients. Astonishingly, mice with a mutated CLOCK gene demonstrate a strikingly similar behaviour to manic patients: reduced sleep duration, hyperactivity, less anxious behaviour and increased demand for brain stimulation through sucrose and cocaine (McClung 2007; Schuch et al. 2018; Shi et al. 2008).
The SNPs included in this research (rs534654, rs1801260 and rs12649507) are all significantly associated with BD susceptibility as shown by numerous studies (Kim et al.

2015; Shi et al. 2008; Dmitrzak-Weglarz et al. 2015; Schuch et al. 2018; Lamont et al. 2007; Park et al. 2019). Additionally, rs534654 showed a significant association with rapid cycling in BD patients and violent suicidal attempts (Pawlak et al. 2015; Shi et al. 2008). A similar association applies to rs1801260, for BD patients suffering from early stressful life events have a higher probability of attempting suicide when carrying the C allele compared to T allele carriers (Benedetti et al. 2015).
Now concerning our five personality traits, one GWAS was capable of identifying an association between CLOCK gene variants and the personality trait agreeableness. Some genomewide linkage scans also describe a connection between CLOCK and neuroticism, however these findings did not reach genomewide significance (Terracciano et al. 2010).

After all, we are still trying to unravel the enigma of circadian medicine and the unquestionable link between circadian rhythm and health. New aspects are found on an almost regular basis, like gender and dietary influences, however, much still lies in the dark, marking this as another promising field concerning research in mental health (Schuch et al. 2018; Rijo-Ferreira and Takahashi 2019).

PER3

Now, after the short introduction to the circadian clock and its expression in the before mentioned paragraph, we know that PER3 is just another important gene in this network.
PER3 polymorphisms are associated with numerous psychiatric and non-psychiatric disorders, only marking its importance within our endogenous timing system. Schizophrenia, schizoaffective disorders, sleeping disorders (e.g. delayed sleep phase disorder) and bipolar disorders all show a significant association with PER3 polymorphisms (Lamont et al. 2007; Karthikeyan et al. 2014; Nievergelt et al. 2006; Benedetti et al. 2008).
Moreover, PER3 expression can be linked with anxiety disorders, altered stress response and alcohol addiction (Wang et al. 2012).
Now concerning personality traits, the SNPs rs10462021, rs10864315, rs228682, rs228642 have not been investigated on a large scale yet, however, another polymorphism has shown significant higher extraversion scores in healthy subjects, suggesting a correlation between PER3 expression and the personality trait (Jiménez et al. 2017; Putilov et al. 2017).

An in vitro study was capable of highlighting another interesting association between PER3 functioning and metabolic processes. PER3 seems to suppress adipogenesis, the differentiation of adipocytes from fibroblast-like progenitor cells, for PER3 knockout mice present themselves with elevated body fat percentage compared to their healthy counterparts (Zhang et al. 2013).

Interestingly, PER3 has also become attractive for cancer research, providing further insight regarding tumour susceptibility. Genetic alterations have a vast impact on breast tumorigenesis for example, as deletion of PER3 is related with tumour recurrence and poor prognosis (Climent et al. 2010).

In summary, many studies have observed the vast impacts of PER3 expression not only on mental health, but also on physiological processes and tumour susceptibility, marking its importance for future research in all these disciplines.

Table 5 BD candidate genes in correlation with personality traits

Gene	SNP Coding	Location	Function	Association with personality
COMT	rs4680	22q11.2	Inactivating catecholamines; Regulation of central dopamine levels	Influences extraversion scores, neuroticism scores and personality development
BDNF	rs6265	11p13	Regulates neuronal growth, development, survival and plasticity; Modulates hippo-campal volume	Influences neuroticism scores
5-HTR2A	rs6311 rs6313	13q14.2	Regulates cardiovascular system, respiration, thermoregulation, circadian rhythm, appetite, aggression, sexual behaviour and learning	Influences extraversion scores

CLOCK	rs534654 rs1801260 rs12649507	4q12	Activator of other clock genes – regulation of sleep, metabolism, immune, cardiovascular and neuronal system	Influences agreeableness scores
PER3	rs10462021 rs10864315 rs228682 rs228642	1p36.23	Part of the endogenous circadian clock - regulation of sleep, metabolism, immune, cardiovascular and neuronal system	Influences extraversion scores

Now in order to understand these genetic interactions and influences on personality it is important to understand what genes, genetic polymorphisms and genetic processes are and how important they are for a healthy organism.

1.4 Basics Of DNA

1.4.1 DNA Structure

In 1944, Oswald T. Avery and his team were able to reveal that the deoxyribonucleic acid, DNA for short, serves as the carrier for the genetic information of all living organisms. The macromolecule lies within the nucleus of our cells, in its typical ladder like structure, the double helix, which has first been described by James Watson and Francis Crick in 1953 (Nordheim and Knippers et al. 2018; Klug and Cummings et al. 2002).

Each strand of the helix is built up by nucleotides (nucleoside monophosphates). The main structure of each nucleotide consists of an organic base, either a purine or a pyrimidine base, sugar (deoxyribose) and a phosphate group (Murken et al. 2011).

The two purine bases are adenine and guanine, the two pyrimidine bases cytosine, uracil and thymine (Nordheim and Knippers et al. 2018).

In order to connect the two strands of the helix, specific complimentary base pairs form hydrogen bonds with adenosine and thymine, or uracil in ribonucleic acid (RNA), forming two hydrogen bonds and guanine and cytosine forming three. (Klug and Cummings et al. 2002). These bonds connect the strands of the double helix in the centre of the structure with the sugar groups and phosphate portraying the outer 'backbone' of the helix. The backbone is provided stability by phosphodiester bonds forming between the C-5' position of one nucleotide with the C-3' of the next nucleotide within one strand. Due to this connection, a C-5' position and a C-3' position are left free.

The two DNA strands are antiparallel to each other, which means that, from bottom to top, one strand starts with its free C-5' position and ends with its C-3'position while its complimentary strand runs from C-3' to C-5'. In addition, the two connected strands wind clockwise around an imaginary central axis, giving it the characteristic look of a helix (Klug and Cummings et al. 2002; Nordheim and Knippers et al. 2018).

DNA includes the blueprint of life in its sequence; a triplet of nucleotides encodes for one amino acid, which build up together amino acid chains and finally proteins. The linear sequence of the nucleotides in our DNA is relevant for the linear sequence of amino acids, the basic components of proteins. A triplet of nucleotides codes one amino acid. Proteins are built by 20 different amino acids, linked together to form long chains with varying number and sequence of the amino acids. Transcription and translation of the protein-coding gene are the steps of procedure in order to form the final protein (Nordheim and Knippers et al. 2018).

1.4.2 From Gene to Protein

The process in order to receive a protein out of a genetic code can be divided in two phases: A) Transcription of the genetic code into mRNA and B) translation of the mRNA into an amino acid sequence (Nordheim and Knippers et al. 2018).

