Individual diff

border p tra erences in

line ersonality its A genetic perspective

Marijn Distel

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voor het bijwonen van de openbare verdediging van mijn proefschrift

Individual differences in

# borderline personality traits

A genetic perspective

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#### INDIVIDUAL DIFFERENCES IN

## **BORDERLINE PERSONALITY**

# **TRAITS**

A GENETIC PERSPECTIVE

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#### INDIVIDUAL DIFFERENCES IN BORDERLINE PERSONALITY TRAITS

#### A GENETIC PERSPECTIVE

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door

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geboren te Alkmaar

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#### TABLE OF CONTENTS

Chapter 1	The genetic epidemiology of borderline personality traits and disorder
Chapter 2	Research design
Chapter 3	Personality, health and lifestyle in a questionnaire family study: A comparison between highly cooperative and less cooperative families
Chapter 4	Assessment of borderline personality disorder features in population samples: Is the PAI-BOR scale measurement invariant across sex and age?
Chapter 5	Heritability of borderline personality disorder features is similar across three countries
Chapter 6	Familial transmission of borderline personality disorder features:  Genetic or cultural transmission?
Chapter 7	Genetic covariance structure of the four main features of borderline personality disorder
Chapter 8	Chromosome 9: Linkage for borderline personality disorder features
Chapter 9	The Five Factor Model of personality and borderline personality disorder: A genetic analysis of comorbidity
Chapter 10	Life events and borderline personality: The influence of gene-environment correlation and gene-environment interaction . 149
Chapter 11	Summary and discussion
Individuele	verschillen in borderline persoonlijkheidskenmerken Een genetisch perspectief (Dutch summary)185







References	193
Appendices	
I	Nederlandse vertaling van de Personality Assessment Inventory- Borderline kenmerken schaal (PAI-BOR): Normgegevens, factorstructuur en betrouwbaarheid215
П	De Personality Assessment Inventory- Borderline kenmerken schaal in relatie tot de Revised NEO Personality Inventory en de NEO Five Factor Inventory
III	Invitation letter
IV	Information brochure
V	Reminder letter
VI	Retest invitation letter
VII	Offspring address request letter and offspring address form 242
VIII	Offspring invitation letter and application form
List of publi	cations
Dankwoord	







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# THE GENETIC EPIDEMIOLOGY OF BORDERLINE PERSONALITY TRAITS AND DISORDER

This chapter is based on:

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#### INTRODUCTION

N COMPARISON TO many other traits that are studied in the field of behavioral genetics and psychiatric genetics, borderline personality disorder (BPD) has received very little attention. This is remarkable, as the disorder is clearly familial and places a large burden on the individual, on family members, and on society as a whole. Therefore, in this thesis I focus on the genetic determinants of BPD, while recognizing the possible importance of other determinants such as the experience of traumatic life events.

BPD is a severe personality disorder characterized by disturbances in emotional regulation, impulse control, interpersonal relationships, and identity (American Psychiatric Association, 2000) and is frequently co-morbid with other personality disorders and with axis-I disorders (Skodol et al., 2002a). A recent large scale study in the United States of America showed that BPD affects 1-2% of the general population. BPD is the most common personality disorder in clinical settings representing 10% of the patients in outpatient settings, 15-20% of the patients in inpatients settings and 30-60% of the patients diagnosed with personality disorders (Lenzenweger et al., 2007; Widiger & Trull, 1993; Widiger & Weissman, 1991).

As studies of the genetic determinants of BPD are scarce, the available knowledge about the etiology of BPD comes from studies on social and environmental causes. Several studies demonstrated that traumatic life events such as sexual abuse (e.g. Zanarini et al., 2002; Paris et al., 1994a, 1994b), physical abuse (e.g. Helgeland & Torgersen, 2004; Westen et al., 1990), parental divorce or illness (e.g. Parker et al., 1999; Paris et al., 1994a, 1994b) or parental psychopathology (e.g. Trull, 2001a; Torgersen, 1984; Baron et al., 1985a) are important risk factors for the development of BPD. As expected, none of these studies has come up with the definite causal determinant of BPD or can explain all of the risk in affected individuals. Moreover, important questions remain: (1) To what extent do genetic risk factors contribute to individual differences in BPD features? (2) Do individuals with a high genetic risk for BPD also have a higher risk than others to experience traumatic life events and does this explain the association between the experience of life events and BPD? (3) Why do not all subjects who experience a traumatic life event develop BPD? Is a genetic liability required to develop the disorder? (4) Why have not all BPD patients experienced a traumatic life event? Do some patients have such a high genetic liability that they do not need this environmental trigger? (5) Is BPD in some patients not caused by a main effect of genes or environment, but by the interaction between genes and environment?

In this chapter, I first introduce the main symptoms and assessment methods of BPD. Next, current knowledge regarding the association between BPD and demographic characteristics and the co-morbidity with other axis-I and axis-II disorders is reviewed.

Following this, I describe family- and twin studies into the genetics of BPD, and discuss the valuable information that can be achieved by conducting extended twin studies and genetic linkage studies for BPD. A brief outline of the contents of this thesis concludes this chapter.

#### BORDERLINE PERSONALITY DISORDER: MAIN SYMPTOMS

The main characteristics of BPD might be subdivided into four factors based on factor analytic studies of personality features of individuals with BPD: affective instability, identity problems, impulsivity/ self-harm and negative relationships. Affective instability refers to the highly reactive moods of individuals with BPD in response to stimuli from the individual's environment. The basic mood often shifts between periods of anger, panic, anxiety or despair and is rarely relieved by periods of well-being or satisfaction. *Identity* problems are a second main characteristic, involving a poorly defined concept of self. The self image of persons with BPD may shift a lot, including sudden changes in opinions, sexual identity, types of friends, or career plans. The third factor, impulsivity, often results in self-damaging behavior. Common forms of impulsive behavior are excessive spending, reckless driving, binge eating, substance abuse and promiscuity. Negative relationships are the fourth main feature of BPD patients. Individuals with BPD often engage in unstable and stormy relationships, partly caused by the former three mentioned characteristic of BPD patients. They idealize potential lovers in an early stage of a relationship and demand to spend a lot of time together. However, they easily switch from idealization to devaluation when they get the feeling that the other person is not equally committed. In addition to these four main characteristics, intense and inappropriate anger, feelings of emptiness, fear of abandonment, suicidal and self-mutilating behavior and transient dissociative or paranoid symptoms are also common.

### DIMENSIONAL MODELS OF BORDERLINE PERSONALITY DISORDER

Recently, the nature of personality disorders and their relationship to normal personality has received extensive attention (Widiger & Trull, 2007; Trull et al., 1990; Trull & Widiger, 2008a). Several models have been proposed to conceptualize personality disorders as maladaptive variants of continuously distributed personality traits. In this view, BPD is thought of as the upper extreme of a constellation of personality traits, rather than being a distinct disorder. Dimensional or quantitative scales provide information

II





about the degree to which symptoms of a disorder are present instead of a sole statement about whether the disorder is present or not. The term "dimensional" is used to describe many different approaches to quantifying personality and personality pathology. There are three major possibilities: (1) quantify each personality disorder construct by indicating the degree to which the symptoms of a personality disorder are present, (2) identify those personality traits that underlie the personality disorder constructs and provide a description of personality pathology from a trait perspective or (3) use personality trait models that are independent from current diagnostic classification schemes to both characterize and perhaps redefine personality pathology and personality disorder.

An example of the second dimensional approach is Liveley's *Dimensional Assessment of Personality Pathology - Basic Questionnaire* which identifies four higher-order dimensions underlying personality pathology: *emotional dysregulation, dissocial behavior, inhibitedness, and compulsivity.* BPD symptoms appear to be best represented by the factors emotional dysregulation and dissocial behavior (e.g. Bagge & Trull, 2003). An example of the third dimensional approach is the *Five Factor Model* (FFM) of personality which uses five major domains to describe personality, typically referred to as *neuroticism, extraversion, openness to experience, agreeableness,* and *conscientiousness.* FFM traits that appear to underlie BPD symptoms include high scores on neuroticism and low scores on conscientiousness and agreeableness (Lynam & Widiger, 2001; Trull et al., 2003).

In this thesis, we adopted the first dimensional approach and assessed BPD features with the *Personality Assessment Inventory-Borderline features scale* (PAI-BOR; Morey, 1991), a commonly used dimensional self-report measure of BPD features. The PAI-BOR scale taps the four important components of BPD described above. The PAI-BOR consists of 24-items that are scored on a likert scale (0 to 3; *false, slightly true, mainly true, very true*) to provide a dimensional understanding of BPD features. Several studies (discussed in more detail in chapter two) have shown the PAI-BOR to be a reliable and valid measure of BPD features, and support the usefulness of the PAI-BOR in assessing BPD features in the general population as well as in clinical settings (Kurtz et al., 1993; Stein et al., 2007; Morey, 2003). The present thesis reports on the investigation of the influence of non-response bias for the Dutch translation of the PAI-BOR (chapter three) and whether the PAI-BOR is measurement invariant with respect to sex and age, in order to reliably compare scores between these groups (chapter four).

12





# Table 1.1. Criteria for borderline personality disorder as described in the Diagnostic and Statistical Manual for mental disorder (fourth edition)

The main characteristics of borderline personality disorder include instability in interpersonal relationships, self-image, affects, and control over impulses. Specific features include:

- 1. Extreme efforts to avoid real or imagined abandonment.
- 2. Unstable and intense interpersonal relationships.
- 3. Identity disturbance: disturbed, distorted, or unstable self-image or sense of self.
- 4. Impulsivity that is potentially self-damaging (e.g. excessive spending, substance abuse, reckless driving, binge eating).
- 5. Recurrent suicidal behaviour (gestures or threats) or self-mutilating behaviour.
- 6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
- 7. Chronic feelings of emptiness.
- 8. Inappropriate, intense anger or lack of control of anger.
- 9. Dissociation (e.g., depersonalization or derealization) or paranoid thoughts that occur in response to stress.

#### THE DIAGNOSTIC AND STATISTICAL MANUAL FOR

#### MENTAL DISORDERS

In addition to dimensional models of BPD, a set of clinical criteria exists that are used in patient settings. The Diagnostic and Statistical Manual for mental disorders (DSM-IV-R; American Psychiatric Association, 2000) describes nine criteria for BPD, described in Table I.I. At least five out of nine must be present for a BPD diagnosis to be made, resulting in 256 different combinations of criteria from which it is possible to achieve a BPD status.

#### PREVALENCE OF BORDERLINE PERSONALITY DISORDER

Table 1.2 shows 22 studies reporting prevalence rates for BPD which vary from 0.0 to 5.9%. The main limitation of many of these studies is that they are not representative of the

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Table 1.2	Thon	revalence o	f RDD in 2	2 studios		
Author	Year	Instrument	Place	Sample description	N	Prevalence
Baron et al.	1985	SIB DSM-III	?	Randomly selected relatives of 90 normal control probands.	376	1.6
Drake & Vaillant	1985	Clin Int DSM-III	Boston, USA	Normal control male probands originally recruited in a study of juvenile delinquency.	369	0.8
Zimmerman & Coryell	1989	SIDP DSM-III	Iowa, USA	First degree relatives of normal controls (23%) and of psychiatric patients with schizophrenia (16%), psychotic (31%) and nonpsychotic depression (29%) or another psychiatric disorder (1%).	797	1.6
Reich et al.	1989	PDQ DSM-III	Iowa, USA	Randomly drawn from a midwestern university community.	235	1.3
Swartz et al.	1990	DIS a DSM-III	Continental USA	Community sample from the USA	1,541	1.8
Maier et al.	1992	SCID-II DSM-III-R	Mainz, Ger- many	Normal unscreened controls (24%), their spouses (13%) and their relatives (63%).	452	1.1
Black et al.	1993	SIDP DSM-III	Iowa, USA	First degree relatives of obsessive compulsive probands (49%) and of normal control probands (51%).	247	3.2
Bodlund et al.	1993	SCID-screen DSM-III-R	Umea, Sweden	Normal control subjects.	133	3.8
Kendler et al.	1993	SIS DSM-III-R	Ireland	Relatives of 150 unscreened control subjects selected from a rural county.	580	0.0
Moldin et al.	1994	PDE DSM-III-R	New York, USA	Parents (38%) and offspring (62%) followed as normal control families in the New York High-Risk Project.	302	2.0
Blanchard et al.	1995	SCID-II DSM-III-R	New York, USA	Normal unscreened control subjects.	93	1.1
Klein et al.	1995	PDE DSM-III-R	New York, USA	Relatives of 45 normal controls.	229	1.7
Lenzenweger et al.	1997	IPDE DSM-III-R	New York, USA	Undergraduate students enrolled at Cornell University. Screened by means of a questionnaire. A sample of those expected to have a personality disorder and those not expected to have a personality disorder were interviewed.	258	1.3 c

interviewed.





Table 1.2. The prevalence of BPD in 22 studies							
Author	Year	Instrument	Place	Sample description	N	Prevalence	
Jackson & Burgess	2000	IPDE ICD-10	Australia	Community sample from Australia	10,641	1.0	
Torgersen et al.	2001	SIDP-R DSM-III-R	Oslo, Nor- way	Randomly drawn from the National Register of Oslo.	2,053	0.7 b	
Ekselius et al.	2001	DIP-Q DSM-IV, ICD- 10	Gotland, Sweden	Randomly selected from the community of Gotland.	557	5.4/4.8d	
Samuels et al.	2002	IPDE DSM-IV	Baltimore, USA	Adult household residents who were not examined by a psychiatrist in an earlier stage of the study and screened for several Axis I disorders.	742	0.5 b	
Crawford et al.	2005	SCID-II DSM-IV	New York, USA	Community sample from two upstate New York counties.	644	3.9	
Coid et al.	2006	SCID-II DSM-IV	United Kingdom	Community sample from England, Wales or Scotland.	626	0.7 b	
Lenzenweger et al.	2007	IPDE DSM-IV	Continental USA	Community sample from the USA.	5,692	1.4 b	
Şar et al.	2007	SCID-II DSM-III-R	Sivas, Tur- key	Women from 500 house-holds in Sivas.	628	3.5	
Grant et al.	2008	AUDADIS-IV	USA	Community sample from	34,653	5.9	

SIB = Schedule for Interviewing Borderlines; Clin Int = semi structured psychiatric interview; SIDP = Structured Interview for DSM-III Personality disorders; PDQ = Personality Diagnostic Questionnaire; DIS = Diagnostic Interview Schedule; SCID-II = Structured Clinical Interview for DSM-III-R personality disorders; SIS = Structured Interview for Schizotypy; PDE = Personality Disorder Examination; IPDE = International Personality Disorder Examination. DSM-III-R and DSM-IV version; SIDP-R = Structured Interview for DSM-III-R; DIP-Q = DSM-IV and ICD-IO Personality Questionnaire; AUDADIS-IV = Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV version. a Borderline personality disorder was not included in the DIS but an algorithm was constructed to approximate prevalence of borderline personality disorder. b Weighted prevalence rates, c When the two stage procedure is taken into account. d According to the DSM-IV and ICD-IO classification system, respectively.

population. The sample from Lenzenweger et al.'s (1997) study for example only consists of college students, which makes it impossible to generalize the results. Other samples consist of relatives of psychiatric patients (Zimmerman & Coryell, 1989; Baron et al., 1985b; Black et al., 1993), or controls screened for psychiatric disorders (Moldin et al., 1994; Klein et al., 1995), which may have respectively upwardly or downwardly biased the prevalence rates, given that BPD often co-occurs with axis-I disorders. In addition, several studies suffer from small sample sizes (Reich et al., 1989a; Black et al., 1993; Bodlund et al., 1993; Blanchard et al., 1995; Klein et al., 1995; Lenzenweger et al., 1997).

