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SUMMARY AND DISCUSSION



SUMMARY

BORDERLINE PERSONALITY DISORDER (BPD) is characterized by instability in mood, affect, thoughts and behavior. This thesis examines the extent to which genetic and environmental factors influence BPD features, and aims to characterize the environmental factors that may be involved as well as identify the genomic areas that contribute to heritability. To this end, I analyzed data on BPD features of twins and their family members registered with the Netherlands Twin Register, the East Flanders Prospective Twin Survey and the Australian Twin Register together with data on normal personality traits, life events and DNA markers. In total, over 15,000 twins and family members completed the Personality Assessment Inventory-Borderline Features scale (PAI-BOR), a self-report questionnaire tapping features of psychopathology that are clinically associated with BPD. The PAI-BOR consists of four subscales (affective instability, identity problems, negative relationships and self-harm) each composed of six items. For this project, a Dutch translation of the PAI-BOR was created which was approved by the test author and the publishing company.

The first chapter of this thesis served as an introduction into BPD and reviews the current knowledge regarding genetic influences on BPD. The symptoms and assessment methods of BPD and the association with demographic characteristics and other axis-I and axis-II disorders were described. Following this, I reviewed family- and twin studies into the genetics of BPD, and discussed the additional value of extended twin studies and genetic linkage studies. *In chapter two*, an overview of the data collection process was presented.

In chapter three we investigated whether PAI-BOR scores of individuals who participated in the study were comparable to the scores of individuals who did not participate in the study. In other words, we investigated whether a nonresponse bias was present. Obviously, there are no scores available for nonparticipating subjects. Therefore, data from respondents from families in which only a few family members participated were used as a proxy for the missing data of their nonresponding family members. As expected, the participating members of less cooperative families showed somewhat higher scores on the PAI-BOR scale than the participating members of highly cooperative families, suggesting nonresponse may be higher among subjects with more BPD features. However, these differences were small and we conclude that PAI-BOR data are relatively unbiased with respect to nonresponse.

In chapter four the psychometric characteristics of the Dutch translation of the PAI-BOR were examined. Using a series of multigroup confirmatory factor models we established that the PAI-BOR is measurement invariant with respect to sex and age. This implies that the distribution of observed variables given the underlying latent factors is the same across men and women and across individuals of different ages and that dif-

ferences between these groups cannot be ascribed to the instrument assessing different information in different groups. That is, given a certain score on the latent BPD factors, the probability that an individual provides a certain response on a certain item is similar for individuals from different groups. PAI-BOR scores of men and women and of individuals with varying ages can thus be compared.

Chapter five presents the first large scale twin study for BPD features carried out in 5,496 twins from the Netherlands, Belgium and Australia. The genetic analysis showed that 42% of the individual differences in BPD features can be attributed to genetic factors; the remaining variance can be attributed to unique environmental factors (58%). Shared environmental factors do not influence individual differences in BPD features. Heritability estimates did not depend on sex or culture, i.e. they were equal for men and women and participants from the Netherlands, Belgium and Australia. There was a mean effect of sex and age; women and younger individuals show more BPD features than men and older individuals.

In chapter six I analyzed PAI-BOR data from twins and also from their parents, their siblings and spouses. The inclusion of parents and siblings of twins into the model resulted in enough statistical power to test for the influence of non-additive or dominant genetic effects. Parent and spouse data also allowed for the examination of assortative mating and cultural transmission. Dominant genetic effects were indeed present and estimated at 24%. Additive genetic effects explained 21% the variance in BPD features, so that the broad-sense heritability was estimated at 45%. BPD features are thus genetic in origin but only partly transmitted from parents to offspring because dominant genetic effects influence BPD features only in combination with other genes. Resemblance between spouses ($r = 0.22$) was best explained by phenotypic assortative mating reflecting the tendency of individuals to select their partner based on the partner's phenotype. Assortative mating however had only a small effect on the genetic variance (1% of the total variance). Remarkably, no effect of cultural transmission from parents to offspring was detected, meaning that a parent's BPD features only influence a child's BPD features through their common genes.