1.4.2.1 Transcription

In order to synthesize mRNA from a DNA template coding for a protein, the enzyme RNA polymerase is needed. This enzyme reads one strand of the helix, the template strand, in its 3' to 5' direction while separating it locally from its partner strand. The synthesis of the mRNA takes place in 5' to 3' direction, with the enzyme connecting the nucleotides that are complementary to the template strand at the 3'OH end of the mRNA, creating a long chain. For this process, the RNA polymerase needs to know where to start and which strand is the template strand. The so-called promoter, a specific nucleotide sequence, provides this information. One of the sequences, TATAAT, also known as TATA box, lies approximately 10 base pairs upstream from the start of the RNA synthesis. The other sequence, TTGACA lies 35 base pairs upstream. These consensus sequences can be found more or less similar in our different genes.

Now in order to initiate the transcription, the RNA polymerase glides along the DNA strand until it recognizes the promoter and sticks to it, creating the closed promoter complex. With the unwinding of the DNA approximately 12 base pairs around the start point of the transcription the open promoter complex is formed and if ribonucleoside triphosphates are present, the RNA polymerase binds the first 5' ribonucleoside triphosphate complimentary to the DNA.

During the process of chain elongation, the enzyme runs along the template strand and binds the complimentary ribonucleotides through phosphodiester bonds, creating a RNA chain antiparallel to the DNA. While running along the strand, the RNA polymerase will get to another specific sequence, consisting of G and C nucleotides and an adenine rich section, that acts as a termination signal (Klug and Cummings et al. 2002; Murken et al. 2011; Nordheim and Knippers et al. 2018).

After the transcription, the mRNA runs through different modifications. A 5'-methylguanosin is added as the 5'-cap structure that provides better binding between mRNA and ribosomes, an important factor for translation. At the 3'-end a poly-A-sequence is added, providing for better stability (Murken et al. 2011)

Through the complex process of splicing, non-coding introns are removed, creating mature mRNA (Klug and Cummings et al. 2002; Murken et al. 2011).

1.4.2.2 Translation

Translation of the mature mRNA takes place in the cytoplasm of our cells in association with our ribosomes, small cellular structures that consist of a small and a large subunit.
Triplet ribonucleotides of the mRNA code for specific amino acids, creating polypeptide chains where each amino acid has its own designated position. One triplet code is also called codon. In order to translate the codon into an amino acid, tRNA is used. Each codon has a specific tRNA that consists of the complimentary ribonucleotide sequence, the anticodon, and an amino acid binding region. Within our ribosomes, the codon of mRNA and anticodon of tRNA form hydrogen bonds and peptide bonds develop between the amino acids carried by neighbouring tRNAs, polymerizing the amino acids and creating a polypeptide (Klug and Cummings et al. 2002; Nordheim and Knippers et al. 2018).
The initiation of translation starts with the smaller ribosomal subunit that identifies the 5'-cap structure and binds to different initiation factors and the mRNA. A specific sequence (AUG) on the mRNA functions as the initial start codon for translation. Within the small ribosomal subunit, the start-tRNA is linked to the AUG of the mRNA. After the development of this complex, the large ribosomal subunit attaches itself on the small subunit and the process of elongation starts. The small and large subunit form a peptidyl (P site) and an aminoacyl site (A site). The start-tRNA binds to the P site and the following tRNA binds to the A site.
The ribosome reads the mRNAs triplets from 5' to 3' direction. This way each complimentary tRNA binds to its specific triplet within the A site and the enzyme peptidyl transferase of the large ribosomal subunit forms the peptide bonds between the amino acids before the tRNA occupying the P site exits the complex through its third side, the exit site (E site). Then the ribosome slides down the mRNA until it reaches the next triplet and the next complimentary tRNA binds to the mRNA in the A site. This process repeats itself over and over again until the ribosomes encounter specific stop triplets that signal the termination of translation: UAA, UGA, UAG. They do not code for an amino acid, therefore they are also called nonsense codons or stop codons that signal releasing factors to separate the amino acid chain from the translation complex and the ribosome dissociates back into its two subunits (Klug and Cummings et al. 2002; Murken et al. 2011)
The newly formed proteins can either function immediately or they are in need of modifications (phosphorylation and dephosphorylation, acetylation and methylation,

hydroxylation and many other) in order to take up their work as enzymes, hormones, cellular membrane structures and so forth (Murken et al. 2011).
These complicated steps and modifications also highlight how important a smooth process is and what impact disturbances in this delicate system have. Mutations changing the promotor or termination of translation sequence, changes in the posttranslational procedure or protein folding can all possibly lead to decreased cell functioning or even cell death (Murken et al. 2011; Nordheim and Knippers et al. 2018).

1.4.3 Mutations

Mutations are hereditary changes of the genetic information that occur in all kinds of cells in living organisms and viruses. These changes are the basic elements of evolution and creating new genotypes. Mutations can either be of advantage or disadvantage for the affected cell or the whole organism, however they tend to be a rather rare occurrence.
(Murken et al. 2011; Nordheim and Knippers et al. 2018).

1.4.3.1 Classifications Of Mutations

Somatic and gametic mutations
Somatic mutations are not passed down to the offspring and can provoke the loss of function or even death of the cell. However, not all cells of the organism carry this mutation and are capable of compensating the defect. The somatic mutation of proto-oncogenes plays an important role in the development of cancerous cells
Unlike somatic mutations, gametic mutations are passed down to the offspring and every single cell of an affected organism carries these mutations. (Murken et al. 2011; Nordheim and Knippers et al. 2018).

Spontaneous and induced mutations
Spontaneous mutations of the DNA develop without external assistance, mostly due to normal cellular events and molecular mechanisms. A common cause for this mutation are mistakes in base pairing during DNA replication that lead to genetic changes. Other spontaneous lesions are depurination and deamination. The more common one, depurination, is caused by the loss of guanine or adenine due to a damaged glycosidic bond between the base and the deoxyribose. Depurination is strongly associated with the genesis of cancer. Deamination is the process of removing an amino group from a molecule. Unfortunately, deamination of cytosine yields uracil and ends in a change of pair (G-C into A-T) (Griffiths et al. 2000).

Other mutations occur because of an interference from outside. These induced mutations are basically the result of our cells coming into contact with so called mutagens, physical (radiation) and chemical (nitrous acid, hydroxylamine and many more) agents that lead to DNA changes (Griffiths et al. 2000; Klug and Cummings et al. 2002; Murken et al. 2011)(Griffiths et al. 2000).

1.4.3.2 Types Of Mutations

Chromosome mutations – number aberrations

These mutations cause an alternation of the total number of chromosomes within an organism. This can either affect the whole set of chromosomes, which is called polyploidy, or individual chromosomes, called aneuploidy. A well-known example for aneuploidy is trisomy 21 or Down syndrome (Murken et al. 2011).