Seven large scale studies assessed the prevalence of BPD in well characterized community samples from Australia, the USA, the UK or Norway, using validated structural interviews for ICD-IO (Jackson & Burgess, 2000), DSM-III-R (Torgersen et al., 2001) and DSM-IV (Crawford et al., 2005; Grant et al., 2008; Coid et al., 2006; Samuels et al., 2002;

Lenzenweger et al., 2007). Jackson & Burgess (2000) assessed 10,641 Australian individuals aged 18 years and over with the International Personality Disorder Examination (IPDE) ICD-10 screener (Loranger et al., 1997) administered by an interviewer and report a prevalence rate of 1%.

Torgersen et al. (2001) administered structured interviews for DSM-III-R in 2,053 individuals between the ages of 18 and 65 years representing 57% of the originally randomly selected sample of 3,590 citizens from the national register of Oslo, Norway. Contrary to most other studies, a fixed list of potential subjects was selected instead of households resulting in valuable information about who participated and who did not. Participants were significantly more often women (63%), aged 40 years or older (61%) and living in the town periphery (61%) instead of in the center of the city. The reason for the different participation rates between the demographic groups were incorrect addresses and relocations without providing a new correct address. Prevalence rates were weighed for the differences between the interviewed sample and the population at large although differences were small. The prevalence in this study was estimated at 0.7%.

Samuels et al. (2002) selected in the first stage of their study in 1981, all household residents between the ages of 18 and 64 years old of eastern Baltimore of whom 3,481 were interviewed using the Diagnostic Interview Schedule (DIS). A total of 810 of these individuals were also examined by psychiatrists. In the 1990s, 1,920 of the surviving subjects were re-interviewed. The sample from Samuels et al.'s 2002 study was selected from these subjects and included all participants who were examined by psychiatrists and all participants who were identified as having an axis-I disorder by the DIS. In addition, a random sample was selected from the remaining subjects, of which 742 were fully assessed with the IPDE for DSM-IV (IPDE; Loranger, 1999). Their mean age was 47 years (range 34-94 years) and 63% were women. Weighted (0.5%) and unweighted (1.2%) prevalence rates were reported.

The study by Crawford et al. (2005) reports a prevalence rate of 3.9% based on participants drawn from the Children In Community (CIC) sample, a large epidemiological sample of children in New York that was assessed for the first time in 1975 and followed since. The 2005 study is based on 644 subjects (53% women) assessed with the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II; First et al., 1997) at age 33.

The sample studied by Coid et al. (2006) was drawn from those participating in the British National Survey of Psychiatric Morbidity. Initially 8,886 adults living in England, Scotland and Wales completed the phase 1 screening interview. The sample selection for the second phase was based on scores on the diagnostic instruments used in phase I. All persons who screened positive for psychosis (N = 339), half of those who screened positive for antisocial or borderline personality disorder (N = 64), one in 14 of those who screened positive for other personality disorder (N = 136) and one in 14 of those

who showed no evidence of either personality disorder or psychosis (N = 398) were selected of whom 638 were assessed by the SCID-II. The final sample consisted of 626 participants (57% women, age range I6-74 years) who completed both the SCID-II and a screening interview. Prevalence rates (0.7% for BPD) were estimated using weights to adjust for the effects of differential probabilities of selection and non-response in both phases of the survey.

The study of Lenzenweger et al. (2007) was based on the National Comorbidity Survey Replication (NCS-R), a nationally representative survey in the United States, in which all 9,282 respondents were administered a part I diagnostic interview that assessed core disorders. The sample used in the 2007 study was selected in part II and consisted of all phase I respondents who met criteria for a core disorder and 25% of other part I respondents. All 5,692 phase II participants completed a series of personality disorder screening questions from the IPDE and three sets of possible correlates (sociodemographics, role impairment and 12-month treatment) were examined. The sample was weighted to adjust for sampling effects and several correlates. Clinical reappraisal interviews with the IPDE were carried out with 214 part II respondents. Based on these interviews, the coefficients from best fitting regression equations of personality disorder diagnoses predicted by IPDE screening questions in the clinical reappraisal group were used to predict the probability of each personality disorder diagnosis to part II respondents who were not part of the clinical reappraisal group. The prevalence rate of BPD was estimated at 1.4%.

Recently, Grant et al. (2008) conducted a large scale epidemiological study in which 34,653 individuals aged 18 years and older were assessed using the Wave 2 Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV; Grant et al., 2001). Participants were assessed on 18 multiple symptom items. A requisite number of symptoms had to be endorsed of which at least 1 had to have caused significant distress or impairment in daily functioning to receive a BPD diagnosis. The prevalence rate was estimated at 5.9%.

Prevalence rates for BPD based on these seven studies thus range from 0.5% (Samuels et al., 2002) to 5.9% (Grant et al., 2008). Crawford et al. (2005) and Grant et al. (2008) reported the highest prevalence rates of respectively, 3.9 and 5.9%. The higher prevalence reported in the study by Crawford et al. is most likely due to differences in sample composition, as this study was based on 33 year-old participants while the other studies covered a much broader age range. As BPD is more often diagnosed in younger individuals this could have caused the high prevalence. The high prevalence rate of 5.9% reported by Grant et al. may be due to the fact that they assessed BPD diagnoses on lifetime basis instead of current diagnoses. Also, the criteria to receive a diagnosis of BPD (if only one of the required symptoms resulted in impairment in daily functioning a diagnosis was made) might have biased the prevalence rate upwardly.





In clinical settings BPD is much more common with prevalence rates up to 10% in outpatients and 20% of inpatients (Widiger & Weissman, 1991).

#### DEMOGRAPHIC CORRELATES

#### Age

Generally BPD symptoms appear by early adulthood (American Psychiatric Association, 2000), and the symptoms and/or severity of the disorder usually diminish with age (Stone, 1990; Grant et al., 2008; Torgersen et al., 2001; Lenzenweger et al., 2007). Two longitudinal studies present results about the longitudinal course of BPD in treatment seeking adults. The McLean Study of Adult Development (MSAD; Zanarini et al., 2005, 2007) studied the longitudinal course of BPD in a group of 362 patients (77% females) of whom 24 BPD symptoms and comorbid diagnoses were assessed every two years by the Structured Clinical Interview for DSM-IV axis-I Disorders (SCID-I; Spitzer et al., 1992), the Revised Diagnostic Interview for Borderlines (DIB-R; Zanarini et al., 1989) and the Diagnostic Interview for DSM-III-R Personality Disorders (DIPD-R; Zanarini et al., 1987). Results showed that half of the symptoms at baseline had declined substantially over time. These 12 symptoms mainly included symptoms reflecting help-seeking suicidal- and self mutilating behavior. The 12 symptoms that did not decline over time and thus seem to be more stable encompassed affective symptoms and interpersonal symptoms reflecting issues concerning feelings of loneliness, anger and dependency. The authors conclude that some symptoms of BPD are manifestations of acute illness while others are more enduring aspects of the disorder. The Collaborative Longitudinal Personality Disorder Study (CLPS; Skodol et al., 2005; Gunderson et al., 2000) presented a similar model dividing symptoms into symptomatic behaviors (e.g. abandonment fears, self-mutilation), which are episodic and reactive in nature, and traits (e.g. affective instability, impulsivity, anger), which are more fundamental and enduring. Thus, both clinical studies report a decline in part of the symptoms. A third longitudinal study, the Children In Community study (CIC; Cohen et al., 2005), assessed BPD in 658 individuals drawn from the general population at ages 14, 16, 22 and 33 and report a decline in symptom levels from adolescence to adulthood (Johnson et al., 2000; Skodol et al., 2007).

#### Sex

The DSM-IV (American Psychiatric Association, 2000) states that 75% of the individuals diagnosed with BPD are women. This estimate is based on a meta-analysis by Widiger and Trull (1993) who summarized the results of 75 studies, most based on





clinical samples. However, several large scale community studies revealed no significant gender differences in BPD (Torgersen et al., 2001; Grant et al., 2008; Jackson & Burgess, 2000; Lenzenweger et al., 2007). It is suggested that the gender difference found in clinical samples is caused by different base rates of men and women in clinical samples as women are more likely to seek help (Widiger, 1998; Corbitt & Widiger, 1995).

#### COMORBIDITY WITH OTHER DISORDERS

Epidemiological and clinical studies have established that BPD and axis-I and II disorders are highly comorbid (Gunderson, 2001). For axis-II disorders, Nurnberg et al. (1991) found that 82% of the BPD outpatient population without a current axis-I disorder received at least one other personality disorder diagnosis. Lenzenweger et al. (2007) reported significant co-occurrence between BPD and paranoid, schizoid, antisocial, avoidant, dependent and obsessive-compulsive disorder. For axis-I disorders, Fabrega et al. (1992) found that of the 390 persons diagnosed with BPD, about two thirds received a concurrent axis-I diagnosis. In general, studies into the co-occurrence of BPD and axis-I disorders report that BPD patients often meet criteria for major depression, bipolar I and II disorder, eating disorders, substance use disorders and several anxiety disorders (including Post Traumatic Stress Disorder [PTSD]) (Skodol et al., 1993, 1995, 1999a, 1999b; Lenzenweger et al., 2007; Zimmerman & Mattia, 1999; Zanarini et al., 1998). Using the PAI-BOR Trull et al. (1995) assessed BPD features in a large group of college students and found individuals scoring two standard deviations or more above the mean to have high comorbidity rates for mood and anxiety disorders.

Although there seem to be no gender differences in the prevalence of BPD in the general population, as discussed previously, there are gender differences in comorbid diagnoses. Johnson et al. (2003) compared 175 women and 65 men with a BPD diagnosis and found that women were more likely to be diagnosed with PTSD (51% vs. 31%) and eating disorders (42% vs. 19%), while men were more likely to be diagnosed with substance use disorder (58% vs. 85%) and schizotypal (10% vs. 25%), narcissistic (5% vs. 22%) and antisocial (10% vs. 30%) personality disorder. Recently, McCormick et al. (2007) assessed 163 BPD patients (84.7% women) using the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al., 1992) and found that women were more likely than men to have an anxiety disorder (particularly generalized anxiety disorder and agoraphobia), somatoform disorders, and histrionic personality disorder. Antisocial personality dis-



Table 1.3. Family studies of BPD								
Study	N probands/ relatives	Assessment proband (instrument)	Assessment relatives (instrument)	% relatives with BPD	Limitations			
Stone et al. (1981)	BPD 39/135 Psychotic 36/118 Normal 21/68	Interview (BPO criteria)	Partly direct interviewed	BPD 6.7 Psychotic 13.6 Normal 4.4	- BPO criterion instead of DSM - Relative raters generally knew pro- band's diagnosis - Some of the rela- tives assessed through probands			
Loranger et al. (1982)	BPD 83/338 Sz 100/482 BiP 100/537	Chart review	Chart review	BPD 8.6 SZ 1.0 BiP 0.6	<ul> <li>No comparison subjects from the general population</li> <li>Not controlled for comorbid depression</li> <li>Only female BPD probands</li> </ul>			
Pope et al. (1983)	BPD 33/130 BiP 34/173 Sz 39/181	Chart review	Chart review	BPD 0.8 a BiP 0.6 Sz 2.2	- No normal comparison subjects - For comparison groups (BiP & Sz) cluster B diagnoses instead of BPD diagnoses are reported			
Baron et al. (1985)	BPD 17/60 BPD SPD 20/84 SPD 16/56 Normal 90/376	Structured Interview (SIB)	Directly interviewed (most relatives of normal controls) and through probands (FHRDC/Family history version of SIB)	BPD 5.1 BPD/ SPD 1.8 SPD 0.0 Normal 1.7	- Student sample - 15 of 17 probands had 'probable' BPD - Relative raters not blind to proband's diagnosis - Some of the rela- tives assessed through probands			
Links et al. (1988)	BPD 69/320	Structured Interview (DIB)	Partly direct interviewed (DIB)	BPD 10.9	<ul><li>No comparison groups</li><li>No information on proband comorbidity</li></ul>			
Zanarini et al. (1988)	BPD 48/240 APD 37/139 DOPD 26/109	Structured Interview (DIB-R, DIPD)	Through probands (FHQ)	BPD 18.3 APD 2.9 DOPD 7.3	<ul><li>No interrater reliability</li><li>No normal comparison subjects</li></ul>			

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Assessment

% relatives

Limitations

Table 1.3. Family studies of BPD N probands/

Study

Assessment

	relatives	proband (instrument)	relatives (instru- ment)	with BPD	
Reich et al. (1989)	BPD 12/31 No PD 15/51	Questionnaire (PDQ)	Question- naire (PDQ)	BPD 6.5 No PD 0.0	- PDQ is likely to produce false positives - No other PD comparison group - Relatives assessed through probands
Johnson et al. (1995)	BPD ?/39 AvPD ?/62 No PD 17/46	Structured Interview (SCID-II)	Directly interviewed (SCID-II)	BPD 10.3 AVPD 3.2 No PD 0.0	- Adolescent sample - Number of BPD probands not clear
Riso et al. (2000)	BPD (no MD)11/54 MD 119/563 Normal 45/229	Structured Interview (PDE, FH/PD)	Partly direct interviewed	BPD 22.2 MD 21.5 Normal 7.0	- Some of the relatives assessed through probands
Zanarini et al. (2004)	BPD 341/1580 OPD 104/472	Structured Interview (DIB-R, DIPD-R)	Through probands (FHQ-R)	BPD 13.0 b OPD 7.8 b	<ul><li>No normal comparison subjects</li><li>Relatives assessed through probands</li></ul>
Bandelow et al. (2005)	BPD 66/66 Normal 109/?	Structured Interview (SCID)	Through probands	BPD 9.1 Normal 0.0	<ul><li>Relatives assessed through probands</li><li>Number of relatives not clear</li></ul>

BPD = Borderline Personality Disorder; BiP = Bipolar Disorder; Sz = Schizophrenia; SPD = Schizotypy; APD = Antisocial Personality Disorder; DOPD = Dysthymic Other Personality Disorder; AvPD = Avoidant Personality Disorder; MD = Mood Disorder; OPD = Other Personality Disorder; PD = Personality Disorder.