In chapter seven the four subscales of the PAI-BOR were analyzed in a multivariate genetic model to investigate the association between affective instability, identity problems, negative relationship and self-harm at the level of genetic and environmental influences. The common pathway model explained the data most parsimoniously. This model implies that the covariation among the four scales is determined by a single latent factor representing the BPD construct. Genetic and environmental factors thus influence affective instability, identity problems, negative relationships, and self-harm through the same mechanism. This is the optimal case for future research that addresses the question which genes influence BPD, for example by conducting a genome-wide linkage analysis to identify chromosomal regions that may harbor the genes that influ-

ence the development of BPD. The heritability estimates for affective instability, identity problems, negative relationships, and self-harm were 31%, 31%, 35% and 26%, respectively and the remainder of the variance was explained by unique environmental factors.

In chapter eight I report on the first genome wide linkage analysis conducted to identify chromosomal regions that may harbor the genes that influence BPD development. Evidence for linkage was found on chromosomes 1, 4, 9 and 18. The highest linkage peak was found on chromosome 9p24 at marker D9S286 with a LOD score of 3.548. As many genes are located in this region, association studies are warranted to detect the actual genes that influence individual differences in BPD features.

In chapter nine I examined the phenotypic and genetic association between BPD features and the Five Factor Model (FFM) personality traits. The FFM of personality consists of the personality traits neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness and is one of the suggested models to conceptualize personality disorders as maladaptive variants of continuously distributed personality traits. Correlations between BPD features and the FFM personality traits ranged from 0.06 for openness to experience to 0.68 for neuroticism. A combination of high neuroticism and low agreeableness predicted BPD features best. Genetic factors that influence individual differences in neuroticism, agreeableness, conscientiousness and extraversion appear to account entirely for the genetic liability to BPD features. Genetic influences on normal personality may thus be a valuable source of information in the search for biological pathways leading to BPD. For unique environmental influences the picture is different; only part of the variance is shared between BPD features and normal personality traits. The unique environmental influences specific to BPD features may cause personality traits to develop into BPD.

In chapter ten I turned to investigate whether genes that influence BPD features increase the likelihood of exposure to life events (gene-environment correlation; r_{GE}) and if exposure to life events moderates the heritability of BPD features (gene-environment interaction; $G \times E$). Analyses that involve r_{GE} and $G \times E$ move beyond the additive effect of genes and environment by examining the joint effect of genes and environment. This requires other approaches to data analysis than conducted so far in this thesis, including the discordant twin design. Life events that were evaluated included exposure to divorce/break-up, traffic accident, violent assault, sexual assault, robbery or job-loss. I also investigated the effect of the total number of experienced life events. Exposure to divorce/break-up, traffic accident, violent assault, sexual assault, or job-loss and the total number of experienced life events were associated with more BPD features. For divorce/break-up, violent assault and job-loss this association could partly be explained by r_{GE} . Thus, the genes that influence BPD features also increase the likelihood of being exposed to these life events. In addition, reciprocal or unidirectional causal mechanisms play a role in explaining the association between BPD features and life events. Besides the ad-

ditive effect of genetic factors and life events on BPD features, interactions between the genetic predisposition and life events exist. Additive genetic influences on BPD features interact with the exposure to sexual assault, with the estimate of the genetic variance being lower in exposed individuals. This suggests that sexual assault has such a large impact that it also leads to more BPD features in genetically less vulnerable individuals. In individuals who experienced a divorce/break-up, sexual or violent assault or job-loss, the estimate of the environmental variance for BPD features was higher than in non exposed individuals, leading to a lower heritability estimate in exposed individuals. These results indicate the importance of both genetic vulnerabilities and life events in the development of BPD.

DISCUSSION

In this thesis I present the largest dataset on BPD features to date, including PAI-BOR data from more than 15,000 twins and their family members from the Netherlands, Belgium and Australia. Figure 11.1 shows the distribution of PAI-BOR scores for men and women in the combined Dutch and Belgian sample ($N = 11,872$). Women have higher mean PAI-BOR scores than men (16.71 versus 14.67).