Chromosome mutations – structural defects

Chromosome mutations also occur as structural defects on single chromosomes. These can appear as deletion, insertion, duplication, translocation and inversion (Murken et al. 2011).
A rather interesting example for such chromosomal defects is the velocardiofacial syndrome (DiGeorge syndrome), a microdeletion on chromosome 22q11.22. With an incidence rate of 1:5000 among new-borns also the most frequent microdeletion concerning the human genome. This defect leads to heart abnormalities, hypoplasia of the thymus and parathyroid glands, cleft palate and short stature. In adolescence, these patients have a significant risk for suffering from psychiatric disorders like schizophrenia, mood and anxiety disorders or ADHD, which sparked great interest for this specific chromosomal section among genetic researches. The gene coding for the earlier mentioned COMT is also located on chromosome 22q11 and further genetic observations identified links between deletions within this area and an increased risk for developing psychiatric and neuronal impairment. Such alterations of major enzymes within the neurotransmitter systems have since become of great interest in the search of genetic risk factors for psychiatric disorders (Kraus et al. 2018; Montag et al. 2012)

Gene mutations

These mutations are rather small changes within the sequence of one chromosome.
One or a few neighbouring nucleotides can be substituted by other nucleotides, for example thymine gets replaced by guanine, creating a so called point mutation. If the mutation does not change the sequence of the amino acids in the end product, it is

described as a neutral mutation. When a missense mutation occurs, the sequence is changed and the protein might function less or even experience a total loss of function.
Nonsense mutations are caused by the exchange of a nucleotide, which forms a stop triplet in the middle of a gene, forcing the development of a protein to a premature stop. The resulting fragments are not capable of carrying out their tasks properly which ends in a loss of function (Murken et al. 2011; Nordheim and Knippers et al. 2018).
Through insertions and deletions of one or two nucleotides, the sequence of amino acids is disarranged as a result of the frame shift. This can lead to serious conditions. Cystic fibrosis, for example, develops due to the deletion of the codon for phenylalanine in the 508th position (Nordheim and Knippers 2018).

SNPs

Here I would also like to mention the single nucleotide polymorphisms (SNPs), though strictly spoken, SNPs are not mutations but genetic variants. The human genome varies among single individuals as a result of substitutions every 1,000 nucleotides. These variations result from mutations, however, if a mutation can be found in more than 1% of the population, it is described as a polymorphism (Murken et al. 2011). More than 50 million SNPs have been identified in the human population, with common SNPs occurring in more than 5% of humankind (Nordheim and Knippers et al. 2018).
GWAS try to link SNPs with different human diseases. These cross-sectional case-control studies compare the sequenced (genotyped) genome of cases with healthy controls from the same population and detect the frequency of genetic variants among the two groups. Complex statistical methods are required in order to determine if a polymorphism occurs more often among the case group or the healthy control group.
In order to detect these polymorphisms that contribute to disease susceptibility, SNP microarrays are used. These microarrays contain millions of single-stranded DNA oligonucleotides in a specific arrangement within a solid substrate. The fragmented and fluorescence labelled sample DNA is added and hybridized with the SNP microarray through complimentary binding reactions. After being washed, fluorescence signal intensities are measured and interpreted and complex data analyses are carried out (Iwamoto et al. 2007; LaFramboise 2009).
Many GWAS concerning the genetic basis for multiple psychiatric disorders have been published, expanding the knowledge of aetiology and discovering genetic loci that are strongly associated with a disorder (Collins and Sullivan 2013; Corvin et al. 2010).

1.5 Hypothesis

According to current literature, there is an unquestionable linkage between BD susceptibility, genetic polymorphisms and personality traits. Especially the correlation between genetic predisposition and psychiatric conditions has been a huge subject of research lately, identifying more and more gene loci and polymorphisms (e.g. CLOCK, ODZ4, TRANK1, SYNE1) that have an influence on mental health.

Concerning BD and personality, we know now, that some constellations can be seen repetitively among BD patients (e.g. higher neuroticism scores).

Now, taking all this into account, the question of a possible association between genetic polymorphisms and personality scores in BD patients arises.

With this thesis, I want to raise the following question: Do the various genotypes differ in the 'Big Five' personality scores in BD patients?

Hypothesis:

There is a significant difference between the genotypes of COMT, BDNF, 5-HTR2A, CLOCK and PER3 and the personality scores of the 'Big Five' in BD patients.

2 Methods

The following diploma thesis is based on the data collected during the BIPFAT and BIPGEN studies, which were conducted at the Department of Psychiatry and Psychotherapeutic Medicine at the Medical University of Graz, starting on the 12th of January, 2012.
Both studies serve in order to find answers concerning metabolic correlations and genetic principles of BD.

The BIPFAT and BIPGEN studies were permitted by the ethics committee of the Medical University of Graz in agreement with the Declaration of Helsinki (ICH Guidelines for Good Clinical Practice) with the reference numbers 24-123 ex 11/12 and 23-199 ex 10/11.

2.1 Sample

This study includes the data of 83 patients with BD. All participants were diagnosed with BD by undergoing a structured clinical interview (SCID-I) according to DSM-IV criteria and treated at the dedicated outpatient clinic of BD.
Both in- and outpatients of the department were included and received in-depth information about aims and procedures of each study before giving their written consent. Afterwards, fasting blood samples were taken and each participant ran through different cognitive tests, lifestyle questionnaires and interviews concerning their psychiatric history before undergoing an electroencephalogram and magnetic resonance imaging of the brain.

Out of the 83 patients, 40 were male and 43 female. BD I was diagnosed in 55 patients and BD II in 28. The minimal age was 18.01 years, the maximal age 69.15 with a mean age of 44.6 years and a standard deviation of 13.1 years. The mean age, when receiving the diagnosis BD, was 37.2 years.
81.93% admitted to having had suicidal thoughts (without concrete plans) before recruitment and 11 patients also admitted to having had experience with substance abuse.
45.8% successfully completed the Abitur, 50.6% graduated from school whilst 2.4% dropped out of school.
The mean weight was 85.07 kg (±21.67 kg) and the mean BMI 28.56 (±6.75) with 68.67% suffering from overweight (BMI >24.9).

2.1.1 Exclusion criteria

Participation was not possible, if the patient was diagnosed with one of the following: Morbus Parkinson, Alzheimer's disease, Chorea Huntington, multiple sclerosis, lupus erythematosus, chronic inflammatory bowel disease, rheumatoid arthritis, malignant diseases and chronic obstructive pulmonary disease.
Other excluding criteria were severe personality and addictive disorders.

2.2 Personality analysis

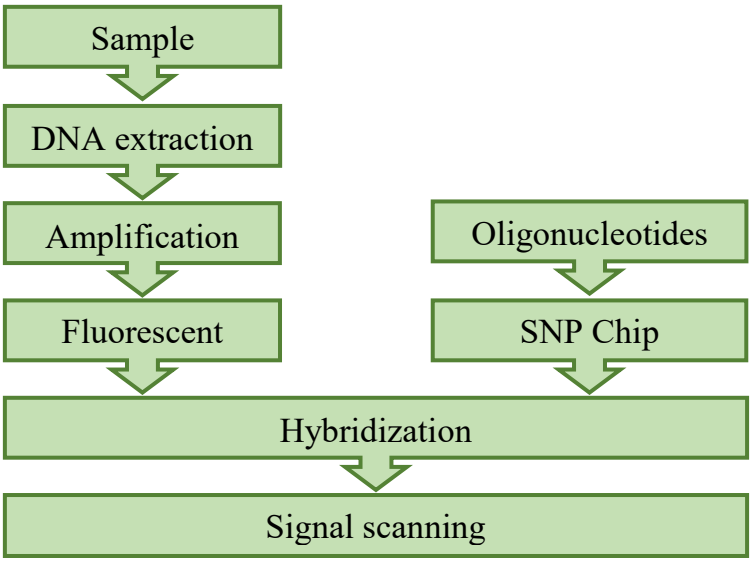
We used the German version of the NEO-FFI after Costa and McCrae (1989), translated by Borkenau and Ostendorf in 1993, in order to receive a quantitative analysis of the participants' personality. Here, every patient received a questionnaire in paper form with 60 items (12 for every factor). Level of acceptance and response to each statement are recorded by a 5-point Likert-scale as follows: 0 - strongly disagree, 1 - disagree a little, 2 - neither disagree nor agree, 3 - agree a little and 4 - strongly agree.
Afterwards, the numerical values of all statements were summed up separately for each factor and divided by the number of answered items.