SIB = Schedule for Interviewing Borderlines; FHRDC = Family History Research Diagnostic Criteria; DIB = Diagnostic Interview for Borderlines; DIB-R = Revised Diagnostic Interview for Borderlines; DIPD = Diagnostic Interview for DSM-III-R Personality Disorders; FHQ = Family History Questionnaire; PDQ = Personality Diagnostic Questionnaire; SCID-II = Structured Clinical Interview for DSM-III-R Personality Disorders; PDE = Personality Disorder Examination; FH/PD = Family History Interview for Personality Disorder; DIPD-R = Diagnostic Interview for DSM-III-R Personality Disorders- Revised; FHQ-R = Revised Family History Questionnaire; SCID = Structured Clinical Interview for DSM-IV.

a 7.7% of the relatives received a diagnosis when histrionic, BPD and antisocial PD were considered together. b For DSM-III-R BPD diagnosis. For estimated DSM-IV BPD diagnoses prevalence rates are 16% for relatives of BPD probands and 9.1% for relatives of OPD patients.





- No other PD comparison group

order was more common in men. In contrast to earlier studies (Johnson et al., 2003; Zanarini et al., 1998), they did not find PTSD and eating disorders to be more common in women or substance use disorders to be more common in men.

#### **FAMILY STUDIES**

Table 1.3 summarizes the results of family studies on BPD. A number of these studies report increased rates of BPD in the relatives of individuals with BPD compared to relatives of control probands (Baron et al., 1985a; Johnson et al., 1995; Zanarini et al., 1988, 2004; Bandelow et al., 2005; Loranger et al., 1982). Prevalences or morbidity risks for BPD in relatives of BPD probands ranged from 9.1% (Bandelow et al., 2005) to 24.9% (Zanarini et al., 1988). The high prevalence reported by Zanarini et al. is probably caused by the fact that information on psychopathology of relatives was derived from the BPD probands themselves. Reich et al. (1989) found a trend in the direction of familiality which did not reach significance. Stone et al. (1981) did not find a higher prevalence of BPD among relatives of BPD probands, while Pope et al. (1983) only found BPD to be more prevalent in the relatives of depressed BPD probands.

As described in a comprehensive review by White et al. (2003) most studies published on the familiality of BPD have limitations in the methodology employed. Amongst other limitations, the sample sizes are generally small varying from 17 (Baron et al., 1985a) to 83 BPD probands (Loranger et al., 1982) and are often not representative of the population (e.g. Loranger et al. [1982] assessed only female BPD probands). Only Zanarini et al. (2004) used a larger sample of 341 BPD probands, but the main limitation of their study is the assessment method used.

Two studies assessed the prevalence of individual borderline symptoms or features, instead of actual diagnoses, in relatives of BPD probands. Silverman et al. (1991) found that the prevalence rates for affective and impulsive personality disorder traits were significantly higher in the relatives of BPD probands than in the relatives of probands with other personality disorders or in the relatives of schizophrenic probands. Zanarini et al. (2004) assessed the prevalence rates of all nine BPD DSM criteria symptoms in first degree relatives of BPD patients, and reported that the prevalence rates of five (inappropriate anger, affective instability, paranoia/dissociation, general impulsivity, and intense, unstable relationships) were significantly higher in first degree relatives of BPD patients than in first degree relatives of axis-II comparison subjects.

#### TWIN STUDIES

Several family studies support the idea that BPD and BPD related traits are familial, but these studies cannot disentangle the effects of genes from the effects of environment





shared by family members and cultural inheritance. Twin studies can disentangle the effects of common environment and genes by making use of the different genetic relatedness of monozygotic (MZ) and dizygotic (DZ) twins. MZ twins are genetically (nearly) identical while DZ twins and siblings share on average 50% of their segregating genes. If genetic factors are important for a trait, MZ twins will be more similar than DZ twins or other first degree relatives. If MZ twins are as similar as DZ twins, familiality is mainly due to common environmental factors.

Compared to the number of studies of other disorders in psychiatric genetics, genetic studies of BPD remain relatively scarce. Only four twin studies so far provided data on BPD diagnoses and features. Torgersen (1984) reported a MZ concordance rate of 0.0% and a DZ concordance rate of 11.1% for BPD, suggesting that shared environmental factors influence the variance in BPD. However, the low number of twin pairs (N = 25) limit any conclusions concerning evidence supporting a genetic or environmental liability for BPD. In 2000, Torgersen et al. assessed 221 twin pairs with the SCID-II (Spitzer & Williams, 1985). Results suggested a heritability of 69%, though this estimate must be considered approximate due to the still relatively small number of twins, the ascertainment method (sampling those who were treated for mental disorder), and the fact that the zygosity and diagnostic status of co-twins was not hidden from the interviewers.

More recently, Torgersen et al. (2008) assessed personality disorder traits in 1,386 twin pairs between the age of 19 and 35 years using the Structured Interview for DSM-IV Personality Disorders (SIDP-IV; Pfohl et al., 1995). The prevalence rate for BPD of 0.4%, and even lower for several other personality disorders, was too low to analyse the data categorically, so a dimensional representation based on sub-clinical criteria was used to study the degree to which genetic and environmental factors influence cluster B personality disorders (borderline, antisocial, narcissistic, histrionic personality disorders). The heritability of BPD was estimated at 35% with the remaining variance explained by individual specific environment.

Using a dimensional measure of BPD we were able to assess BPD features in a large sample of twins from three countries. Chapter five presents heritability estimates based on these data.

#### TWIN FAMILY STUDIES

The combination of data from twins and other family members (their parents, spouses, siblings and/or offspring) offers a powerful approach to study the importance of several mechanisms that cannot be assessed in twin or family data alone (Boomsma et al., 2002a).





23

05/08/09 11:14:10

Parents of twins can be included to simultaneously study genetic and cultural transmission. In the classical twin design, variance due to cultural transmission will be accounted for as common environmental variance. In an extended twin design cultural transmission can be distinguished from other common environmental influences, assuming that cultural transmission from parents to offspring is based on the measured phenotype of the parents rather than on a latent variable (Eaves et al., 2005). Environmental factors as part of cultural transmission may be taught by parents to their offspring in the form of customs or preferences, and have direct effects on behavioral phenotypes through processes of social learning or modelling. In contrast, non-transmissible shared-environment comprises environmental conditions shared by relatives reared together within the same generation (Cloninger et al., 1979). If both genetic and cultural transmission are of importance, i.e. parents transmit both genes and non-genetic information to their children this will induce a correlation between genes and environment. This so called "passive" gene-environment correlation or covariance occurs because parents shape the child's environment based on their own genetic factors which correlates with the child's genetic propensities (Eaves et al., 2005). Spouses of twins can be included to study marital resemblance which can be due to social homogamy, marital interaction or phenotypic assortment (Heath & Eaves, 1985a). Social homogamy refers to the tendency of spouses to have similar social backgrounds. Marital interaction means that spouses living together experience mutual influences which makes them resemble each other, or that one spouse actively influences the other spouse (Penrose, 1944). Phenotypic assortment refers to the tendency of individuals to select their partner based on the partner's phenotype. Spouse similarity as a result of phenotypic assortment will lead to increased genetic resemblance between family members if the trait is heritable, while social homogamy and marital resemblance would not (Falconer & Mackay, 1996). If phenotypic assortment exists, it is therefore important to include it into the genetic analyses, to obtain unbiased heritability estimates. Data from twins and siblings only, as analyzed in the twin-sibling studies described above, may not provide sufficient statistical power to disentangle additive and non-additive genetic effects, or dominance, even when sample sizes are large. MZ twins are perfectly correlated for all non-additive genetic effects. DZ twins and siblings share 1/4 of the dominance (the interaction between alleles at a locus) and less of the epistatic genetic effects (the interaction between genes at different loci). In contrast, while the correlation for additive genetic effects in parents and offspring is 0.5 (unless the expression of genetic effects depends on age), parents and offspring are not correlated for dominant genetic effects. Therefore, if dominance is of importance, the correlation between parents and offspring is expected to be lower than the correlations among DZ twins and siblings. Chapter six describes a study in which we applied an extended twin design to the PAI-BOR data, accounting



for the possible influence of cultural transmission, assortative mating and passive geneenvironment correlation.

#### LINKAGE STUDIES

Since we know now that variation in BPD and BPD features have a genetic component, the next step is to find and study the genes involved. Through linkage analysis, the location of genes influencing BPD may be determined. Linkage is based on allele sharing within families or pedigrees and can be investigated by correlating allele sharing for DNA markers in, for example, pairs of siblings with the differences between siblings on a quantitative trait. If a marker is linked to a quantitative trait there will be greater than expected allele sharing for siblings who are more similar for the trait (Vink & Boomsma, 2002). Linkage for complex traits is often performed with sibling pairs. If a pair of siblings has received the same combination of alleles from a parent at a certain marker locus of the genome, the pair is said to share the parent's alleles at the locus identical by descent (IBD). Because offspring receive the alleles from two parents, the pair can share 0, I or 2 alleles IBD at a locus. If the marker locus is close to a causal gene, then IBD status at the marker locus reflects IBD status at the causal locus. IBD status will then be associated with trait resemblance in sibling pairs (Haseman & Elston, 1972). If siblings are genotyped but their parents are not, it is possible, based on information about allele frequencies, to estimate the probability that a pair of siblings shares 0, 1 or 2 alleles IBD.

Chapter eight presents the first linkage study conducted for the manifestation of BPD features. The analyses were based data from 711 sibling pairs with PAI-BOR and genotype data, and 561 additional parents with genotype data.

#### OUTLINE OF THE THESIS

BPD is a common personality disorder with a prevalence rate of 1 to 2%. Much research into the etiology of BPD so far has focused on the social and environmental determinants. In this thesis I contribute to the clarification of the etiology of BPD in terms of genetic vulnerability. Data on BPD features of twins and their family members registered with the Netherlands Twin Register (Boomsma et al., 2006a), the East Flanders Prospective Twin Survey (Derom et al., 2006) and the Australian Twin Registry (Jardine et al., 1984) are analyzed to determine the influence of genetic factors in explaining individual differences in BPD features. In chapter two the data collection process is outlined. Chapter three compares PAI-BOR scores of individuals from highly cooperative and less cooperative families to estimate possible response bias when collecting data on BPD fea-

25

tures in a population based sample. The response bias is investigated for BPD features and several other personality and lifestyle variables. The aim of chapter four was to investigate whether the Dutch translation of the PAI-BOR is measurement invariant with respect to sex and age. This is an important issue in order to reliably compare scores between different groups of subjects. Next, I present a series of genetic studies to explain individual differences in BPD features. In chapter five, we present heritability estimates for BPD features based on data from the Netherlands, Belgium and Australia. In chapter six, I extended the classical twin design by adding siblings, spouses and parents of twins to the model. This provided the opportunity to assess cultural transmission of BPD features from parents to their offspring, the presence of assortative mating and its influence on the genetic variance and the presence of non-additive genetic effects on individual differences in BPD features. Chapter seven describes a study in which we investigated to what extent the covariance among the four subscales of the PAI-BOR (affective instability, identity problems, negative relationships and self-harm) could be explained by common genes. This is an important issue in the search for genes influencing BPD and BPD features. In chapter eight, I present the results of the first genome wide linkage analysis to help identify chromosomal regions that may harbor the genes which influence the development of BPD. The aim of the study described in chapter nine was to explain the genetic etiology of the relationship between BPD and the personality traits of the Five Factor Model (FFM). The FFM of personality is one of the proposed models to conceptualize personality disorders as maladaptive variants of continuously distributed personality traits. Epidemiological studies into the relationship between the FFM and BPD show that BPD patients tend to score high on neuroticism and low on agreeableness and conscientiousness. In chapter nine we examine whether this association is also present at the level of genetic and environmental influences. In chapter ten we investigate the interaction between genetic and environmental vulnerabilities for BPD features. Genetic vulnerabilities do not cause a mental disorder by themselves. Although biological markers determine vulnerability, environmental factors often determine whether a disorder develops. Finally, in chapter eleven, I discuss the implications of the results of this thesis for clinical settings and future research.









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27





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# **RESEARCH DESIGN**





#### INTRODUCTION

VER 15,000 TWINS and their family members from the Netherlands, Belgium and Australia completed the Personality Assessment Inventory Borderline features scale (PAI-BOR; Morey, 1991), a 24-item questionnaire that taps characteristics that are clinically associated with borderline personality disorder (BPD). In this chapter, the PAI-BOR questionnaire is described and an outline of the data collection process is given.