T-scores are standardized scores with a mean of 50 and a standard deviation of 10 and are often used to interpret raw scores on a questionnaire. The manual of the PAI-BOR states that a score on the PAI-BOR of 59T or below reflects an average score, i.e. a person who reports being emotionally stable. Scores ranging from 60T through 69T are indicative for a person reporting moodiness, sensitivity and uncertainty about certain life goals. Scores in this range are not uncommon in young adults. Individuals with a score at 70T or above show significant BPD features but a BPD diagnosis is not necessarily suggested unless there are elevations on all four subscales of the PAI-BOR. Scores at or above 92T are typically associated with personality functioning within the BPD range. Table 11.1 presents the prevalence rates of these categories for men and women in the combined Dutch and Belgian sample. Although women have a higher mean PAI-BOR score than men, the prevalence rates are similar. The prevalence rate in the most severe category (i.e. raw score of ≥ 48 for men and ≥ 52 for women) is 0.2% for both men and women. The prevalence rate of BPD in our sample seems somewhat lower than prevalence rates generally reported for BPD (1-2% of the general US population). However, a subgroup of the individuals in the third category (i.e. raw scores between 30 and 48 for men and between 33 and 52 for women) is likely to receive a clinical diagnosis depending on the pattern of their scores. The prevalence rate found in our sample thus seems comparable to those reported in other studies based on the general population. However, the cut off T-scores reported in the PAI-BOR manual are based on the general

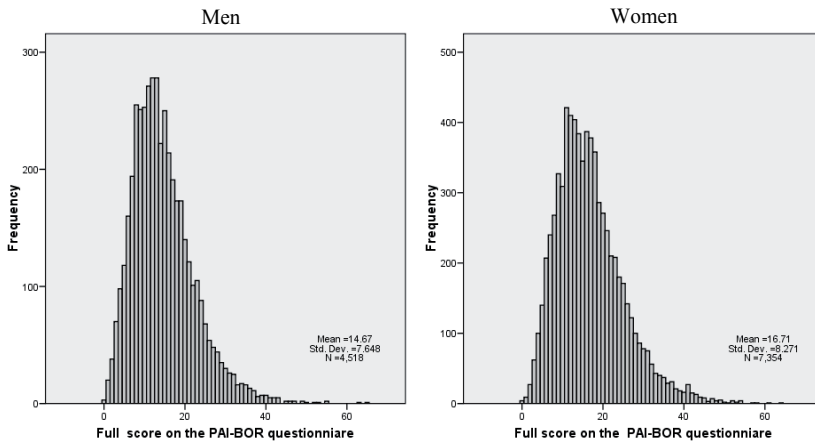


Figure 11.1 Distribution of full PAI-BOR scores in the combined Dutch and Belgian sample for men and women.

US population. The exact cut-off points applicable to our sample based on Dutch and Belgian subjects are unknown. Following the prevalence rate for BPD in the general US population of 2%, a BPD diagnosis would be suggested in our sample for individuals with raw scores at 37 or above.

BPD features show a genetic architecture in which non-additive genetic influences account for about half of the genetic variance. Non-additive, or dominant genetic influences are often found for normal personality traits (Lake et al., 2000; Keller et al., 2005a; Rettew et al., 2008). Lake et al. (2000) examined individual differences for neuroticism in 45,850 members of extended twin families from Australia and the United States, and found that additive genetic effects explained 28% to 36% of the variation and dominant genetic effects explained 13% to 17% of the variation. Neuroticism is suggested to be at the core of many features of BPD (e.g. negative emotionality, sensitivity to stress) (Nigg & Goldsmith, 1994) and we found a strong phenotypic ($r = 0.68$) and genetic ($r = 0.95$) correlation between BPD features and neuroticism. The finding of non-additive genetic effects for BPD features and normal personality traits may shed light on the evolutionary origins of the genetic variation in these traits. Genetic variation between individuals results from the interplay of spontaneous mutations that introduce new genetic variants, the sexual process that recombines those variants, and natural selection, which determines whether all resulting genotypes are equally transmitted from one generation to another (Cela-Conde & Ayala, 2007). Several mechanisms of mutation and natural selection can influence this process. Non-additive genetic variation is expected under the influence of two processes: mutation selection or balancing selection (Keller et al., 2005a). Under mutation selection balance, genetic variation is maintained by a balance

Table 11.1. Number of individuals (%) in each severity category of borderline personality disorder features