2.3 Genotyping

Blood samples were taken at 8:30 a.m., collected in EDTA (ethylene-diamine-tetra-acetic acid) tubes and sent to the Institute of Human Genetics Graz. Here DNA-isolation took place with the salting out technique.
Genotyping took place with the Omniexpress1.1 bead chip from Illumina. As the name suggests, this method uses chips with small compartments that contain tiny beads, which are covered in DNA fragments. These fragments are generated to bind with single DNA strands with a complimentary sequence that lie right next to a particular SNP. Interestingly enough, these generated fragments do not include the studied polymorphic region for the following reason: After the DNA strands bind to a bead with their complimentary sequence, the bead is incubated with a mixture of fluorescent nucleotides and DNA polymerase. Now the DNA polymerase tries to work in the same manner, as it does within our cells. It will elongate the DNA strands with the complimentary fluorescent nucleotides. For example, if a person has the SNP genotype GG, fluorescent Cs will be inserted at the position and the bead will glow in the fluorescent colour of the marked nucleotide under ultraviolet light. Of course, the same goes for other genotypes, like AG, where fluorescent Cs and Ts will be inserted, mixing their colour under ultraviolet light.

Obviously, not all SNPs of the whole human genome can be tested through these beads. The producing company and designer of the chips decides which SNPs will be covered.
The following figure gives a quick overview of the steps of SNP microarray genotyping (Useful Genetics 2015; Bumgarner 2013).

Figure 3 Steps of SNP microarray genotyping (own figure, based on Useful Genetics 2015; Bumgarner 2013)



Further information about the interesting but also very complicated topic of chip designing and microarray-based genome typing can be found on Illumina's website *(https://emea.illumina.com/techniques/microarrays.html)*.
Furthermore, SNPs must pass quality control checks that include data completeness, Hardy–Weinberg equilibrium, Mendelian incompatibilities, distributions and familial correlations for quantitative traits. All classic quality control steps were performed with PLINK1.7 by our collaboration partner Dr. Urs Heilbronner. The whole genome data analyses toolset Plink1.7. was used for extracting the genotypes of our selected SNPs, based on our hypothesis. This software programme is provided for free and can be found by the following link: http://zzz.bwh.harvard.edu/plink/

2.4 Statistical analysis

IBM SPSS version 25 was used for the analyses of this thesis' data. The significance level was set for $p < 0.01$ after Bonferroni correction regarding multiple testing. The data were normally distributed and the Levene´s test showed no significant result so covariance analysis (ANCOVA) correcting for age could be applied in order to identify differences of

personality between the varied genotypes in BD patients. If the number of participants with a specific genotype was below 10, they were divided into two groups to ensure a representative statistical analysis. For example, group 1 with AA plus AG and group 2 with GG.

Despite different sources of literature identifying age and gender as covariates, only the variable age showed a significant impact on the five factor scores openness for experience and extraversion in the BD cohort (see Table 6 in the next chapter).
Therefore, age was inserted as covariate in our model for openness for experience and extraversion.

3 Results

Two out of the investigated genotypes showed a significant difference of personality scores in our BD cohort after Bonferroni correction ($p < 0.01$). The SNPs rs228682 and rs 228642, both PER3 polymorphisms, showed significant *p-values <0.01* for the personality score neuroticism. However, we were also capable of identifying trends ($p < 0.1$) for different genotypes of COMT, 5-HTR2A and PER3 with the COMT SNP rs4680 and 5-HTR2A SNP 6311 reaching *p-values <0.05*.

The statistical result for each genotype and personality trait is displayed in Table 8 to Table 12. The quantitative analysis of the 83 participants' personality is summarized in Table 7 with means and standard deviations for each dimension. The result of the covariance analyses for age is depicted in Table 6.

Table 6 Five factor scores and their correlation with age in the BD sample

Five Factors	Correlation with age *p-value* *(Pearson's correlation)*
Neuroticism	*.271* (-.088)
Extraversion	*.036** (-.166)
Openness for experience	*.006*** (-.217)
Agreeableness	*.712* (.029)
Conscientiousness	*.861* (.014)

(* The correlation is significant on a level of $p<0.05$; ** The correlation is significant on a level of $p<0.01$)

Table 7 Means and standard deviations for the dimensions of the 'Big Five' of the sample population

Factor	***Total N=83 Mean (±standard deviation)***	***Male N=40 Mean (±standard deviation)***	***Female N=43 Mean (±standard deviation)***
Neuroticism	27.88 (±9.04)	26.92 (±9.03)	28.72 (±8.97)
Extraversion	25.64 (±7.52)	24.95 (±7.78)	26.28 (±7.21)
Openness for experience	28.89 (±7.01)	27.75 (±7.41)	29.95 (±6.44)
Agreeableness	31.02 (±6.14)	30.03 (±6.76)	31.95 (±5.33)
Conscientiousness	31.47 (±7.83)	31.60 (±6.48)	31.35 (±8.91)

Table 8 Results of covariance analysis (ANOVA) for correlations between genetic polymorphisms and the NEO personality dimension neuroticism in patients with BD

Gene	*SNP*	*Neuroticism*			
		p-value	*F*	*df*	η_p^2
COMT	rs4680	*p = .967*	*F = .034*	*df = 2*	$\eta_p^2 = .001$
BDNF	rs6265	*p = .587*	*F = .298*	*df = 1*	$\eta_p^2 = .004$
5-HTR2A	rs6311	*p = .503*	*F = .452*	*df = 1*	$\eta_p^2 = .006$
	rs6313	*p = .691*	*F = .372*	*df = 2*	$\eta_p^2 = .009$
CLOCK	rs534654	*p = .177*	*F = 1.855*	*df = 1*	$\eta_p^2 = .023$
	rs1801260	*p = .316*	*F = 1.168*	*df = 2*	$\eta_p^2 = .029$
	rs12649507	*p = .963*	*F = .038*	*df = 2*	$\eta_p^2 = .001$
PER3	rs10462021	*p = .143*	*F = 2.194*	*df = 1*	$\eta_p^2 = .027$
	rs10864315	*p = .197*	*F = 1.694*	*df = 1*	$\eta_p^2 = .021$
	rs228682	***p = .003*** **	*F = 6.351*	*df = 2*	$\eta_p^2 = .140$
	rs228642	***p = .008*** **	*F = 7.355*	*df = 1*	$\eta_p^2 = .085$