#### DATA COLLECTION

Personality Assessment Inventory- Borderline features scale

The Personality Assessment Inventory (PAI; Morey, 1991) is a self report measure of clinically relevant aspects of personality and psychopathology. The borderline scale of the PAI (PAI-BOR) assesses BPD features with four subscales: affective instability, identity problems, negative relationships and self-harm. Each subscale consists of six items. The first subscale affective instability (AI) contains items on for example, mood shifts, the intensity of moods, and the ability to control anger. Identity problems (IP) are concerned with a person's self image, concept of self and feelings of emptiness. Negative relationships (NR) are concerned with the intensity and stability of a person's relationships with other people. The last subscale, self-harm (SH), is concerned with a person's tendency to act impulsive and reckless and to engage in self destructive activities. A description of each item is given in chapter four (Table 4.1). For the item selection and the standardization process of the PAI-BOR, Morey (1991) used three groups of subjects; census matched community subjects (N = 1,000), college student subjects (N = 1,051) and clinical subjects (N = 1,246). The internal consistencies of the PAI-BOR full scale in the three groups were 0.87, 0.86 and 0.91, respectively. The internal consistencies of the four subscales ranged from 0.62 (SH) to 0.71 (AI) in the community sample, from 0.65 (IP) to 0.78 (AI) in the college sample and from 0.68 (NR) to 0.81 (AI) in the clinical sample. The test-retest reliability correlations for the full scale were 0.90, 0.82 and 0.86 for the three samples, respectively. The 24 to 28 day's test-retest reliability correlations of the four subscales ranged from 0.81 (AI and NR) to 0.85 (IP) in the community sample, from 0.67 (IP) to 0.85 (AI) in the college sample and from 0.72 (NR) to 0.82 (AI) in the clinical sample. A total of 78 subjects (mean age 32.0, 70.5% females, and 61.5% inpatients) from the clinical sample received a BPD diagnosis. Their data were used to assess the validity of the PAI-BOR. This borderline group had a higher mean score on the full PAI-BOR scale and all subscales than any other diagnostic or behavior subgroups from

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30

the clinical sample. Several additional studies reported good concurrent, convergent and discriminant validity of the PAI-BOR. Bell-Pringle, Pate & Brown (1997) found that the PAI-BOR discriminates between BPD patients (N = 22) and controls (N = 22) with 80% accuracy. Stein, Pinsker-Aspen & Hilsenroth (2007) found similar results comparing PAI-BOR scores of 17 BPD patients and 38 non-BPD patients. The PAI-BOR full score and the sub scores IP and SH were significantly higher for the BPD group and the presence or absence of BPD could be classified correctly in 73% of the subjects. Trull (1995) compared nonclinical young adults scoring in the clinical significant range on the PAI-BOR with those who scored below this threshold and found them to differ on measures of mood, personality, coping and general psychopathology. In addition, Trull found PAI-BOR scores to be significantly correlated with the borderline scale of the Personality Disorder Questionnaire-Revised (PDQ-R; Hyler & Rieder, 1987). The PAI-BOR also proved to be able to discriminate BPD in comorbid samples. Kurtz & Morey (2001) compared PAI-BOR scores of 21 patients presenting for treatment of Major Depressive Episodes (MDE) with BPD, 24 patients with MDE but without BPD, and 20 controls. The BPD patients scored significantly higher on the full PAI-BOR scale and on the AI and IP subscales. In addition, the PAI-BOR score correlated 0.78 with the number of criteria met on the Diagnostic Interview for Personality Disorders-Revised (DIDP-R; Zanarini et al., 1992), indicating high convergent validity in comorbid samples. In a non-clinical sample (N = 119), Kurtz, Morey & Tomarken (1993) assessed BPD, paranoid personality disorder (PAR) and antisocial personality disorder (ANT) with the PAI and the Minnesota Multiphasic Personality Inventory (MMPI) personality disorder scales (MPD; Hathaway & McKinley, 1989; Morey et al., 1985). Good discriminant validity was found for the PAI-BOR indicated by a higher correlation between the PAI-BOR score and the MPD borderline score than between the PAI-BOR score and the MPD-ANT or the MPD-PAR score. In addition, convergent validity was found for both the PAI-BOR and the MPD. Jacobo et al. (2007) analyzed PAI-BOR and Structured Clinical Interview for DSM disorders (SCID-II; First et al., 1997) data from 48 BPD patients. The total number of SCID-II BPD criteria correlated significantly with the PAI-BOR (r = 0.63). In this thesis, I analyzed PAI-BOR data of twins and their family members registered with the Netherlands Twin Register (NTR; Boomsma et al., 2006a), the East Flanders Prospective Twin Survey (EFPTS; Derom et al., 2006) and the Australian Twin Registry (ATR; Jardine et al., 1984). Participation rates of the three samples are shown in Table 2.1. A complete list of the measures included in the Dutch and Belgian survey is given in Table 2.2.

#### The Netherlands Twin Register

The present study is part of an ongoing study on health, lifestyle and personality in twins and their family members registered with the Netherlands Twin Register (NTR), which was established 1987 (Boomsma et al.,2002b, 2006a). For this thesis, data of ado-

05/08/09 11:14:10

Table 2.1. Participation of twins and their family members registered with
the Netherlands, Belgian and Australian twin registries

		The Netherlands	Belgium	Australia
Male	Twins	1,411	323	1,223
	Siblings	543	6	97
	Parents	1,229	315	-
	Spouses	625	11	-
	Offspring	113	-	-
Female	Twins	3,296	622	2,249
	Siblings	936	17	155
	Parents	1,580	400	-
	Spouses	367	2	-
	Offspring	218	-	-
Sex unknown		8	П	-
Total		10,326ª	1,707	3,724

<sup>&</sup>lt;sup>a</sup> Data of 906 Dutch twins and family members of twins are currently being processed and therefore not included in this table.

lescent and adult twins and their family members are used. They were initially recruited through city councils in 1990-91 and in 1992-93. After 1993, an effort was made to recruit older twins through a variety of approaches. Siblings and spouses of twins were recruited in the study since 1995 and 2000, respectively. Every two to three years since 1991, all twins and their registered family members were invited to complete a questionnaire (i.e. 1991, 1993, 1995, 1997, 2000, 2002 and 2004). Parents did not participate in 1997 and 2000. All surveys included questions on physical and mental health (e.g. general health, medicine use, depression, ADHD), personality (e.g. neuroticism, sensation seeking, extraversion, anger, anxiety) and lifestyle (e.g. alcohol use, smoking, exercise). In this thesis, I analyzed survey data from the 2004 data collection which included the PAI-BOR for the first time.

#### The East Flanders Prospective Twin Survey

In 2004, for the first time, Dutch speaking twins and their parents registered with the East Flanders Prospective Twin Survey (EFPTS; Derom et al., 2006) in Belgium were asked to take part in the study. The EFPTS is a population-based prospective register of multiple births in the Belgian province of East Flanders and was started in 1964. The twins (and higher order multiple births) are ascertained at birth and basic perinatal data recorded, chorion type and zygosity are established. In November 2004, young adult twins and their parents were contacted by mail via the NTR to complete the Dutch sur-



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#### Table 2.2. Overview of the collected data (NTR/EFPTS)

- Personal and family details (demographic information)
- The Personality Assessment Inventory-Borderline Features scale (Morey, 1991)
  - -Affective instability
  - -Identity problems
  - -Negative relationships
  - -Self-harm
- The NEO-Five Factor Inventory (Costa & McCrae, 1992)
  - -Neuroticism
  - -Extraversion
  - -Openness to experience
  - -Agreeableness
  - -Conscientiousness
- State-Trait Anger Expression Inventory (van der Ploeg et al., 1982)
  - -Trait anger
- Three Item Loneliness Scale (Hughes et al., 2004)
- Conners' Adult ADHD Rating Scales (Conners et al., 1999)
  - -DSM-IV Inattentive Symptoms
  - -DSM-IV Hyperactivity/ Impulsive Symptoms
  - -DSM-IV Total ADHD Symptoms
  - -ADHD Index
- General health
  - -Medicine use
  - -Headaches and migraine
  - -Height
  - -(birth) Weight
  - -For women: age at menarche and menopause
- General life style
  - -Physical exercise
  - -Smoking behavior
  - -Alcohol use
- Fagerström Test for Nicotine Dependence (Fagerström, 1978; Heatherton et al., 1991)
- CAGE (alcohol abuse) (Ewing, 1984)
- Education, employment status and profession
- Life events
  - -Divorce/ break-up
  - -Traffic accident
  - -Violent crime
  - -Sexual crime
  - -Robbery
  - -Job-loss

vey which was enclosed with a letter and a brochure. A reply envelop was included to send the questionnaire to the NTR with freepost.

#### The Australian Twin Registry

The Australian Twin Register (ATR) was founded in 1978 (Jardine et al., 1984). Data of Australian participants analyzed in chapters five and seven of this thesis were drawn form the ATR as well as from a twin group previously recruited by the Queensland Institute of Medical Research (QIMR) through media appeals and by word of mouth, as part of ongoing studies of melanoma risk factors (McGregor et al., 1999; Zhu et al., 1999) and cognition (Wright & Martin, 2004). Twins approached by the ATR were asked to participate in the Personality Features in Adulthood study; this was renamed Health, Lifestyle and Personality study for the QIMR approach. Targeted participants included were born between 1972 and 1987. In chapter nine of this thesis more Australian subjects were included in the analyses. These participants were all drawn form the ATR as part of an ongoing study of cannabis use. All participants of this study were born between 1972 and 1979.

#### Data collection

The NTR and EFPTS data collection of the seventh survey started in November 2004. The survey was sent to twins and their family members registered with the NTR and the EFPTS, together with a letter (see appendix III) and an introductory brochure (see appendix IV) explaining the purpose and procedure of the study. In the letter, family members who were not yet registered with the NTR or EFPTS were encouraged to register. After registration they were invited to complete the survey. Data on spouses of twins were only collected in the Dutch sample. Spouses of twins were invited to complete the survey if they participated before or when they were actively registered with the NTR. When the spouse participated before but the address was unknown, the questionnaire was send to the twin. In March 2005 Dutch and Belgian non-respondents received a letter to remind them that they had not yet completed the survey. Participants who did not have the questionnaire anymore were encouraged to request a new one through telephone or email. In addition, a pfd of the questionnaire was available through the NTR website (www.tweelingenregister.org). Participants could print the survey and return it by mail with freepost. Twins and their family members who registered with the NTR after November 2004 were invited to participate in the study immediately after registration. In November 2005, an effort was made to recruit offspring of twins and siblings for registration with the NTR. Dutch adult twins and siblings who participated in the longitudinal survey study and indicated in the 2000 or 2002 survey that they have offspring of 18 years or older were asked by mail to give out the addresses of their children. A total of 627 twins and 272 siblings were approached of whom 325 individuals



34



gave permission to invite some or all of their children by giving out their addresses. We invited 703 children of twins and siblings to participate in the study by sending them an application form and a survey. A total of 352 (50%) offspring returned the application form of whom 331 (94%) also returned a completed survey. In September 2007, a total of 565 subjects received a shortened version of the questionnaire. The shortened questionnaire contained questions on personal information, medicine use, headaches and migraine, ADHD (i.e. CAARS), loneliness, alcohol use (e.g. CAGE) and smoking behavior (e.g. FTND), borderline personality disorder (i.e. PAI-BOR), physical exercise, the big five personality traits (i.e. NEO-FFI) and life events. A total of 286 individuals (51%) completed the questionnaire.

The ATR data collection started in 2004. A selection of the twins was approached by the ATR to participate in the study. If they agreed to participate, contact details were forwarded to QIMR for approach with details for completing the survey either online or on paper. Other twins were approached directly by QIMR. Twins who had not responded within two weeks of the approach by QIMR were contacted by trained QIMR interviewers, and encouraged to participate. Twins who could not be contacted on the existing contact details were traced through existing QIMR protocols and recontacted. Twins who completed the survey were offered a voucher as reward. Data collection as part of the cannabis study (data used in chapter nine) commenced in December 2006 and is still ongoing. Twins and siblings were requested by mail to complete a questionnaire on paper or over the internet (approximately 75% of respondents completed the questionnaire over the internet). In addition, multiple attempts to contact individuals by phone were made. The Australian cannabis study also involved a telephone interview covering diagnostic criteria for substance use disorders, common psychiatric disorders and related phenotypes.

#### Response

In November 2004, the seventh survey was sent to 28,859 individuals; 13,322 twins and multiples, 3,420 siblings, 10,156 parents and 1,961 spouses of twins from 7,202 families registered with the NTR. In March 2005, all non-respondents except spouses of twins and individuals who informed us that they did not want to participate received a letter to remind them that they had not yet completed the survey. In February 2005 (just before the reminder was send) 3,134 twins (23.5%), 1,051 siblings (30.7%), 1,943 parents (19.1%) and 850 spouses (43.3%) completed the survey. At the end of 2005, a total of 4,017 twins (30.2%), 1,264 siblings (37.0%), 2,391 parents (23.5%) and 945 spouses of twins (48.2%) returned a completed survey. After 2005, the data collection continued and mid-May 2009, the data collection consisted of data from 4,707 twins and 1,479 siblings, 2,809 parents, 992 spouses of twins and 331 offspring of twins and siblings.



Female

Twins Siblings

**Parents** 

	Table 2.3. Cross sectional participation of twins and their family members registered with the Netherlands Twin Register														
		1991 1993 1995 1997 2000 2002 2004													
Male	Twins	1,541	1,880	1,507	1,246	1,521	1,444	1,411							
	Siblings	-	-	732	673	592	576	543							
	Parents	1,438	1,774	1572	1	2	1,266	1,229							
	Spouses	-	-	-	-	443	1,003	625							
	Offspring	-	-	-	-	-	-	113							

		,	,	,			,	,
	Spouses	-	-	-	-	264	519	367
	Offspring	-	-	-	-	-	-	218
Unknown								
sex		2	1	2	2	2	12	8
Total		6,431	7,918	8,151	4,753	6,795	10,299	10,326a,b

1.904

746

1.688

1.984

843

3.088

882

3.075

875

1.529

3.296

936

1.580

<sup>a</sup> Data of 1,707 Belgian twins and their family members are not included in this table.

2.343

1.920

1.843

1.607

An overview of the cross-sectional and longitudinal participation of the twins and their family members registered with the NTR in the seven data waves is shown in Table 2.3 and 2.4, respectively. Most individuals participated more than once. Twins were invited to complete a questionnaire at each data wave (7 times), parents and siblings 5 times, spouses 3 times and a selection of offspring was invited in 2005 (as part of the 2004 data collection) for the first time. At each data wave new participants were invited to participate so not all participants had the opportunity to reach the maximum number of completed questionnaires.

Data of 906 Dutch participants (22% men, 78% women) are currently being processed and therefore not yet included in Tables 2.2, 2.3 and 2.4. This group of individuals mainly consists of newly registered participants and participants recruited as part of a project called 'DZ twinning'. For this project families in which multiple women are mothers of DZ twins were selected. These mothers and their family members were invited for several assessments (blood collection, buccal swabs, telephone interview) among which the completion of the 2004 survey.

In Belgium, a total of 3,979 twins and their parents were approached of whom 932 (23.4%) returned the survey. In the first Australian study a total of 1,118 twins were approached of whom 699 (62.5%) completed the survey. The second Australian study is still ongoing and therefore response rates are currently unavailable.