T-score	Men (N = 4,518)		Women (N = 7,354)	
	Raw score	N (%)	Raw score	N (%)
< 59 T	< 22	3,771 (82%)	< 25	6,181 (83%)
60 – 69 T	22 – 30	543 (12%)	25 – 33	830 (11%)
70 – 92 T	30 – 48	195 (4%)	33 – 52	329 (4%)
> 92 T	≥ 48	9 (0.2%)	≥ 52	14 (0.2%)

Note. PAI-BOR scores are missing for 142 individuals from the total number of Dutch and Belgian individuals (N = 12,033) who completed a questionnaire. For 19 individuals the sex is unknown.

between the increase in a trait's genetic variation due to new mutations per generation and their removal by stabilizing selection, usually many generations later. Besides the reduction of genetic variance, stabilizing selection decreases environmental sensitivity by favouring the genotypes with the least variability. If a trait is affected by many genetic loci, the chance that the trait will be affected by a mutation increases. Many accumulated mutations in a trait will make it harder for selection to deplete the (additive) genetic variance resulting in a balanced state of mutation and selection. For personality traits and personality disorders, in which many loci are likely to be involved, high values of additive and medium values of non-additive genetic effects would be expected if they were subject to mutation selection balance (Penke et al., 2007; Roff, 1997). Since we found roughly equal values for additive and non-additive genetic effects for BPD features, as also often reported for normal personality traits (Eaves et al., 1998; Rebollo & Boomsma, 2006b; Keller et al., 2005a), it seems unlikely that mutation selection balance can explain the maintenance of genetic variance in personality (Penke et al., 2007). Under balancing selection both extremes of a trait dimension are equally favoured by selection resulting in the maintenance of genetic variation. Balancing selection in different directions results in lower values for additive and higher values for non-additive genetic effects than found for selectively neutral traits because selection depletes additive genetic effects at a higher rate than non-additive genetic effects. Compared to traits under mutation selection balance, balancing selection also results in higher values for dominance because balancing selection affects fewer genetic loci than mutation selection balance. It is therefore possible that balancing selection explains the maintenance of genetic variation in (borderline) personality (Penke et al., 2007). There are several forms of balancing selection of which frequency dependent selection and environmental heterogeneity seem to be the most plausible mechanisms to explain genetic variance in personality traits. Under frequency dependent selection, the fitness of a genotype depends on the

frequency of other genotypes in the population (Gromko, 1977). Frequency dependent selection occurs when different genotypes make use of different limiting resources and can only maintain genetic variation if it is negative, i.e. the fitness of a genotype increases as it becomes rarer (Asmussen et al., 2004; Barton & Keightley, 2002). While under frequency-dependent selection fitness depends on the fluctuations of genotype frequencies, under environmental heterogeneity fitness depends on the environment (fluctuations in time or space). Both frequency dependent selection and environmental heterogeneity can maintain genetic variation in the population if they occur such that the trait's net fitness effect is nearly neutral averaged across all relevant environments and periods. Kassen (2002) argues that genetic variation is maintained through environmental heterogeneity which is, at least in some cases, mediated by frequency dependent selection. More specifically for personality traits, Nettle (2006) discussed the positive and negative effects on fitness of the personality dimensions of the FFM and concluded that it seems most likely that the fitness effects of the personality dimensions differ across environments, thereby maintaining the genetic variation. Extraversion, for example, may have negative fitness effects in some environments and positive fitness effects in other environments. However, exact positive and negative fitness effects for (borderline) personality traits across different environments need to be identified.

Consistent with other axis I and II psychiatric disorders (Kendler et al., 2008; Torgersen et al., 2008) and normal personality traits (Bouchard & Loehlin, 2001; Jang et al., 1996c; Yamagata et al., 2006) we did not find evidence that shared environmental factors contribute to the etiology of BPD. There was no effect of vertical cultural transmission, reflecting the non-genetic influence of the parents' BPD features on the environment of their offspring. Only genetic transmission thus explains the resemblance in BPD features between parents and offspring. However, since it is not possible to simultaneously estimate genetic dominance and shared environmental effects with data from twins reared together we cannot totally rule out the influence of shared environmental effects. To address this issue, other research designs should be applied, such as the adoption design which separates genetic and environmental influences.