(*p-values <0.05* are marked with a *, *p-values <0.01* are marked with a **; *p-values <0.1*, indicating a trend, are written in **bold)**

Table 9 Results of covariance analysis (ANOVA) for correlations between genetic polymorphisms and the NEO personality dimension extraversion in patients with BD

Gene	*SNP*	*Extraversion*			
		p-value	*F*	*df*	η_p^2
COMT	rs4680	$p = \mathbf{.088}$	$F = 2.501$	$df = 2$	$\eta_p^2 = .060$
BDNF	rs6265	$p = .599$	$F = 0.278$	$df = 1$	$\eta_p^2 = .003$
5-HTR2A	rs6311	$p = .410$	$F = .686$	$df = 1$	$\eta_p^2 = .008$
	rs6313	$p = .713$	$F = .340$	$df = 2$	$\eta_p^2 = .009$
CLOCK	rs534654	$p = .532$	$F = .395$	$df = 1$	$\eta_p^2 = .005$
	rs1801260	$p = .474$	$F = .753$	$df = 2$	$\eta_p^2 = .019$
	rs12649507	$p = .380$	$F = .979$	$df = 2$	$\eta_p^2 = .024$
PER3	rs10462021	$p = .684$	$F = .167$	$df = 1$	$\eta_p^2 = .002$
	rs10864315	$p = .533$	$F = .391$	$df = 1$	$\eta_p^2 = .005$
	rs228682	$p = .201$	$F = 1.630$	$df = 2$	$\eta_p^2 = .040$
	rs228642	$p = .106$	$F = 2.671$	$df = 1$	$\eta_p^2 = .032$

(*p-values <0.05* are marked with a *, *p-values <0.01* are marked with a **; *p-values <0.1*, indicating a trend, are written in **bold)**

Table 10 Results of covariance analysis (ANOVA) for correlations between genetic polymorphisms and the NEO personality dimension openness for experience in patients with BD

Gene	*SNP*	*Openness for experience*			
		p-value	*F*	*df*	η_p^2
COMT	rs4680	$p = \mathbf{.018*}$	$F = 4.201$	$df = 2$	$\eta_p^2 = .096$
BDNF	rs6265	$p = .545$	$F = .370$	$df = 1$	$\eta_p^2 = .005$
5-HTR2A	rs6311	$p = \mathbf{.070}$	$F = 3.363$	$df = 1$	$\eta_p^2 = .040$
	rs6313	$p = .170$	$F = 1.814$	$df = 2$	$\eta_p^2 = .044$
CLOCK	rs534654	$p = .629$	$F = .235$	$df = 1$	$\eta_p^2 = .003$
	rs1801260	$p = .867$	$F = .143$	$df = 2$	$\eta_p^2 = .004$
	rs12649507	$p = .692$	$F = .370$	$df = 2$	$\eta_p^2 = .009$
PER3	rs10462021	$p = .169$	$F = 1.927$	$df = 1$	$\eta_p^2 = .024$
	rs10864315	$p = .426$	$F = .639$	$df = 1$	$\eta_p^2 = .008$

	rs228682	$p = .493$	$F = .714$	$df = 2$	$\eta_p^2 = .018$
	rs228642	$p = .849$	$F = .036$	$df = 1$	$\eta_p^2 = .000$

(*p-values <0.05* are marked with a *, *p-values <0.01* are marked with a **; *p-values <0.1*, indicating a trend, are written in **bold)**

Table 11 Results of covariance analysis (ANOVA) for correlations between genetic polymorphisms and the NEO personality dimension agreeableness in patients with BD

Gene	*SNP*	*Agreeableness*			
		p-value	*F*	*df*	η_p^2
COMT	rs4680	$p = .225$	$F = 1.518$	$df = 2$	$\eta_p^2 = .037$
BDNF	rs6265	$p = .593$	$F = .289$	$df = 1$	$\eta_p^2 = .004$
5-HTR2A	rs6311	$p = .622$	$F = .245$	$df = 1$	$\eta_p^2 = .003$
	rs6313	$p = .617$	$F = .485$	$df = 2$	$\eta_p^2 = .012$
CLOCK	rs534654	$p = .930$	$F = .008$	$df = 1$	$\eta_p^2 = .000$
	rs1801260	$p = .954$	$F = .047$	$df = 2$	$\eta_p^2 = .001$
	rs12649507	$p = .850$	$F = .163$	$df = 2$	$\eta_p^2 = .004$
PER3	rs10462021	$p = .958$	$F = .003$	$df = 1$	$\eta_p^2 = .000$
	rs10864315	$p = .972$	$F = .001$	$df = 1$	$\eta_p^2 = .000$
	rs228682	$p = .293$	$F = 1.247$	$df = 2$	$\eta_p^2 = .030$
	rs228642	$p =$ ***.082***	$F = 3.102$	$df = 1$	$\eta_p^2 = .037$

(*p-values <0.05* are marked with a *, *p-values <0.01* are marked with a **; *p-values <0.1*, indicating a trend, are written in **bold)**

Table 12 Results of covariance analysis (ANOVA) for correlations between genetic polymorphisms and the NEO personality dimension conscientiousness in patients with BD

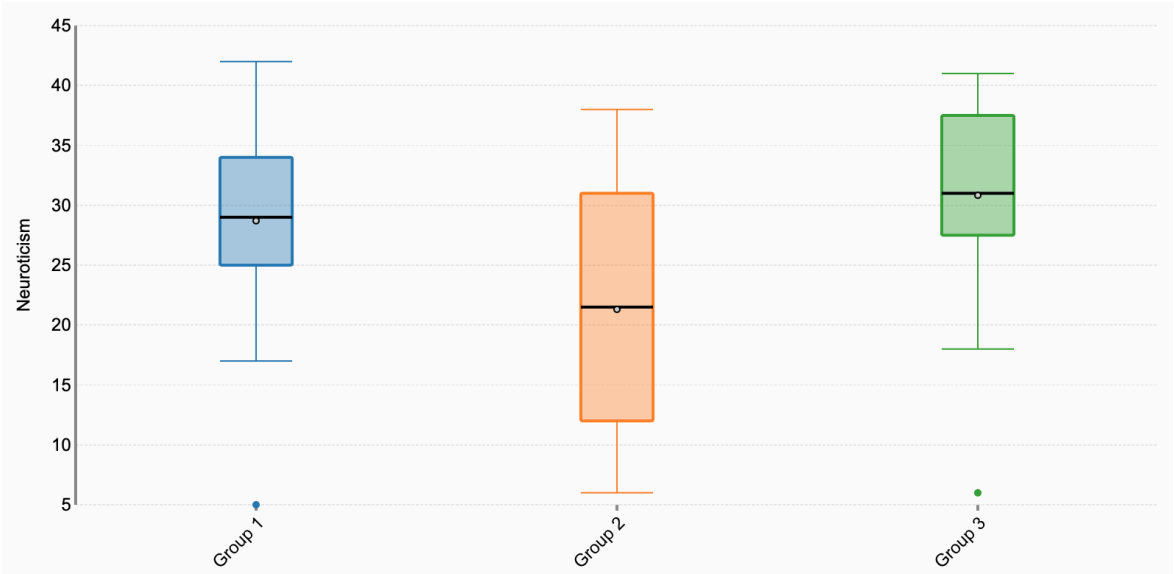
Gene	*SNP*	*Conscientiousness*			
		p-value	*F*	*df*	η_p^2
COMT	rs4680	$p = .451$	$F = .804$	$df = 2$	$\eta_p^2 = .020$
BDNF	rs6265	$p = .123$	$F = 2.427$	$df = 1$	$\eta_p^2 = .029$
5-HTR2A	rs6311	$p =$ ***.034****	$F = 4.631$	$df = 1$	$\eta_p^2 = .054$