<sup>&</sup>lt;sup>b</sup> Data of 906 Dutch twins and their family members are currently being processed and therefore not included in this table.

Table 2.4. Longitudinal data collection of the Dutch participants in the 7th survey (upper part) and the total longitudinal data collection (bottom part)

			Male	:				Fema	е		?	Total
	Twins	Siblings	Parents	Spouses	Offspring	Twins	Siblings	Parents	Spouses	Offspring		
2004												
2004 sample 2004 & 0 other					-							
surveys	204	97	178	39	113	563	210	298	29	218	8	1,957
2004 & I other												
survey	212	85	209	466	-	519	132	279	263	-	-	2,165
2004 & 2 other												
surveys	243	126	124	120	-	728	181	171	75	-	-	1,768
2004 & 3 other												
surveys	207	142	384	-	-	388	243	440	-	-	-	1,804
2004 & 4 other	202	0.2	22.4			417	170	20.1				1.407
surveys	203	93	334	-	-	416	170	391	-	-	-	1,607
2004 & 5 other surveys	208					428		1				637
2004 & 6 other	200	-			-	720	-	'	-	-	_	037
surveys	134	_	_	_	_	254	_	_	_	_	_	388
34.70/3						23 .						
Total	1,411	543	1,229	625	113	3,296	936	1,580	367	218	8	10,326
Total NTR												
sample												
I survey	1,183	563	895	581	113	1,650	588	1,089	331	218	14	7,225
2	000	240	720	F/F		1.154	412	70.1	299			F 102
2 surveys	802	340	739	565	-	1,154	412	791	299	-	-	5,102
3 surveys	672	235	477	120	-	1,179	303	539	75	_	- 1	3,601
3 3di ve/3	072	255	177	120	-	1,177	303	337	73			3,001
4 surveys	452	176	452	-	-	655	278	520	-	-	_	2,533
5 surveys	312	93	334	-	-	569	170	391	-	-	-	1,869
6 surveys	241	-	-	-	-	466	-	I	-	-	-	708
7	134					254						388
7 surveys	134					234						368
Total	3,796	1,407	2,897	1,266	113	5,927	1,751	3,331	705	218	15	21,426

Note. 2004 data of 906 Dutch twins and their family members are currently being processed and therefore not included in this table. For some individuals information on sex was missing (indicated with a question mark).

Non-response studies in the Dutch sample

Figure 2.1 gives an overview of the response to the seventh survey from November 2004 to November 2005 in the Netherlands. In November 2004, the seventh survey was sent to 28,859 individuals. In November 2005, 8,617 individuals had completed the survey. A total of 20,242 individuals did not return a questionnaire of whom for 17,671 individuals the reasons for not participating were unknown. A total of 1,554 invited twins and family members informed us about their reasons, or the reasons of their family members for not participating. A total of 1,301 individuals did not want to participate in any research of the NTR anymore, others temporarily did not want to participate (N = 41), were too ill to participate (N = 11), or did not want to participate because their co-twin was ill or deceased (N = 9). A total of 41 individuals gave other reasons for not participating, 151 individuals were deceased and 25 individuals were duplicate registered.

A total of 1,017 surveys were returned undeliverable. The reason for not participating was thus known for 2,571 individuals. For the remaining nonrespondents (N = 17,671)reasons for not participating were unknown. Part of the invited individuals did not actively register with the NTR but were recruited in 1991 by contacting city councils in the Netherlands for the addresses of twins. It is therefore plausible that some of these individuals received the invitation but were never willing to participate. Others, however, might not have received the invitation because they moved to a different address without informing the NTR. To gain a better insight in the group of nonrespondents we contacted two groups of nonrespondents. A group of nonrespondents who never participated in research of the NTR (nonrespons study I in Figure 2.I) and a group of nonrespondents who participated before (nonrespons study II in Figure 2.1) and asked whether they received the questionnaire and what their reason was for not participating. Table 2.5 shows the results of both non-response studies. In total we were able to check the addresses and reasons for not participating of 81 and 42 nonrespondents in non-response study I and II, respectively. A total of 64 individuals gave a reason for not completing the survey. In both studies, the most common reason given was being too busy (N = 29). A total of 24 participants of the 64 individuals who gave a reason for not participating wanted their names removed from the participants list of the NTR; the others were willing to complete the questionnaire anyway or were willing to participate a next time. Addresses proved incorrect for 34 individuals (42.0%) from the group of nonrespondents who never participated (non-response study I) and for 10 individuals (23.8%) from the group of nonrespondents who participated before (non-response study II). In other words, taken the two groups together, a substantial group of all targeted participants (35.8%) probably never received the questionnaire. In addition, as depicted in Figure 2.1, some individuals did not complete the survey because their survey was sent to an incorrect address (N = 1,017), because the targeted participant had deceased (N = 151) or because the participant was registered twice (N = 25) (see Figure 2.1). Figure 3.1 shows

the response rates after adjusting for the estimated number of incorrect addresses and the number of sent questionnaires of which we know they never reached the targeted participant (N = 151 + 25 + 1,017 = 1,193), by subtracting this number from the number of sent questionnaires. After this adjustment, the estimated or true response rates for the two groups are 13.6% and 52.2% respectively. Based on these results we decided that subjects from families of which all members never completed a questionnaire although they were invited several times, will not be invited to complete a questionnaire in the 2009 data collection wave.

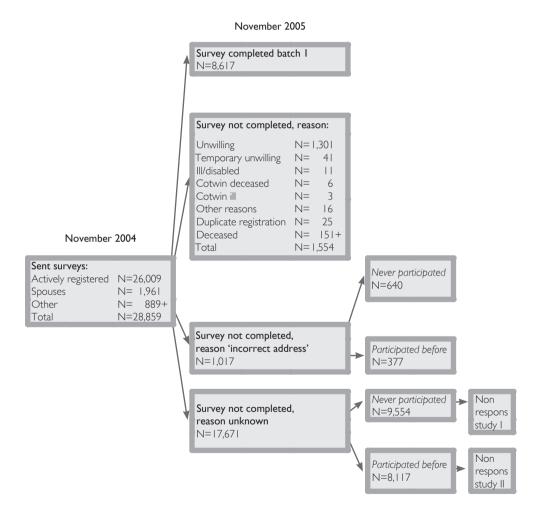


Figure 2.1. Overview of the response to the seventh survey from November 2004 to November 2005 in the Netherlands.



Table 2.5. Results of the non-resp	oonse studies	
	Never participated (study I)	Participated before (study II)
Reason for not participating given		
Did not feel like it, too busy	16	13
Too many questions	1	3
No time because of moving	-	2
Questions too personal	-	I
Questions too alike	-	2
Personal reasons	1	1
Participant sees no use	2	-
Twin or other family members do not want to participate	-	2
Forgotten	3	3
Questionnaire not received	-	L
Visually handicapped	T	-
No specific reason	10	4
Total reasons given	34 (42%)	32 (76%)
Wrong address	34 (42%)	10 (24%)
Person deceased	l (1%)	-
Unable to contact but correct address	12 (15%)	-
Unable to contact	18	20
Total	99*	62*

<sup>\*</sup>A total of I and 38 selected individuals for nonrespons study I and 2 respectively were not contacted because meanwhile they were contacted for the biobank study.





#### Additional data collection

#### Test-retest data

In July 2005, a total of 240 Dutch twins and siblings (I per family) aged 30-40 years who completed the questionnaire in November 2004 were asked to complete a shortened version of the seventh questionnaire for a second time to get more insight in the reliability of the PAI-BOR and other surveys. The retest questionnaire contained questions on personal information, medicine use, headaches and migraine, ADHD, loneliness, alcohol use (CAGE) and smoking behavior (e.g. FTND), BPD, physical exercise, and life events. A total of 200 individuals (83.3%) (Mean age = 34.6, SD = 2.8) completed the questionnaire (Table 2.6). Participants who completed the retest questionnaire received a pedometer.

Table 2.	Table 2.6. Number of sent and completed retest questionnaires									
		Sent		Completed						
	Males	Females	Total	Males	Females	Total				
Twins	79	88	167	66 (83.5%)	72 (81.8%)	138 (82.6%)				
Siblings	36	37	73	28 (77.8%)	34 (91.9%)	62 (84.9%)				
Total	115	125	240	93 (80.9%)	106 (84.8%)	200 (83.3%)				

#### Student sample

In 2004, a group of first year psychology and pedagogy students were invited to complete the PAI-BOR, the NEO Five Factor Inventory (NEO-FFI; Costa & McCrae, 1992) and the NEO Personality Inventory-Revised (NEO-PI-R; Costa & McCrae, 1992) to be able to investigate whether the NEO-FFI and the NEO-PI-R explain an equal amount of variance in PAI-BOR scores. A total of 306 students completed the PAI-BOR and the NEO-FFI. There were 49 males and 257 females with a mean age of 20.9 years (SD = 4.5, range 17 - 59). A total of 283 of these 306 students also completed the NEO-PI-R.

#### Adolescent sample

A total of 467 adolescent twins and siblings who participated in a longitudinal study into the development of intelligence and problem behavior (Hoekstra et al., 2008) were invited to complete the PAI-BOR, the NEO-FFI, three loneliness items and the CAARS. A total of 246 individuals (53%) completed the questionnaire. There were 103 males and 143 females with a mean age of 20.3 years (SD = 2.1, range 13 - 30).



05/08/09 11:14:11









PERSONALITY, HEALTH AND

LIFESTYLE IN A QUESTIONNAIRE

FAMILY STUDY: A COMPARISON

BETWEEN HIGHLY COOPERATIVE

AND LESS COOPERATIVE

FAMILIES

Marijn A. Distel, Lannie Ligthart, Gonneke Willemsen, Dale R. Nyholt, Timothy J. Trull & Dorret I. Boomsma (2007). Personality, health and lifestyle in a questionnaire family study: A comparison between highly cooperative and less cooperative families. *Twin Research and Human Genetics*, 10, 348-353.

## **ABSTRACT**

tensive study, showing at most relatively modest effects. Nonresponse bias with respect to personality has been less thoroughly investigated. The present study uses data from responding individuals as a proxy for the missing data of their nonresponding family members to examine the presence of nonresponse bias for personality traits and disorders as well as health and lifestyle traits. We looked at the Big Five personality traits, borderline personality disorder (BPD) features, attention-deficit/hyperactivity disorder, anger, and several measures of health (body mass index, migraine) and lifestyle (smoking, alcohol use). In general, outcomes tend to be slightly more favorable for individuals from highly cooperative families compared to individuals from less cooperative families. The only significant difference was found for BPD features (p = 0.001). However, the absolute difference in mean scores is very small, less than 1 point for a scale ranging from 0 to 72. In conclusion, survey data on personality, health and lifestyle are relatively unbiased with respect to nonresponse.





## INTRODUCTION

F NONRESPONSE INFLUENCES data collected in survey research, this may seriously limit the validity of the findings. As such, nonresponse has received much attention and several methods have been used to estimate nonresponse bias in population studies. In some studies, respondents and nonrespondents were compared with respect to information that was already available, using data from official population statistics registers or health insurance databases (Bergstrand et al., 1983; Etter & Perneger, 1997; Reijneveld & Stronks, 1999; van den Berg et al., 2006). In other studies, nonrespondents were contacted by telephone or reply card to obtain information on the characteristics of interest. This information was used to estimate nonresponse bias (Hill et al., 1997; Korkeila et al., 2001; Vink et al., 2004). Longitudinal studies also provide information on differences between nonrespondents and respondents. In some cases, nonrespondents in a follow-up study can be characterized using information obtained at the beginning of the study (Eerola et al., 2005; Heath et al., 2001; Van Loon et al., 2003). Vink and colleagues (2004) proposed an additional method to study nonresponse bias in family samples. When a trait has a familial component, a possible nonresponse bias can be estimated by using data from respondents as a proxy for the missing data of their nonresponding family members. Data from highly cooperative families (i.e. many invited family members participate) are compared to data provided by the participating members of less cooperative families (i.e. few invited family members participate). A difference between these two groups indicates a possible nonresponse bias.

These various study designs tend to show that nonrespondents smoke more often and drink more alcohol (Barchielli & Balzi, 2002; Heath et al., 2001; Hill et al., 1997; Kotaniemi et al., 2001; Macera et al., 1990; Van Loon et al., 2003). Also, nonrespondents tend to be less educated, more often divorced or widowed, have lower annual incomes, and a lower socio-economic status (Barchielli & Balzi, 2002; Goyder et al., 2002; Korkeila et al., 2001). In most studies, no differences between respondents and nonrespondents were found for body mass index (BMI), major depression and social anxiety (Eerola et al., 2005; Korkeila et al., 2001). Vink et al. (2004), however, found an effect for anxious depression. In conclusion, nonresponse has been found to influence a variety of traits, but in general the effects were small.

Nonresponse bias with respect to personality has been less extensively investigated than lifestyle variables such as smoking behavior and alcohol use. The few studies that examined the effect of nonresponse on personality focused on the Big Five personality traits. Dollinger & Leong (1993) investigated differences in personality between individuals who volunteered to be followed up in longitudinal research and individuals who did not. They found volunteers to be more agreeable, more open to experiences and a little more extraverted. Rogelberg et al. (2003) showed that respondents were

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more agreeable and more conscientious than nonrespondents. These results suggest that nonresponse may be associated with personality as well as with lifestyle and other demographic factors. It is not unlikely that individuals with high scores on personality traits such as impulsivity, affective instability, relationship problems and identity problems, which are the core features of borderline personality disorder (BPD; American Psychiatric Association, 2000), are less likely to complete a survey. If this is true, nonrespondents will exhibit more BPD features, resulting in an underrepresentation of individuals with BPD features in the study sample.

It is particularly important to quantify the effect of response bias in much needed population based studies of personality and mental health. Most studies on personality and other mental health variables utilize clinical samples, but although clinical samples are very important, for example in characterizing the syndromes of a disorder and evaluating treatment programs, there are also some limitations. Clinical samples are always biased to some degree and not representative of the disorder as it appears in the community. In clinical settings, the most severe cases (the individuals seeking treatment) are more likely to be selected in a study sample. Thus while clinical studies tend to sample the most severe cases, nonresponse bias might cause affected individuals to be underrepresented in population studies.