Individuals with BPD tend to score high on neuroticism and low on agreeableness and conscientiousness, reflecting their affective instability, antagonism and low sense of self efficacy (identity problems), respectively (Widiger et al., 2002). In addition, BPD, personality traits underlying BPD, such as affective instability and impulsivity, and normal personality traits, such as the FFM personality traits (neuroticism, agreeableness, conscientiousness, extraversion and openness to experience) show roughly the same level of genetic influence (around 50%) (Torgersen et al., 2008; Livesley et al., 1998; Jang et al., 1996b, 1996c). Consequently, a group of prominent personality researchers has suggested that personality disorders might represent the extreme ends of normal personality traits (Widiger & Trull, 1992; Trull et al., 2003; McCrae et al., 2001). Consistent

with this idea we found that the FFM traits and BPD features share all genetic variation. This new insight provides additional opportunities in the search for biological pathways leading to BPD since genes involved in normal personality are also likely to be involved in BPD. However, not all variation in BPD features is shared with normal personality traits. Environmental factors specific to BPD features explain 33% of the total variation. We hypothesize that through complex non-linear pathways involving environmental risk factors and genetic vulnerabilities, extreme forms of personality traits may lead to personality disorders. Individuals most at risk seem to be those high in neuroticism and low in agreeableness.

Both genes and environment thus contribute to the risk of developing BPD, as is true for most psychiatric disorders. However, the effect of environmental factors is not only additive to the effect of genetic factors. We showed that genetic influences on BPD are correlated with and moderated by experiencing certain life events. The exposure to divorce/break-up, traffic accident, violent assault, sexual assault, or job-loss is significantly associated with more BPD features. The effect was strongest if the life event had recently taken place, as can be seen in Figure 11.2. Also the total number of life events was associated with more BPD features. Similar results were previously reported for parental divorce, loss or illness which are more common in patients with BPD than in non-patients or patients with other personality disorders (Westen et al., 1990; Parker et al., 1999; Bandelow et al., 2005; Paris et al., 1994a, 1994b; Zanarini et al., 1997; Ogata et al., 1990; Helgeland & Torgersen, 2004; Horesh et al., 2008). The association between the exposure to divorce/break-up, violent assault, and job-loss could partly be explained by shared genetic factors. Reciprocal or unidirectional causal mechanisms also play a role, increasing the number of BPD features. In addition, the exposure to certain life events moderates the genetic and environmental influences on BPD features. Genetic factors become relatively less important in individuals who experienced a divorce/break-up, job-loss or violent assault and sexual assault. The effect was strongest for the exposure to sexual assault. This suggests that sexual assault has such a large effect that even in less genetically vulnerable individuals it is associated with more BPD features. Some life events thus have main effects on BPD features while others interact with genetic or environmental influences on BPD features. These results emphasize that it is important during treatment of BPD to pay attention to problems in relationships and at work.

Linkage and association studies have provided valuable information about the genes involved in many diseases, disorders and traits (Teare & Barrett, 2005; Psychiatric GWAS Consortium Coordinating Committee, 2009). For BPD I conducted the first genome wide linkage scan and found that chromosomal region 9p24.1 was linked to variance in BPD features in Dutch adults (LOD = 3.55). Three other regions (1q31.1, 4p16.1 and 18q23) were suggestively linked to BPD features (LOD = 1.60, 1.49 and 1.44, respectively). Around the location of our most pronounced linkage peak (9p24.1) a potentially inter-