	rs6313	$p = .061$	$F = 2.898$	$df = 2$	$\eta_p^2 = .068$
CLOCK	rs534654	$p = .867$	$F = .028$	$df = 1$	$\eta_p^2 = .000$
	rs1801260	$p = .132$	$F = 4.479$	$df = 2$	$\eta_p^2 = .049$
	rs12649507	$p = .441$	$F = .826$	$df = 2$	$\eta_p^2 = .020$
PER3	rs10462021	$p = .321$	$F = .995$	$df = 1$	$\eta_p^2 = .012$
	rs10864315	$p = .146$	$F = 2.151$	$df = 1$	$\eta_p^2 = .026$
	rs228682	$p = .675$	$F = .395$	$df = 2$	$\eta_p^2 = .010$
	rs228642	$p = .947$	$F = .004$	$df = 1$	$\eta_p^2 = .000$

(*p-values* <0.05 are marked with a *, *p-values* <0.01 are marked with a **; *p-values* <0.1, indicating a trend, are written in **bold)**

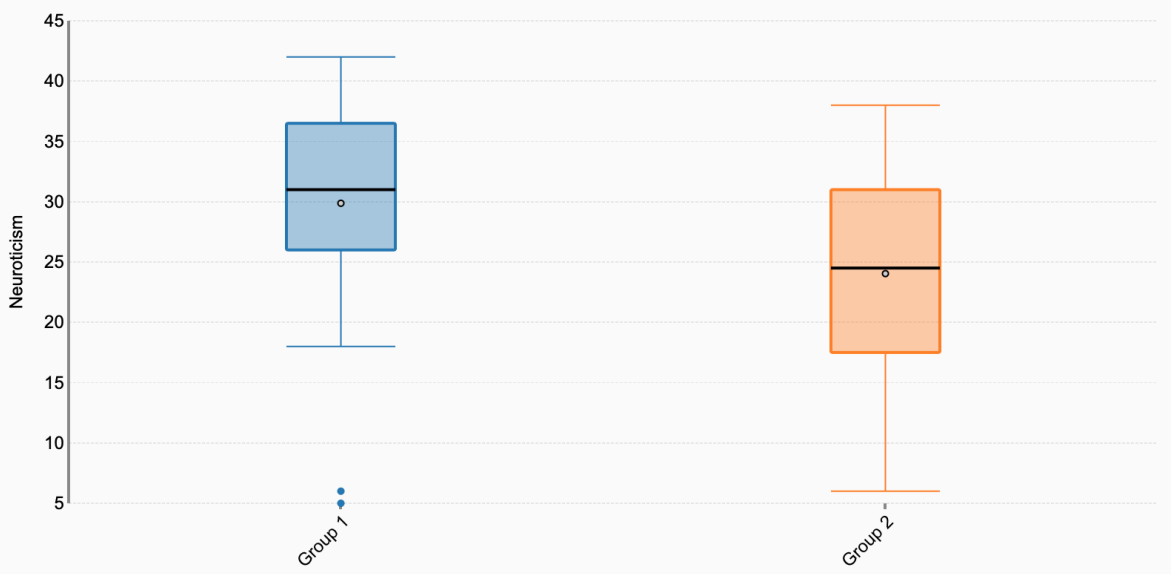
The SNP rs228682 of PER3 shows a significant difference for the personality score neuroticism ($F(2/78) = .03$, $p = .003$, $Eta = .140$). Genotypes AG and AA show higher scores for neuroticism (AG with a mean ±standard deviation = 28.71 ±7.92; AA with a mean ±standard deviation = 30.83 ±8.39) than the genotype GG (mean ±standard deviation = 21.31 ±10.22), as seen in Figure 4.

Figure 4 Genotypes of SNP rs228682 and their personality scores for neuroticism; X-axis with genotypes of PER3 SNP rs228682; Group 1 with AG, group 2 with GG and group 3 with AA; Y-axis with personality scores for the trait neuroticism



The PER3 polymorphism rs228642 shows significant difference for the personality score neuroticism, too (*F(1/79) = .01, p = .008, Eta= .085*). AG+GG genotypes show higher levels (Mean ±standard deviation = 29.87 ±8.46) than the AA genotype (Mean ±standard deviation = 24.04 ±9.31) as seen in Figure 5.

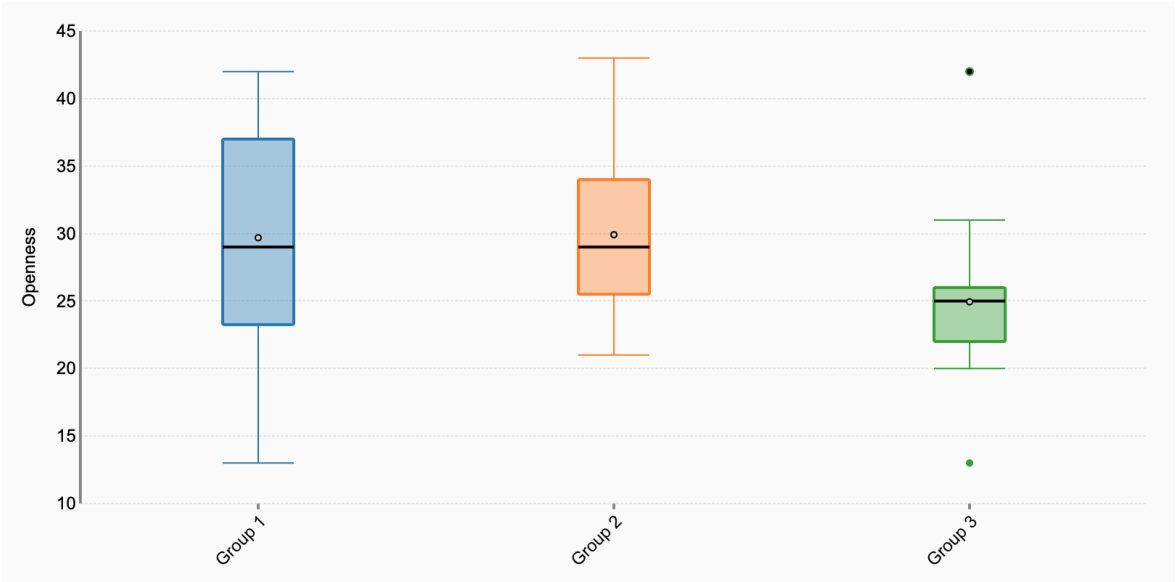
Figure 5 Genotypes of SNP rs228642 and their personality scores for neuroticism; X-axis with genotypes of PER3 SNP rs228642; Group 1 with AG+GG, group 2 with GG; Y-axis with personality scores for the trait neuroticism



The SNP rs4680 of COMT shows a significant difference for the personality score openness for experience (*F(2/80) = .03, p = .018, Eta= .096*), but does not withstand Bonferroni correction.