In the present article we describe data from a Dutch family study on personality, health, and lifestyle and compare data on family members from highly cooperative and less cooperative families (Vink et al., 2004) to investigate to what extent nonresponse bias affects questionnaire data on personality.

## **METHODS**

# **Participants**

This study is part of an ongoing study on personality, health and lifestyle in twin families registered with the Netherlands Twin Register (NTR; Boomsma et al., 2006a). Surveys on personality, health and lifestyle were sent to the twin families every 2 to 3 years. For the present study data from the 2004 to 2005 survey were used. Twins and their siblings, parents and spouses were contacted by mail and invited to complete a survey which was enclosed with the letter. Questionnaires were sent to 27,666 individuals from 7,036 families. The average number of family members in the families that were invited to complete a questionnaire was 3.9 (SD = 1.6).

Figure 3.1 shows an overview of the number of participants and the response rates in the study. The figure is subdivided into two groups; individuals who participated before (left side) and individuals who did not participate before (right side). Of those 16,612





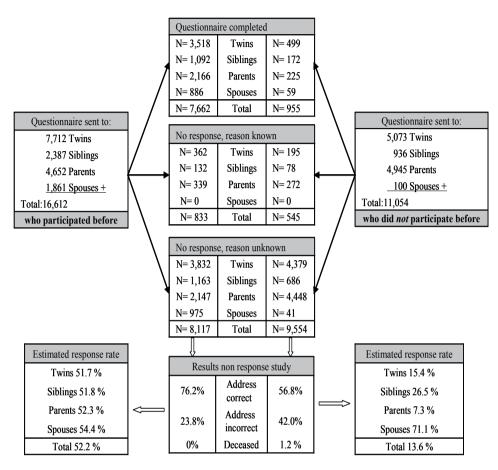


Figure 3.1. Overview of the number of participants in the study. The left side of the figure depicts the number of invited individuals who participated before and the right side depicts the number of invited individuals who did not participate before.

individuals who participated at least once before in a study of the NTR, 7,662 individuals (46.1%) returned the questionnaire. Of those who were sent the questionnaires, II,054 had never before participated in NTR research, because they never returned a questionnaire or because they registered only recently and therefore were invited to complete a questionnaire for the first time. In this group 955 (8.6%) individuals completed the questionnaire. A group of 1,378 individuals informed us after they received the invitation that they were not willing to participate for various reasons (e.g. death of co-twin, illness, lack of time, lack of interest). For the remaining nonrespondents reasons for not participating are unknown. Part of the invited individuals did not actively register but were recruited in 1991 by contacting city councils in the Netherlands for the addresses of twins. It is therefore plausible that some of these individuals received the invitation



but were unwilling to participate. Others, however, might not have received the invitation because they moved to a different address without informing the NTR. We therefore contacted a subgroup of each of the two groups of nonrespondents for which the reason for nonresponse was unknown (those who participated at least once before [N = 8,117] and those who never participated [N = 9,554, see Figure 3.1]) by telephone and asked whether they received the questionnaire and what their reason was for not participating. Addresses were incorrect in 23.8% and 42.0% of the two groups, respectively. In other words, a substantial group of targeted participants never received the questionnaire. After adjusting for these estimated rates of incorrect addresses by subtracting the number of incorrect addresses from the number of sent questionnaires, the estimated 'true' response rates for the two groups were 52.2% and 13.6%, respectively.

#### Measures

#### Personality related traits

Borderline personality disorder features. BPD features were measured using the Personality Assessment Inventory-Borderline Features scale (PAI-BOR; Morey, 1991). The PAI-BOR consists of 24 items that are rated on a 4-point scale (0 to 3; false, slightly true, mainly true, very true). The items were scored according to Morey's test manual (Morey, 1991), which states that at least 80% of the items must have been completed to calculate a sum score and that missing and ambiguous answers should be substituted by a zero score. The English PAI-BOR was translated into Dutch and then translated back into English by a native English speaking translator. This translation was reviewed and approved by the test author and publishing company (Psychological Assessment Resources). Because the data showed a somewhat right-skewed distribution, a square root data transformation was performed.

ADHD. The Conners' Adult ADHD Rating Scales (CAARS; Conners et al., 1999) was used to assess attention-deficit/hyperactivity disorder (ADHD). In this study, the subscales Inattentive and Hyperactive/Impulsive were used.

Big Five personality traits. The personality dimensions Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness were assessed using the NEO Five-Factor Inventory (NEO-FFI) which is the shortened version of the Revised NEO Personality Inventory (NEO-PI-R) developed by Costa and McCrae (1992).

Anger. Anger was measured using the Dutch adaptation of Spielberger's State-Trait Anger Scale (STAS; Spielberger et al., 1983; van der Ploeg et al., 1982). The trait version of the anger scale was administered, which measures how frequently an individual experiences state anger over time and in response to a variety of situations.

Health and lifestyle

Body Mass Index. BMI was calculated from self-reported height and weight by the formula: weight in kg / (height in m<sup>2</sup>).

Smoking. From the questions 'Have you ever smoked?' (no/a few times to try/yes), and 'How often do you smoke at present?' (I have quit smoking since .../once a week or less/several times a week but not daily/daily) lifetime and current smoking status were determined. Lifetime smoking status was coded as 'smoked' (yes) versus 'never smoked' (no/a few times to try). Current smoking status was coded as 'non-smoker' (never smoked/a few times to try/quit smoking) versus 'smoker' (once a week or less/ several times a week but not daily/daily).

Alcohol use. Regular alcohol use was determined by asking participants how often they used alcohol (I don't drink alcohol/once a year or less/a few times a year/about once a month/a few times a month/once a week/several times a week/daily). 'Several times a week' or more was treated as 'regular alcohol use'. Also included in the survey were four items which together constitute the CAGE, a questionnaire designed to screen for possible alcohol problems (Ewing, 1984). Participants positive for two or more CAGEitems were classified as potentially having alcohol problems.

Migraine. Participants who screened positive for the question 'Do you ever experience headache attacks, for instance migraine?' answered a series of follow-up questions concerning the characteristics of their headaches (frequency, duration, pulsating quality, pain intensity, aggravation by physical activity, and accompanying nausea and photo- or phonophobia). Based on this detailed symptom information a migraine diagnosis consistent with the International Headache Society criteria for migraine could be obtained (Headache Classification Committee of the International Headache Society, 2004).

Perceived health. Participants were asked to rate their general health on a 5-point scale (poor, fair, reasonable, good, excellent). This variable was dichotomised to 'good' (good, excellent) and 'not good' (poor, fair, reasonable).

# Data analyses

Families in which at least one person completed the questionnaire were selected and categorized as highly cooperative families and less cooperative families, based on the percentage of invited family members that completed the questionnaire. When less than 80% of the invited family members completed the questionnaire, the family was considered a 'less cooperative family' and when 80% or more of the family members completed the questionnaire the family was considered a 'highly cooperative family'. The dataset contained 4,499 participants from less cooperative families in which the mean percentage of participating individuals per family was 53% and 4,118 participants from highly cooperative families in which the mean percentage of participating individuals per family was 94%. Multiple regression analyses (continuous measures) and logistic regression

(categorical measures) were carried out in STATA 9.2 (StataCorp, College Station, Texas, USA) to determine the association between family cooperativeness and our selection of personality, health, and lifestyle variables, taking age and sex into account. Dummy coding was used for sex (o = male, I = female) and family cooperativeness (o = less cooperative, I = highly cooperative). Age was included in the analyses as a covariate. STATA's 'robust cluster' option was used to account for the non independence of family members. All other statistical analyses were performed in SPSS 13.0 for windows.

Since the traits of interest are not independent of each other prelis 2.45s (Joreskog & Sorbom, 1993) was used to compute a correlation matrix of Pearson, polychoric and polyserial correlations for the 16 variables. We then estimated the equivalent number of measured independent traits using the matSpD interface (http://genepi.qimr.edu.au/general/daleN/matSpD (Li & Ji, 2005; Nyholt, 2004). This analysis showed that the original 16 variables correspond to approximately 13 independent traits. To correct for multiple testing and to determine the significance of the results Bonferroni correction was applied by dividing the significance level by the number of independent traits. A p-value of 0.05/13 = 0.004 was considered significant.

# **RESULTS**

Mean values and prevalences of the various health, lifestyle and personality variables for individuals from highly and less cooperative families are shown in Table 3.1, as well as the results of the regression analyses. Individuals from highly cooperative families generally seem to have slightly more favorable outcomes than individuals from less cooperative families, but with the exception of BPD features, differences are not significant. Although BPD features are significantly more present in less cooperative families, the difference in BPD features between less cooperative and highly cooperative families is very small (0.76 point for males and 0.64 point for females), especially when considering the broad range of possible scores (0 - 72).

## DISCUSSION

In the present study, the response bias for several personality traits was investigated in a Dutch family sample. To examine whether nonresponse was trait-specific we also determined the response bias for several health and lifestyle measures. As expected, the participating members of less cooperative families showed somewhat higher scores on the PAI-BOR scale, suggesting nonresponse will be higher among subjects with more BPD features. However, the difference between people from less cooperative and highly

Table 3.1. Means (SD) and prevalences of personality, health and lifetime variables for males and females from less cooperative families and highly cooperative families

	Ma	ales	Fem	nales	Significance erativer	
	L N = 1,659	H N = 1,675	L $N = 2,840$	H $N = 2,443$	F <sub>(df1, df2)</sub>	Р
PAI-BOR	14.65 (±7.62)	13.89 (±7.29)	16.60 (±8.22)	15.96 (±8.03)	10.82 (1, 3264)	0.001
CAARS-Inattentive	6.07 (±3.51)	6.11 (±3.38)	6.09 (±3.39)	5.82 (±3.32)	2.86 (1, 3231)	0.091
CAARS-Hyperactive/ impulsive	7.17 (±3.24)	7.01 (±3.22)	7.30 (±3.24)	7.02 (±3.11)	7.99 (1, 3231)	0.005
NEO-Neuroticism	27.97 (±6.77)	27.34 (±6.61)	31.01 (±7.37)	30.86 (±7.25)	3.46 (1, 3245)	0.063
NEO-Extraversion	41.12 (±5.89)	41.08 (±6.01)	41.40 (±5.98)	41.18 (±5.89)	0.24 (1, 3245)	0.624
NEO-Openness	36.53 (±5.88)	36.40 (±5.85)	37.14 (±5.62)	36.96 (±5.52)	0.70 (1, 3245)	0.404
NEO-Agreeableness	42.82 (±4.68)	42.89 (±4.72)	45.53 (±4.57)	45.61 (±4.45)	0.53 (1, 3245)	0.466
NEO-Conscientiousness	44.79 (±5.28)	44.97 (±5.24)	44.91 (±5.11)	45.30 (±5.03)	6.11 (1, 3245)	0.014
STAS-Anger	15.00 (±3.83)	14.83 (±3.79)	15.32 (±3.83)	15.13 (±3.74)	3.31 (1, 3266)	0.069
Body Mass Index	25.00 (±3.20)	24.90 (±3.22)	24.08 (±4.01)	23.95 (±3.92)	3.16 (1, 3253)	0.075
					X <sup>2</sup> (I)	р
% lifetime smoking	58.3	54.8	47.0	45.0	6.92	0.009
% current smoking	25.7	22.3	20.0	18.9	3.24	0.072
% regular alcohol use	61.9	64.6	37.2	38.4	0.84	0.360
% potential alcohol problem	14.3	12.9	6.3	7.8	0.21	0.646
% migraine	4.5	3.8	13.6	14.2	0.04	0.846
% good to excellent health	84.8	87.6	84.8	84.8	3.35	0.067

Note. L = individuals from less cooperative families; H = individuals from highly cooperative families. Means and standard deviations are presented for continuous variables and prevalences for categorical variables. Range of scales: PAI-BOR 0-72, CAARS 0-27, NEO 12-60, STAS 10-40. Comparisons are significant if p < 0.004 (Bonferroni correction) and corrected for age and sex.



cooperative families was relatively small, with a mean difference of less than I point (on a scale ranging from 0 to 72). This indicates that although the difference is statistically significant, its practical importance should not be overestimated. For some of the other measures, such as lifetime and current smoking, a similar trend was observed, with subjects from highly cooperative families having slightly more favorable outcomes, consistent with previous reports on smoking behavior. However, differences were very small; after correcting for multiple testing, none of these effects remained significant.

To examine whether our cut-off criterion of 80% family participation influenced our results we also examined 60%, 70% and 90% cut-off criteria. This did not significantly change the results.

Clearly, data from the relatives of nonrespondents are only an approximation of the true values in the group of nonrespondents; the outcomes of nonrespondents may be less favorable than the outcomes of their participating relatives. However, considering the minor differences between participants from highly cooperative and less cooperative families, the true effect is not expected to be substantial. In conclusion, these results confirm previous findings that questionnaire data on personality, health and lifestyle are relatively unbiased with respect to nonresponse.









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ASSESSMENT OF BORDERLINE
PERSONALITY FEATURES IN
POPULATION SAMPLES: IS THE
PAI-BOR SCALE MEASUREMENT
INVARIANT ACROSS SEX AND
AGE?

Marleen H.M. de Moor, Marijn A. Distel, Timothy J. Trull & Dorret I. Boomsma (2009). Assessment of borderline personality features in population samples: Is the PAIBOR scale measurement invariant across sex and age? *Psychological Assessment*, 21, 125-130.

## **ABSTRACT**

ORDERLINE PERSONALITY DISORDER (BPD) is more often diagnosed in women than in men, and symptoms tend to decline with age. Using a large community sample, the authors investigated whether sex and age differences in four main features of BPD, measured with the *Personality Assessment Inventory-Borderline Features* scale (PAI-BOR; Morey, 1991), are a result of measurement bias or if they represent true differences. The PAI-BOR was completed by four Sex × Age groups (N = 6,838). Multigroup confirmatory factor analysis showed that the PAI-BOR is measurement invariant across sex and age. Compared with men, women reported more borderline characteristics for affective instability, identity problems and negative relationships but not for self-harm. Younger men had higher scores for identity problems and self-harm than did older men. Younger women had higher scores for identity problems and affective instability than did older women. Results suggest that the PAI-BOR can be used to study the etiology of BPD features in population-based samples and to screen for BPD features in clinical settings in both men and women of varying ages.