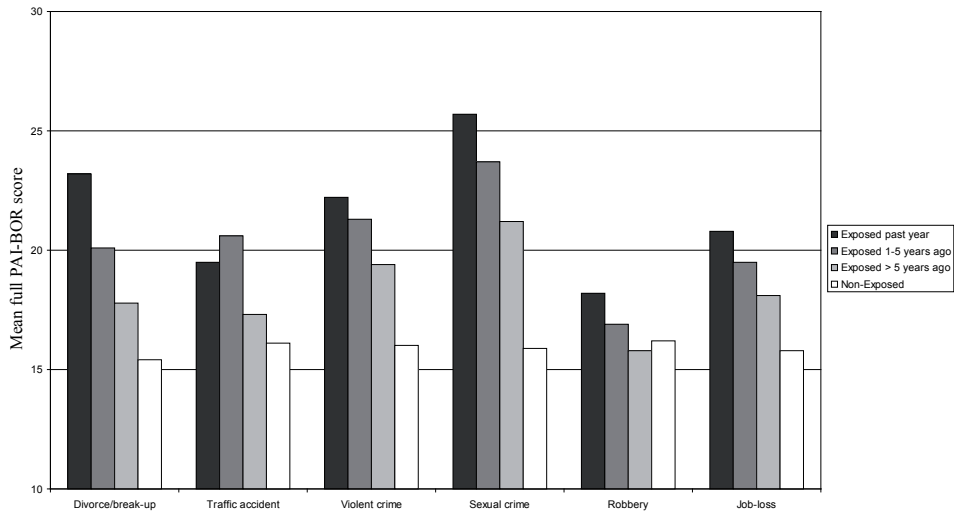


Figure 11.2. Mean PAI-BOR scores for individuals exposed to divorce/break-up, traffic accident, violent crime, sexual crime, robbery or job-loss.

esting gene is located: the protein tyrosine phosphatase receptor type delta (PTPRD). A recent genome wide association study reported an association between ADHD and the PTPRD gene (Anney et al., 2008) and a genome wide linkage scan reported the region of this gene to be associated with nicotine dependence (Li et al., 2007), two phenotypes known to be associated with BPD. BPD and ADHD are both characterized by deficits in affect regulation, impulse control, low self esteem and disturbed interpersonal relationships (Davids & Gastpar, 2005) and individuals with ADHD or BPD both have elevated rates of substance abuse (Sobanski, 2006; Williams et al., 1996). The PTPRD gene is thus a good candidate to include in a biological pathway increasing the risk for both disorders. In addition, genome wide linkage and association studies have shown that the 9p24 region is associated with bipolar disorder (Fallin et al., 2004; Sklar et al., 2008), autism (Allen-Brady et al., 2009; Szatmari et al., 2007; International Molecular Genetic Study of Autism Consortium (IMGSAC), 2001; Marshall et al., 2008) and schizophrenia (Faraone et al., 1998; Sullivan et al., 2008).

In view of the shared genetic factors between BPD features and normal personality traits, linkage studies of normal personality traits may further inform us on the biological pathways leading to BPD. For neuroticism, six linkage studies were conducted and reported several potential quantitative trait loci (Nash et al., 2004; Kuo et al., 2007; Gillespie et al., 2008; Wray et al., 2008; Neale et al., 2005; Fullerton et al., 2003). Wray et al. (2008) found three chromosomal regions which exceeded empirically derived

thresholds for suggestive linkage (top 5 centiMorgan (cM), 14q 103 cM and 18q 117 cM). Of these loci, the 18q region overlaps with the region I found to be suggestively linked to BPD features and was reported to be linked to recurrent early onset and major depression (Camp et al., 2005) and harm-avoidance (Cloninger et al., 1998). Fullerton et al. (2003) found in a sample of twins extremely discordant and concordant for neuroticism loci at 1q, 4q, 7p, 12q and 13q to be significantly linked to variation in neuroticism. In addition, loci at 11q were suggestively linked to neuroticism. In a sample of 129 sibling-pair families selected for nicotine dependence evidence for linkage for neuroticism was found in regions 1p and 11q, replicating previous findings. New evidence for loci associated with neuroticism were found at 3p, 6q and 12p (Neale et al., 2005). Based on a sample of sibling pairs selected for alcohol dependence, evidence for linkage to neuroticism was found on chromosomes 11p, 12q and 15q (Kuo et al., 2007). Only the linkage peak at the 12q region reached genome wide significance. Although Fullerton et al. also found evidence for loci linked to neuroticism on 12q it is unclear whether this can be considered a replication since the locations of the linkage peaks were 60 cM away from each other. Gillespie et al. (2008) reported evidence for linkage on chromosomes 5, 10, 12, 15, 16 and 19 although none reached genome wide significance. The linkage peaks on chromosome 12 and 15 have been reported before (Kuo et al., 2007; Fullerton et al., 2003).