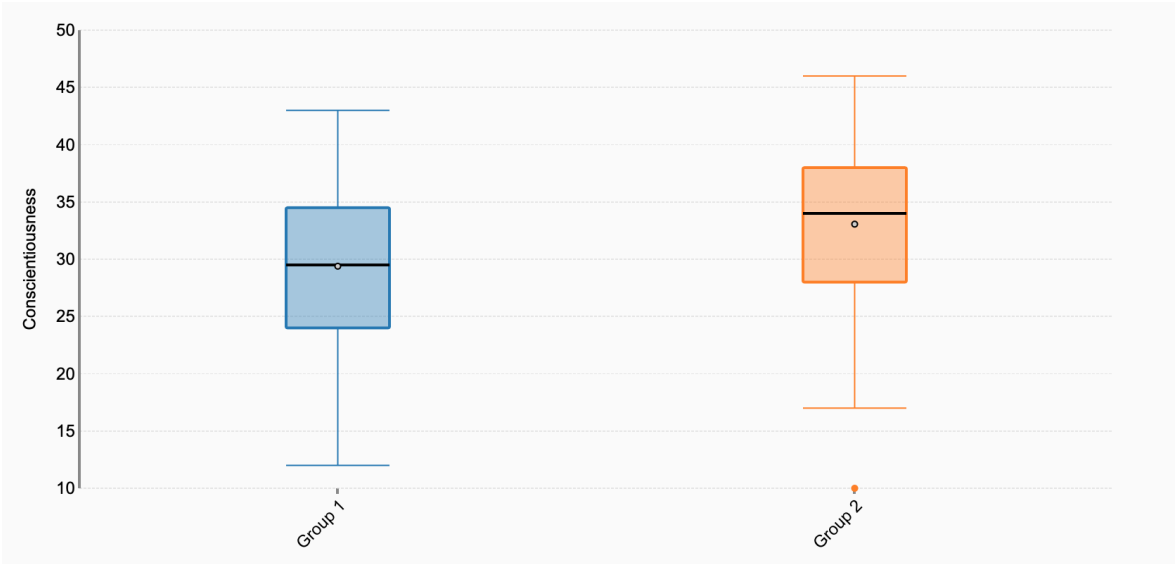
Genotypes GG and AG show slightly higher scores for openness for experience (GG with a mean ±standard deviation = 29.91 ±5.83; AG with a mean ±standard deviation = 29.69 ±7.54) than the genotype AA (mean ±standard deviation = 24.94 ±6.04), as seen in Figure 6.

Figure 6 Genotypes of SNP rs4680 and their personality scores for openness for experience; X-axis with genotypes of COMT SNP rs4680; Group 1 with AG, group 2 with GG and group 3 with AA; Y-axis with personality scores for the trait openness for experience



The SNP rs6311 of 5-HTR2A reaches a *p-value <0.05* concerning score differences of the trait conscientiousness (*F(1/81) = .01, p = .034, Eta= .54*). AG+AA genotypes reach higher levels (Mean ±standard deviation = 33.06 ±7.86) than the GG genotype (Mean ±standard deviation = 29.39 ±7.86) as seen in Figure 7.

Figure 7 Genotypes of SNP rs6311 and their personality scores for conscientiousness; X-axis with genotypes of 5-HTR2A SNP rs6311; Group 1 with GG, group 2 with AG+AA; Y-axis with personality scores for the trait conscientiousness



4 Discussion

4.1 Discussion of the hypothesis

The aim of this study was to investigate, if the various genotypes of BD susceptibility genes differ in the 'Big Five' personality scores in bipolar patients. There is a broad range of literature covering the issues of gene susceptibility for BD and personality traits separately, but only few discuss the genetic correlations of personality in patients with BD. Knowledge about individual personality traits and their underlying genetic correlations in patients with BD can be an important issue when discussing diagnostic and therapeutic aspects. Perhaps psychotherapy, counselling and medical treatment could all function as a possible targeted therapy one day, if the research of genetic mechanisms and BD keeps on gaining more and more knowledge.

Two out of the eleven investigated SNPs showed a significant difference for neuroticism scores in patients with BD. The SNPs rs228682 and rs228642 are both polymorphisms of the CLOCK gene PER3. SNP rs228682 revealed significant higher neuroticism scores in carriers of the genotypes AG and AA (AG with a mean ±standard deviation = 28.71 ±7.92; AA with a mean ±standard deviation = 30.83 ±8.39), whilst GG carriers scored lower (mean ±standard deviation = 21.31 ±10.22). This result is depicted in Figure 4.

The other polymorphism, SNP rs228642, showed a similar correlation. Carries of the AG and GG genotype score higher on the neuroticism trait (Mean ±standard deviation = 29.87 ±8.46) than AA carriers (Mean ±standard deviation = 24.04 ±9.31). Such results in patients with BD have not been described yet, to my knowledge.

Barbato et al. (2010) identified a correlation between PER3 polymorphisms and behavioural changes after sleep deprivation in groups with high, middle and low neuroticism scores. According to these findings, such genetic polymorphisms could influence personality and mood as response to less sleep (Barbato et al. 2010).

Jiménez et al. (2017) examined a different polymorphism of PER3 and personality in healthy individuals and encountered elevated scores for the trait extraversion. A correlation with neuroticism was not described (Jiménez et al. 2017).

As already described in an earlier chapter, CLOCK genes either control or influence an immense amount of physiological processes (e.g. sleep, metabolism, aging, intestinal flora, cancer development) through the circadian clock. Personality development and expression could just be other processes affected by this system. Genetic changes of the circadian

clock might influence personality traits directly or indirectly, through other disturbed physiological processes interacting with personality aspects. Such disturbances could include the sleep-wake cycle in patients with BD. Moreover, PER3 expression can be linked with anxiety disorders (Wang et al. 2012). Interestingly enough, anxiety disorders are characterised by elevated levels of neuroticism, which seems to work as a vulnerability marker for this disorder (Weinstock and Whisman 2006; Malouff et al. 2005; Kendler and Myers 2010; Duggan et al. 1995). PER3 might influence neuroticism scores in patients with BD through higher levels of anxiety or even anxiety disorders as comorbidity. PER3 could also just influence the sleep-wake cycle, which might have effects on neuroticism scores itself. These approaches of PER3 polymorphisms and links between sleep behaviour or anxiety in patients with BD might provide further questions but also further discoveries concerning the fundamental understanding of these polymorphisms and the possible pathomechanisms they create.