# INTRODUCTION

ORDERLINE PERSONALITY DISORDER (BPD) is a severe personality disorder with features such as emotional lability, impulsivity, interpersonal difficulties, identity disturbance, and cognitive impairment (American Psychiatric Association, 2000). Individuals with BPD are well-represented in treatment settings, accounting for 10% of all outpatients and 15-20% of all inpatients (Skodol et al., 2002). In the general population, approximately 1% of adults meet the diagnostic criteria for BPD (Lenzenweger et al., 2007; Torgersen et al., 2001).

A meta-analysis of 75 studies by Widiger and Trull (1993) showed that 75% of those diagnosed with BPD in clinical samples are women. However, this rate could represent sex bias in diagnosis instead of a true sex difference in prevalence rate (Skodol & Bender, 2003). Estimates of sex prevalence rates for BPD in nonclinical studies using structured interviews are inconsistent. Some report higher prevalence rates in women (e.g. Maier et al., 1992) and others report higher rates in men (e.g. Coid et al., 2006). The only two large representative population-based studies (Torgersen et al., 2001; Lenzenweger et al., 2007) did not find sex differences in the prevalence of BPD.

BPD is typically diagnosed for the first time in young adulthood, and many studies report that the prevalence rate decreases with age (Lenzenweger et al., 2007). Two longitudinal studies report on the course of BPD symptoms in treatment-seeking adults. The McLean Study of Adult Development (Zanarini et al., 2007) described a model of borderline psychopathology in which some symptoms are temperamental and others are more acute and resolve rapidly. The Colloborative Longitudinal Personality Disorder Study (Skodol et al., 2005) presented a similar model that divided symptoms into symptomatic behavior which is episodic and reactive in nature, and traits, which are more fundamental and enduring. A third longitudinal study, the Children In Community study (Skodol et al., 2007), assessed personality disorders in a population-based sample of 658 individuals and reported a decline in symptom levels from adolescence to adulthood. The longitudinal course of BPD is of clinical importance because those with a personality disorder present since adolescence are more likely to experience greater impairment in adulthood (Skodol et al., 2007).

The issue concerning sex and age differences in the severity of BPD features is important for clinical researchers studying the nature and causes of BPD and for clinicians treating BPD patients. Large representative general population studies are needed to determine whether the sex and age differences commonly found in BPD features represent true biological or sociocultural differences between men and women or at different ages or whether they reflect measurement bias. Self-report questionnaires are a practical alternative to psychiatric interviews in large population samples, given that features assessed in the questionnaires have predictive value for the disorder under study (Stein





et al., 2007; Jacobo et al., 2007; Hopwood et al., 2008). A commonly used self-report measure of BPD features is the Personality Assessment Inventory-Borderline features scale (PAI-BOR; Morey, 1991). On the basis of a review of the historical conceptualizations of BPD and on empirical studies, potential PAI-BOR items were generated to reflect core factors of the construct, which are affective instability, identity problems, negative relationships, and self-harm/impulsivity. Prior studies have shown the PAI-BOR to be reliable and valid, and support the usefulness of the PAI-BOR in assessing BPD features in the general population as well as BPD features in clinical settings (Kurtz et al., 1993; Trull, 1995).

To investigate sex and age differences, one must first establish that the measurement instrument is invariant with respect to sex and age. Measurement invariance (MI) implies that the distribution of observed variables given the underlying factors is the same across groups (Meredith, 1993). This means that given a certain level of BPD features, all individuals have the same probability of a certain response on a certain item, irrespective of, for example, their age or sex.

We examined whether the PAI-BOR is measurement invariant with respect to sex and age and tested whether the PAI-BOR scale measures the same underlying constructs in young and older adult men and women. Secondly, we tested whether there are differences across sex and age in BPD features in the adult population.

# **MFTHODS**

#### Sample

Data on BPD features came from a large study in adults registered with the Netherlands Twin Registry (Boomsma et al., 2006a). In 2004-2005, data on the PAI-BOR were collected in 8,527 participants from 3,267 families. For more details on the sample see Distel et al. (2007, 2008a). We created four groups: young adult men, young adult women (18-35 years), older adult men, and older adult women (36-90 years). Cutoffs for age were based on studies of the longitudinal course of BPD and normal personality, which showed that BPD symptoms and general personality traits stabilize between the age of 30 and 40 (Stone, 1990; McCrae & Costa, Jr., 1990).

The four Sex × Age groups had unequal sample sizes, with more women than men. To create groups of roughly similar size, we randomly selected 1 individual per family in the two groups of women. This made the observations in these groups now independent, but dependency was still present in the two groups of men. The resulting sample consisted of 6,838 individuals. There were 1,409 men aged 18-35 years, 1,878 men aged 36-90 years, 1,711 women aged 18-35 years, and 1,840 women aged 36-90 years.

## Measures

The Pai-Bor (Morey, 1991) consists of four subscales (each with six items), which reflect four characteristics of BPD: Affective Instability (AI), Identity Problems (IP), Negative Relationships (NR), and Self-Harm (SH). There are four response categories (0 = false, I = slightly true, 2 = mainly true and 3 = very true). Because the most extreme category, *very true*, was not endorsed frequently in this general population sample, we combined this category with the category *mainly true*, thus analyzing three instead of four categories. An overview of the items, the dimensions on which they load, and their endorsement frequencies are given in Table 4.1. According to the manual of the PAI-BOR (Morey, 1991), a total PAI-BOR raw score of 38 or more indicates the presence of significant BPD features, whereas a score of 60 or more indicates typical borderline personality functioning. The sample prevalence of significant BPD features was 1.4% (N = 98), while a BPD diagnosis was suggested for 0.03% of the sample (N = 2).

Table 4.1. Endorsement frequencies of the 24 items of the Personality Assessment Inventory-Borderline Features scale and their dimensions

				M	en			Women					
		18	18-35 years 36-90 years 18-35 years				ars	36	-90 yea	ars			
Factor	Item description	0	- 1	2/3	0	- 1	2/3	0	- 1	2/3	0	I	2/3
Al	1. Mood shifts	0.44	0.44	0.11	0.48	0.44	0.08	0.31	0.51	0.18	0.44	0.45	0.11
Al	4. Moods intense	0.62	0.29	0.09	0.65	0.28	0.07	0.47	0.36	0.18	0.61	0.30	0.09
Al	7. Mood steady <sup>a</sup>	0.21	0.39	0.40	0.22	0.37	0.40	0.11	0.34	0.55	0.18	0.32	0.50
Al	10. Little control over anger	0.87	0.11	0.02	0.83	0.15	0.02	0.87	0.11	0.02	0.85	0.14	0.01
Al	14. Happy per- son <sup>a</sup>	0.37	0.49	0.14	0.31	0.47	0.22	0.33	0.44	0.23	0.28	0.45	0.27
Al	18. Can't express all of anger	0.65	0.22	0.13	0.65	0.24	0.11	0.62	0.24	0.14	0.66	0.22	0.12
IP	2. Attitude about self changes	0.68	0.27	0.06	0.72	0.24	0.03	0.52	0.34	0.14	0.61	0.33	0.06
IP	5. Feel empty	0.71	0.23	0.06	0.74	0.22	0.04	0.56	0.32	0.12	0.59	0.33	0.08
IP	8. Worry about people leaving	0.72	0.23	0.05	0.78	0.17	0.05	0.57	0.33	0.10	0.72	0.21	0.07





Table 4.1. Endorsement frequencies of the 24 items of the Personality	,
Assessment Inventory-Borderline Features scale and their dimensions	5

IP	11. Wonder about life	0.62	0.29	0.10	0.78	0.18	0.04	0.63	0.27	0.10	0.74	0.21	0.05
IP	15. Can't handle separation	0.24	0.41	0.35	0.20	0.39	0.42	0.14	0.38	0.49	0.18	0.40	0.42
IP	19. Don't get bored <sup>a</sup>	0.40	0.40	0.21	0.51	0.32	0.18	0.38	0.40	0.22	0.60	0.24	0.16
NR	3. Relationships stormy	0.77	0.17	0.06	0.81	0.14	0.05	0.78	0.16	0.07	0.85	0.11	0.05
NR	6. Let people know they've hurt me	0.60	0.30	0.10	0.55	0.35	0.09	0.56	0.34	0.11	0.49	0.39	0.12
NR	9. People let me down	0.56	0.32	0.11	0.52	0.37	0.12	0.49	0.37	0.15	0.41	0.41	0.18
NR	12. Rarely lonely <sup>a</sup>	0.43	0.31	0.27	0.41	0.26	0.33	0.29	0.33	0.39	0.34	0.26	0.40
NR	16. Mistakes in picking friends	0.52	0.34	0.14	0.47	0.39	0.14	0.43	0.37	0.20	0.43	0.40	0.17
NR	20. Stay friends with people <sup>a</sup>	0.17	0.60	0.23	0.29	0.53	0.18	0.16	0.59	0.25	0.33	0.53	0.15
SH	13. Do things impulsively	0.74	0.21	0.05	0.80	0.18	0.03	0.75	0.21	0.04	0.74	0.22	0.04
SH	17. When upset hurt self	0.96	0.03	0.01	0.96	0.02	0.01	0.95	0.04	0.01	0.97	0.02	0.01
SH	21. Too impulsive	0.60	0.30	0.10	0.57	0.33	0.10	0.59	0.31	0.10	0.48	0.36	0.16
SH	22. Spend money easily	0.47	0.36	0.17	0.63	0.28	0.09	0.49	0.34	0.17	0.60	0.32	0.08
SH	23. Reckless person	0.80	0.17	0.03	0.91	0.08	0.01	0.88	0.11	0.01	0.94	0.05	0.01
SH	24. Careful about money <sup>a</sup>	0.25	0.48	0.27	0.33	0.46	0.21	0.25	0.47	0.29	0.33	0.43	0.25

Note. Categories 2 and 3 have been combined because of low endorsements of these categories. Al = Affective Instability; IP = Identity Problems; NR = Negative Relationships; SH = Self-Harm.  $^aThis$  item has been recoded, such that a score of 3 corresponds to answering false on the unrecoded items.







## Statistical analysis

Multigroup confirmatory factor analysis for ordinal data was used to test for MI with respect to sex and age (Millsap & Yun-Tein, 2004; Flora & Curran, 2004). Different multigroup confirmatory factor analysis models were fitted to the data in Mplus Version 4.12 (Muthén & Muthén, 2005), using the weighted least squares mean variance adjusted estimator and correcting for any dependency in the data due to the family clustering (Rebollo et al., 2006a; Muthén & Satorra, 1995). In short, the four-factor model (Morey, 1991) was fitted to the items in each Sex × Age group, assuming an underlying latent continuous response for each item in each group. First, all parameters of the model (thresholds that specify the relationships between observed discrete scores and latent continuous responses, the residual variances of the latent responses and the factor loadings that specify the relationships between latent responses and latent factors) were allowed to vary in each group. Next, different sets of constraints on the parameters were applied across groups to test for different types of MI. The first, most general, level of MI is configural invariance. Configural invariance implies that the same factor structure holds for the different groups; in this study, it is the four-factor solution for the PAI-BOR scale with the same items loading on the same factors (i.e., the pattern of the loadings is invariant but the estimates of the loadings may differ). This is tested by fitting the hypothesized factor model to the data in all groups and by evaluating the model fit. If the factor model fits adequately well, one can move forward to test the second level of MI, which is metric invariance. Metric invariance implies that the latent factor scores predict the item responses equally well across groups. This is tested by constraining factor loadings to be equal across groups. This model is compared to the configural invariance model and, if the fit is not appreciably worse, it is taken as evidence of metric invariance. The third step in evaluating MI is to also impose constraints on the thresholds, such that MI of the factor means can be tested (strong factorial invariance). If both thresholds and factor loadings are the same across groups, this means that any difference in latent response means across groups is the result of differences in factor means. A last step is to test, besides the factor loadings and thresholds, whether the residual variances of the latent responses are also equal across groups (strict factorial invariance). If strict factorial invariance holds, differences in factor scores across groups are due to a true difference on the same latent construct and not to differences in measurement of this construct. It is then allowed to interpret differences in both means and covariances of the latent factors across groups as true differences in the latent constructs.

Model fit was evaluated by the adjusted chi-square test (Muthén et al., 1997) and by the root mean error of approximation (RMSEA) (Steiger, 1990). Comparison of models when testing the different stages of MI was based on the adjusted chi-square difference test and the change in value of RMSEA. We included the RMSEA to evaluate model fit, because it is much more robust to sample size and model complexity than the chi-square



Table 4.2. Model fitting results for measurement invariance tested across	S
sex and age	

	Χ²	df	#par	$\Delta \chi^2$	Δdf	RMSEA
Sex						
Configural invariance	7,985.934	558	312	-	-	0.088
Metric invariance	5,817.759	474	264	79.856	39	0.081
Strong factorial invariance	6,951.693	544	224	237.995	54	0.083
Strict factorial invariance	6,196.432	515	176	336.178	75	0.080
Age						
Configural invariance	7,985.934	558	312	-	-	0.088
Metric invariance	5,922.654	476	264	122.447	40	0.082
Strong factorial invariance	7,523.730	548	224	580.532	55	0.086
Strict factorial invariance	6,665.108	517	176	622.160	76	0.083

Note.  $\chi^2$  = adjusted chi-square test statistic; df = adjusted degrees of freedom; #par = number of free parameters in the model;  $\Delta\chi^2$  = adjusted chi-square difference between the fitted model and the comparison model (configural invariance model);  $\Delta df$  = adjusted difference in degrees of freedom between fitted and comparison model (note that this is not simply the difference in number of free parameters); RMSEA = root mean square error of approximation.

test (Schermelleh-Engel & Moosbrugger, 2003) and because it performs well in factor models with categorical data (Yu, 2002). According to the general guidelines available for independent continuous and categorical data (Yu, 2002; Schermelleh-Engel & Moosbrugger, 2003), an RMSEA smaller than 0.05 is considered as good fit, values between 0.05 and 0.08 indicate adequate fit, values between 0.08 and 0.10 mediocre fit, whereas values larger than 0.10 are not acceptable. In addition to the chi-square test and RMSEA, we always closely inspected the parameter estimates to make trustworthy decisions when testing for MI.