Association studies may provide further information on genes involved in BPD and related traits. Based on effects of psychiatric medications on monoamine neurotransmission the main focus in these studies has been on genes influencing serotonin dysfunction, dopamine dysfunction and monoamine oxidase-A deficiency. Reduced serotonergic function in anger (Giegling et al., 2006), aggression (Siever, 2008), suicidal behavior (Bah et al., 2008; Zaboli et al., 2006) and impulsivity (Passamonti et al., 2008; New et al., 1998), and increased serotonergic function in emotional lability (Hoefgen et al., 2005) have led to several serotonergic candidate genes for BPD. Tryptophan hydroxylase (TPH) and the serotonin transporter gene (5-HTT) are the most studied candidate genes. TPH plays a role in the biosynthesis of serotonin (5-HT) and is therefore expected to be related to dysfunction of the 5-HT system. Zaboli et al. (2006) conducted a case control study to determine whether specific TPH single-nucleotide polymorphism (SNP) based haplotypes were associated with BPD in 95 suicidal female BPD patients. They found that several haplotypes were associated with BPD but no individual SNP was associated with BPD. 5-HTT transports serotonin from synaptic spaces into presynaptic neuron. Ni et al. (2006) examined the association between 5-HTT and BPD in 89 BPD patients and 269 healthy controls. For this purpose three polymorphisms were genotyped: the 5-HTT-linked polymorphic region (5-HTTLPR), a variable number of tandem repeat (VNTR) in intron 2 and a SNP within the linked polymorphic region (A/G). Higher frequencies of the 10 repeat and the s-10 haplotype were found in BPD patients compared to healthy controls. No significant differences in allele frequencies or genotype frequencies of

5-HTTLPR and A/G were detected. The authors conclude that the 5-HTT gene may play a role in the etiology of BPD. Pascual et al. (2008) however, were not able to replicate this finding in 86 BPD patients and 100 control subjects. Besides serotonergic dysfunction, there is some evidence that dopamine dysfunction may be associated with BPD. Dopamine dysfunction is associated with emotional dysregulation, impulsivity and cognitive-perceptual impairment (for a review see Friedel, 2004), three important dimensions of BPD. A significant and replicated association between the 9-repeat allele of dopamine transporter 1 (dopamine active transporter, DAT1) and BPD in depressed patients was found (Joyce et al., 2006). Finally, genes involved in the production of monoamine oxidase-A (MAOA), which degrades, amongst others, 5-HTT and dopamine, are suggested to be involved in BPD because it is shown to be associated with aggression (Buckholtz & Meyer-Lindenberg, 2008), impulsivity (Manuck et al., 2000) and mood lability (Furlong et al., 1999). To test whether MAOA is also associated with the BPD diagnosis Ni et al. (2007) genotyped two MAOA polymorphisms (promotor VNTR and rs6323) in 111 BPD patients and 289 control subjects. A high frequency of the high activity VNTR alleles and a low frequency of the low activity haplotype were found in BPD patients suggesting that the high activity allelic variant may play a role in the etiological development of BPD.

Although the above described studies found associations between serotonin dysfunction, dopamine dysfunction and monoamine oxidase-A deficiency and BPD or related traits, the results could not always be replicated and have not led to identification of the main biological problem behind BPD. This suggests that, as is true for most mental disorders, BPD should be considered among the complex traits. It is likely that a large number of genes with all minor effects account for the heritability of BPD features. To detect such small effects, large numbers of SNPs across the whole genome need to be examined in large samples. Genome wide association (GWA) analysis is a method to identify the variations that occur more frequently in people with a particular disorder than in people without the disorder. No GWA study has been conducted for BPD features yet. For normal personality traits, a GWA study on the Eysenck neuroticism dimension (Shifman et al., 2008) and on all FFM personality traits (Terracciano et al., 2009) was performed and a large meta-analysis is currently underway. Neuroticism and agreeableness showed a high genetic correlation with BPD features thus genes involved in these personality traits may also be involved in the development of BPD. For neuroticism some evidence exists for an association with the rs362584 polymorphism in the SNAP25 gene (Terracciano et al., 2009). The SNAP25 gene is located in the 12q region where several studies reported a linkage peak (Fullerton et al., 2003; Kuo et al., 2007) and is important in the regulation of neurotransmitter release, axonal growth and synaptic plasticity (Osensand et al., 1993). Abnormalities in the level of SNAP25 gene have been linked to mood disorders and bipolar I disorder (Scarr et al., 2006; Fatemi et al., 2001). For