CLOCK genes, as genetic basis for affective disorders and personality differences in general, could provide further answers to diagnostic and therapeutic issues in many ways. More studies with adequate sample sizes concerning this topic are needed, in order to reveal these answers.

However, there are still other important results that need to be discussed. As seen in the previous chapter, SNP rs4680 of the COMT gene shows an intriguing trend for the personality trait openness for experience (see Table 10). Genotype carriers AG and GG (Val alleles) reach slightly higher scores than their AA (Met allele) carrying counterparts, as seen in Figure 6. The Val allele is associated with higher COMT activity and therefore lower prefrontal dopamine levels (Kotyuk et al. 2015).

This has an effect on the prefrontal cortical function, with Val allele carriers showing reduced executive function whilst Met allele carriers are more prone to anxiety and affective disorders. There might be an underlying neurobiological aspect for a possible association between prefrontal cortical function and personality aspects (Egan et al. 2001; Craddock and Forty 2006; Hoth et al. 2006; Montag et al. 2012; Pełka-Wysiecka et al. 2012). This might be an interesting approach for further investigations.

COMT is also a well-known susceptibility gene for BD and has been named in numerus studies, however, none have brought COMT genotypes in correlation with the personality trait openness for experience in BD patients. Moreover, most studies concentrate on personality differences due to COMT genotypes in a healthy population.

Montag et al. (2012) describes the Met allele carriers with higher scores of neuroticism whilst Val allele carriers are characterised by higher extraversion scores. However, differences for openness have not been adressed (Montag et al. 2012).
Now, openness for experience as personality trait itself seems to be a distinguishing factor for BD compared to other affective disorders since BD patients score significantly higher than UD patients. Barnett et al. (2011) and Bagby et al. (1996) were both capable of reproducing this result (Barnett et al. 2011; Bagby et al. 1996).
DeYoung et al. (2011) and Harris et al. (2005) describe COMT genotype as contributing factor to differences in opennes scores and therefore intellect/imagination in a healthy population (Harris et al. 2005; Deyoung et al. 2011). To my best knowledge, such association has not yet been confirmed for BD patients.

Another important result I want to mention concerns the 5-HTR2A SNP rs6311. To adress the topic again, as it has already been mentionet in a previous chapter, literature has presented rather inconsistent data regarding affective disorder susceptibility and SNP rs6311 and most researches about interactions with personality traits do not include BD patients. Serretti et al. depicts HTR2A polymorphims to have only a minor impact on personality traits (Serretti et al. 2007). Therefore, an association with conscientiousness has not been made yet. However, other studies described higher extraversion scores and a distinctive social behaviour in A allele carriers (Ham et al. 2004; Saiz et al. 2010; Zhao et al. 2014; Nomura et al. 2006). Since low concentrations of serotonin are associated with aggression, impulsiveness and suicidal tendencies, an interaction between altered functioning of the serotonergic system through genetic polymorphisms and personality aspects seems traceable. Further investigation on the serotonergic system concerning personality and BD susceptibility might reveal even more underlying and still unknown aspects.
These two results are mainly negative regarding their weak p-values. However, it is still possible to hypothesize about an association between COMT SNP rs4680 and openness for experience as well as 5-HTR2A SNP rs6311 and conscientiousness. Further studies with a suitable sample size are needed in order to dissect these findings.

Even weaker values, nonetheless trending results, were identified for COMT SNP rs4680 and extraversion, 5-HTR2A SNP rs6311 and openness for experience, just like rs6313 and conscientiousness and the PER3 SNP rs228642 with agreeableness (as seen in Table 8 to Table 12).

These findings are definitely in need of further research, especially since some of these genes have rarely been investigated in association with personality traits in BD patients and false positive findings are possible.

4.2 Limitations

The biggest limitation of this study is the small case number of only *N=83*. Most genetic research worked with much bigger sample sizes (hundreds or thousands) in order to receive valid results.

In addition, we only investigated a small number of genes and genotypes. With the latest developments in BD susceptibility gene research, even more genetic polymorphisms could play an important role in personality differences, marking this as an important topic for further analysis.

Finally, the genetic influences and pathomechanisms of personality development and variety are still very complex topics with only little validated knowledge. Just like the genetic disposition for BD, not one genetic polymorphism causes variety but the interaction of different polymorphisms and the environment (family conditions, education e.g.) are responsible for personality discrepancy. Identifying and tracing such influences on personality traits emerges as a very difficult task, making it even more difficult to understand the underlying interaction with genetic predispositions.

Furthermore, the personality assessment by the NEO inventories is limited too. The limitations of the NEO inventories are described in chapter 1.2.3.

4.3 Conclusion and Implication

In this thesis, I observed the genetic influences on personality differences in BD patients.

Literature has already brought forth a variety of susceptibility genes that play an important role in BD development and onset in dependency of provoking triggers like early life stress, coping mechanisms and social stability as described by the stress-vulnerability model.

Furthermore, research has come so far to identify specific personality traits in BD patients, with higher levels of neuroticism and openness and lower levels of extraversion, agreeableness and conscientiousness as distinctive scores.

Literature associating these two approaches with each other is rare and inconsistent, marking this as an interesting topic in order to unveil further correlations.

In this diploma thesis, I could find a significant difference between the polymorphisms of PER3 (rs228682, rs228642) and the personality trait neuroticism in BD patients.
I did notice trends, too, especially for COMT SNP rs4680 and openness as well as 5-HTR2A SNP rs6311 and conscientiousness. Additionally, all genes, except BDNF, showed trends for the different personality traits as seen in an earlier paragraph. Further analyses are definitely needed in this promising topic.

The relationship between genetic polymorphisms and personality traits in BD patients is definitely a promising field for further research, however, with the unexplained pathomechanisms and the influences polymorphisms might have on each other, answers to all these unclear questions and possible associations are extremely difficult to find and interpret.
It is still difficult to distinguish direct and indirect influences of genetic polymorphisms on personality traits in patients with BD. Some genes could affect personality development directly by different, mostly unknown, neurobiological processes.
Other genetic variants, however, could modify physiological processes into pathogenic mechanisms that lead to other, altered behaviours as well as personality differences. Such complex correlations and networks are definitely an interesting topic for further research questions.
The field of BD susceptibility and genetics of personality is still expanding and with this research, I was hoping to contribute a small part in order to find more answers and to bring forth further questions that might help unveil this network of gene interaction and BD personality traits.
To receive valid answers and to gain more knowledge about BD pathomechanisms and personality development/variety in BD patients, I would definitely recommend a much larger sample size. Additionally, other promising genes, like TRANK1, SYNE1 or ODZ4 and many others might play a role in personality differences in BD patients too.
Moreover, further research approaches concerning the interactions between physiological systems, like the circadian clock or prefrontal cortical function, could provide information about underlying associations between personality traits and BD susceptibility due to pathogenic mechanisms. All these aspects might provide further assistance for diagnostic and therapeutic issues.
Knowledge about the genetic basis of these systems and the effects on personality can path the way for individual therapy planning and targeted pharmacological therapy in BD.

In consideration of these facts, the result of my diploma thesis might initiate further research and observations in the field of genetic links of the ‘Big Five’ personality traits in BD.

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