agreeableness evidence exists for an association with SNPs within or close to the CLOCK gene (Terracciano et al., 2009) which encodes proteins regulating circadian rhythm affecting both the persistence and length of the circadian cycle (Steeves et al., 1999). The CLOCK gene has been associated with sleep and mood disorders amongst other disorders (Benedetti et al., 2003, 2007; Takao et al., 2007). At the NTR, data for a GWA study of BPD features are available for a large number of subjects. We aim to analyze these data in the near future to examine whether the SNAP25 and the CLOCK gene are also associated with variation in BPD features.

In comparison with genetic studies of other psychiatric disorders, such as depression and schizophrenia, genetic studies of BPD have been rare. With this thesis, a start has been made to clarify the genetic architecture of BPD and its relationship to environmental factors. Several differences between the genetic architecture of BPD and the genetic architecture of other psychiatric disorders emerged. A large proportion of genetic variance in BPD features is non-additive whereas genetic variance in most psychiatric disorders, such as depression and schizophrenia is additive (Sullivan et al., 2000; Tandon et al., 2008). I found all genetic variance in BPD features to be shared with normal personality traits. This result is in line with, but more extreme than, findings for other psychiatric disorders. Genetic correlations from 0.47 to 0.82 were reported between neuroticism and major depressive disorder and internalizing disorders (Kendler et al., 1993b, 2006; Hettema et al., 2006). For many psychiatric disorders, GWA studies have yielded specific common DNA sequences that influence disease susceptibility, although only small proportions of genetic variance have been explained so far (Psychiatric GWAS Consortium Coordinating Committee, 2009). For BPD, GWA is the next strategy to detect small genetic effects that contribute to individual differences in BPD.

The results described in this thesis hold several implications for future research and the prevention and treatment of BPD. First, many patients and their family members struggle with feelings of guilt and blame regarding the causes of the disorder. In addition, fear of recurrence in at risk family members and offspring is often present. Giving the patient and his or her family insight into the etiology of BPD will increase the feeling of control over the illness, which may improve quality of life (Jorm & Griffiths, 2008). Second, a specific profile of scores on the FFM personality traits can be taken as etiological precursor or risk factor to develop BPD. By identifying these profiles more effective prevention and treatment programs can be started. For example, one might suggest that individuals who display a pattern of high neuroticism and low agreeableness should be assigned to interventions that target emotion regulation skills. Also, high-risk environments should be avoided so that these individuals, who are biologically at risk, will not develop BPD. Third, the results of this study empathizes the importance of paying attention to relationship problems, anger control and functioning at work during treatment, since the genes that influence BPD features increase the risk to expe-

rience a divorce/break-up, violent assault or job-loss. Also, exposure to these life events increases the number of BPD features, stressing the importance of preventing these life events even more.

The implications for future research are also several. First, the results of the linkage study show that genes influencing BPD may be located at chromosome 9p24. Future research should aim to identify the genes in this region that influence the development of BPD. Although the effects of single genes are likely to be small, identifying these genes may still provide a better understanding of the biological pathway from genotype to phenotype. To detect small effects of genes, extremely large sample sizes are needed (Craddock et al., 2008). Since we found that the genetic architecture of BPD features is similar across cultures, datasets from different countries can readily be combined for these analyses. In the near future we will perform a GWA analysis for BPD. Second, although we provided a good starting point in chapter ten by exploring the joint effects of genes and six life events on BPD features, still many other life events are to be studied. For example, positive life events or protective familial influences and social networks may also play a role. Positive life events could serve as a protective factor by buffering the effects of negative life events. The eighth wave of data collection of the NTR is currently being carried out, asking for PAI-BOR data as well as extended life event information, which will provide the opportunity to longitudinally study the effect of life events on the development of BPD. These future studies will complement the current research finding of this thesis and enable us to move towards a comprehensive model of the development of BPD in which biological and environmental influences on BPD are integrated.