#### RESULTS AND DISCUSSION

Results from fitting the four-factor model for the different stages of MI tested across sex and age are given in Table 4.2. Estimates of unconstrained factor loadings and residual variances are given in Table 4.3. The fit of the four-factor model with parameters unconstrained across groups was mediocre, as indicated by the RMSEA value of 0.088. The fit of the model when different types of constraints are made was not worse, based on the RMSEA. We tried factor solutions other than the four-factor model as proposed in the PAI-BOR manual (data not shown), but these models did not have better fit. Thus, we





Table 4.3. Estimates of factor loadings and residual variances unconstrained across groups from the four-group confirmatory four-factor model

		S	tandardi: load		or	Standardized residual variances				
		M	en	Wo	men	M	en	Wor	men	
		18-35	36-90	18-35	36-90	18-35	36-90	18-35	36-90	
Factor	Item description	years	years	years	years	years	years	years	years	
Al	I. Mood shifts	0.70	0.71	0.73	0.73	0.52	0.48	0.48	0.47	
Al	4. Moods intense	0.75	0.74	0.81	0.79	0.44	0.41	0.37	0.36	
Al	7. Mood steady <sup>a</sup>	0.63	0.59	0.67	0.59	0.60	0.66	0.55	0.66	
Al	10. Little control over anger	0.60	0.65	0.67	0.66	0.63	0.65	0.50	0.57	
Al	14. Happy person <sup>a</sup>	0.58	0.55	0.68	0.55	0.64	0.69	0.58	0.70	
Al	18. Can't express all of anger	0.57	0.53	0.56	0.55	0.71	0.72	0.67	0.69	
IP	2. Attitude about self changes	0.71	0.73	0.72	0.70	0.47	0.45	0.51	0.51	
IP	5. Feel empty	0.83	0.81	0.82	0.78	0.31	0.36	0.32	0.43	
IP	8. Worry about people leaving	0.60	0.55	0.63	0.59	0.63	0.67	0.62	0.65	
IP	II. Wonder about life	0.62	0.70	0.71	0.70	0.66	0.51	0.49	0.48	
IP	15. Can't handle separation	0.16	0.14	0.05	0.21	0.98	0.98	0.98	0.98	
IP	19. Don't get bored <sup>a</sup>	0.38	0.40	0.38	0.35	0.87	0.86	0.85	0.86	
NR	3. Relationships stormy	0.55	0.51	0.54	0.55	0.76	0.74	0.71	0.65	
NR	6. Let people know they've hurt me	0.60	0.55	0.53	0.48	0.69	0.71	0.70	0.75	
NR	9. People let me down	0.58	0.56	0.61	0.55	0.67	0.68	0.63	0.70	
NR	12. Rarely lonely <sup>a</sup>	0.61	0.53	0.72	0.60	0.62	0.71	0.48	0.64	
NR	16. Mistakes in picking friends	0.52	0.54	0.44	0.51	0.75	0.72	0.79	0.74	
NR	20. Stay friends with people <sup>a</sup>	0.19	0.21	0.23	0.27	0.95	0.96	0.95	0.95	
SH	13. Do things impulsively	0.77	0.80	0.73	0.74	0.43	0.39	0.42	0.49	
SH	17. When upset hurt self	0.70	0.75	0.84	0.81	0.35	0.47	0.35	0.38	
SH	21. Too impulsive	0.73	0.73	0.72	0.68	0.42	0.51	0.42	0.62	
SH	22. Spend money easily	0.60	0.49	0.70	0.46	0.68	0.69	0.61	0.66	
SH	23. Reckless person	0.72	0.59	0.77	0.68	0.60	0.57	0.42	0.42	
SH	24. Careful about money <sup>a</sup>	0.41	0.35	0.48	0.33	0.83	0.85	0.81	0.86	

Note. Al = Affective Instability; IP = Identity Problems; NR = Negative Relationships; SH = Self-Harm.

<sup>a</sup>These items have been recoded, such that a score of 3 corresponds to answering *false* on the unrecoded items.

accepted the four-factor model and concluded that configural invariance holds across sex and age. This conclusion is strengthened by the observation that for most items, there are no striking differences in either factor loadings or residual variances, although for some items the differences are more substantial. The largest differences are found for some of the items from the sh factor. For example, Item 17 ('when upset hurt self') loads somewhat higher on the sh factor in women than in men. Items 22, 23 and 24, about spending money and reckless behavior, load higher on the sh factor in younger than in older adults in both men and women, but the sh factor does not seem to explain more

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variance of the items in younger adults. The differences in factor loadings and residual variances across groups are significant on the basis of the chi-square difference test but are accompanied by minor changes in the RMSEA. When tested across sex or age, the fit of the strict factorial invariance model tested was mediocre (RMSEA = 0.08). Thus, the strict factorial invariance model describes the data reasonably well and not worse than the full configural invariance model. This leads to the conclusion that the PAI-BOR is measurement invariant with respect to sex and age. There are several studies of sex bias, but not many have addressed the issue of measurement invariance. The results from a nonclinical study by Jane & colleagues (2007) are in line with our results, finding that Diagnostic and Statistical Manual of Mental Disorders (4<sup>th</sup> ed.; text rev.; American Psychiatric Association, 2000) BPD criteria as assessed via a semi structured interview were not influenced by sex bias. Boggs et al. (2005) found some evidence for sex bias in Diagnostic and Statistical Manual of Mental Disorders (4<sup>th</sup> ed.; DSM-IV; American Psychiatric Association, 1994) criteria for BPD, but results were not consistent. To our knowledge, the present article is the first to address age invariance in BPD features.

A consequence of measurement invariance is that sex and age differences in means and correlations of the factors can be interpreted as true differences in dimensions of BPD features. Table 4.4 gives the estimates of the factor means and correlations and their confidence intervals. The differences in mean factor scores between any two groups in Table 4.4 can be interpreted as effect sizes because in each group the variance is fixed at I. Women scored, on average, higher on the AI, IP, and NR dimensions of the PAI-BOR in both age groups. The effect sizes are 0.40, 0.40 and 0.33 for AI, IP, and NR in the young age group and 0.14, 0.30, and 0.22 for AI, IP and NR in the older age group, respectively. In the older age group, women scored, on average, higher on the SH dimension also, but their average score is still lower than in young men and women. Other studies using the PAI-BOR found men to have significantly higher scores than women for the total PAI-BOR scale (Trull, 1995), or did not find any sex differences (Morey, 1991). A number of large population-based studies reveal no significant sex differences in the prevalence of BPD (e.g. Lenzenweger et al., 2007; Torgersen et al., 2001). In contrast, for individual DSM-IV (American Psychiatric Association, 1994) criteria, Johnson et al. (2003) found more women to meet the identity disturbance criterion and McCormick et al. (2007) found more women to meet the stress-related paranoia criterion. Our study also suggests that sex differences in BPD features might be dimension specific.

There are also age differences in factor means. In men, average scores on IP and SH are higher in the younger age group, whereas scores on AI and NR are equal between the two age groups. In women, the scores on IP and AI were higher in the younger age group than in the older age group. There are no age differences for NR and SH in women. It is important to note that we compared means of younger and older men and women but we did not study all the possible interactions between sex and age. Largely consistent

Table 4.4. Es	timates of factor me	eans and correlations from the four-group
confirmatory	four-factor model (	(strict factorial invariance model)

		Men			Women				
Factor		18-35 years		36-90 years		18-35 years		36-90 years	
		Esti-		Esti-		Esti-		Esti-	
		mate	95% CI	mate	95% CI	mate	95% CI	mate	95% CI
Means									
Al		0		0.00	-0.08 ; 0.09	0.40	0.32 ; 0.49	0.14	0.06 ; 0.22
IP		0		-0.34	-0.43 ; -0.24	0.40	0.31; 0.49	-0.04	-0.13 ; 0.05
NR		0		0.06	-0.04 ; 0.15	0.33	0.23 ; 0.42	0.28	0.19 ; 0.37
SH		0		-0.31	-0.40 ; -0.22	-0.07	-0.17 ; 0.02	-0.15	-0.24 ; -0.06
Correlations									
Al with	IP	0.82	0.75 ; 0.88	0.81	0.76 ; 0.86	0.92	0.87 ; 0.96	0.83	0.78 ; 0.88
	NR	0.84	0.77 ; 0.90	0.73	0.68 ; 0.79	0.84	0.78 ; 0.91	0.74	0.68 ; 0.79
	SH	0.51	0.44 ; 0.58	0.60	0.54 ; 0.65	0.48	0.41 ; 0.54	0.44	0.38 ; 0.50
IP with	NR	0.86	0.79 ; 0.93	0.75	0.69 ; 0.82	0.91	0.85 ; 0.97	0.80	0.74 ; 0.86
	SH	0.42	0.35 ; 0.50	0.54	0.48 ; 0.61	0.44	0.38 ; 0.51	0.41	0.34 ; 0.47
NR with	SH	0.54	0.46 ; 0.62	0.60	0.53 ; 0.66	0.56	0.49 ; 0.63	0.42	0.36 ; 0.49

Note. The means in the first group were fixed to zero and therefore there are no confidence intervals. CI = confidence interval; AI = Affective Instability; IP = Identity Problems; NR = Negative Relationships; SH = Self-Harm.

with our results, Morey (1991) reported a decrease in mean scores for all four PAI-BOR subscales as a function of age. Other studies reported a lower prevalence of BPD in older subjects (Torgersen et al., 2001; Lenzenweger et al., 2007), and a remission of some symptoms with increasing age, whereas other symptoms are more persistent (Skodol et al., 2005; Zanarini et al., 2007; Skodol et al., 2007).

In young and old men and women, AI, IP, and NR are strongly interrelated, whereas SH is only moderately correlated with the other three dimensions. In women, the dimensions are more strongly correlated in the youngest age group, and the differences between the age groups are significant for the interrelations between AI, IP and NR and for NR with SH. In men, the SH dimension is more strongly correlated with AI and IP in the oldest age group, whereas the AI, IP, and NR dimensions are more strongly correlated in the youngest age group, and these differences are significant for all interrelations except between AI and IP. The moderate correlation between SH and the other dimensions was also found in the clinical sample reported by Morey (1991).

Our main finding that the PAI-BOR is measurement invariant across sex and age has several implications. Sex and age differences in PAI-BOR scores represent true differences

in the dimensions. This is important knowledge for future use of the PAI-BOR in non-clinical and clinical settings. In clinical settings, self-report measures are increasingly recommended as screening instruments for initial evaluations of BPD features instead of time-consuming structured interviews (Hopwood et al., 2008). Our results suggest that the PAI-BOR is a suitable instrument to be used by clinicians in patients of different sexes and varying ages, for example, to determine if a clinical interview is required to further assess BPD features and DSM-IV diagnostic criteria. The PAI-BOR is also useful in assessing BPD features in epidemiological samples, such as those required for studies into the genetic basis of BPD.

It will be important for researchers conducting future studies to attempt to identify the sources of the mean differences in PAI-BOR scores in both age and sex groups. These investigations may be more informative regarding both the etiological influences on the manifestation of BPD features as well as the possibility of different treatment targets depending on a BPD patient's sex and age.









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# HERITABILITY OF BORDERLINE

PERSONALITY DISORDER

FEATURES IS SIMILAR ACROSS

THREE COUNTRIES

Marijn A. Distel, Timothy J. Trull, Catherine A. Derom, Evert W. Thiery, Marisa A. Grimmer, Nicholas G. Martin, Gonneke Willemsen & Dorret I. Boomsma (2008). Heritability of borderline personality disorder features is similar across three countries. *Psychological Medicine*, 38, 1219-1229.

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## **ABSTRACT**

Background Most of our knowledge about borderline personality disorder features has been obtained through the study of clinical samples. Although these studies are important in their own right, they are limited in their ability to address certain important epidemiological and aetiological questions such as the degree to which there is a genetic influence on the manifestation of borderline personality disorder features. Though family history studies of borderline personality disorder indicate genetic influences, there have been very few twin studies and the degree of genetic influence on borderline personality disorder remains unclear.

*Methods* Data were drawn from twin samples from the Netherlands (N = 3.918), Belgium (N = 904) and Australia (N = 674). In total, data were available on 5,496 twins between the ages of 18 and 86 years from 3,644 families who participated in the study by completion of a mailed self-report questionnaire on borderline personality disorder features.

Results In all countries, females scored higher than males and there was a general tendency for younger adults to endorse more borderline personality disorder features than older adults. Model-fitting results showed that additive genetic influences explain 42% of the variation in borderline personality disorder features in both men and women and that this heritability estimate is similar across the Netherlands, Belgium and Australia. Unique environmental influences explain the remaining 58% of the variance.

*Conclusion* Genetic factors play a role in individual differences in borderline personality disorder features in Western society.



# INTRODUCTION

ORDERLINE PERSONALITY DISORDER (BPD) is a severe personality disorder whose features include impulsivity, affective instability, relationship problems, and identity problems (American Psychiatric Association, 2000). BPD is associated with interpersonal and occupational impairment, increased risk for suicide and higher rates of treatment in both medical and psychiatric settings (Skodol et al., 2002). In addition, BPD is frequently co-morbid with Axis I disorders, especially substance use disorders in males, eating disorders in females, anxiety disorders and mood disorders (Zanarini et al., 1998; Zimmerman & Mattia, 1999), and this co-morbidity predicts poorer short- and long-term outcome (Skodol et al., 2002).

Most of our knowledge about BPD has been obtained through the study of clinical samples. Clinical samples are important for characterizing the syndrome as it typically is presented for treatment, assessing the longitudinal course of the disorder, and evaluating the disorder's response to forms of treatment. However, clinical samples are limited in their ability to address certain important epidemiological and etiological questions as they are likely to contain more severe cases and may therefore not be representative of the disorder as it appears in the general population. Also, these clinical cases often exhibit more co-morbidity than cases from the community (Skodol et al., 2002), thereby further clouding the etiological picture. In addition to clinical studies, it is therefore informative to identify BPD features in the general population to gain a full understanding of the nature of BPD and the developmental pathways leading to BPD.

One important etiologic issue for which community samples are essential is the degree to which there is a genetic influence on the manifestation of BPD symptoms. Increased rates of BPD have been found in the relatives of individuals with BPD (e.g., Baron et al., 1985a; Johnson et al., 1995; Loranger et al., 1982; Zanarini et al., 2004), and the heritability of traits that are highly associated with BPD (e.g., neuroticism, negative emotionality) is well documented (Nigg & Goldsmith, 1994). However, our knowledge of the genetic influence on BPD symptoms and features is rather limited.

Only two twin studies so far provided data on BPD diagnoses and features. Torgersen (1984) reported a monozygotic (MZ) concordance rate of 0.0% and a dizygotic (DZ) concordance rate of 11.1% for BPD, suggesting that shared environmental factors influence the variance in BPD. However, methodological problems of that study limit any conclusions. More recently, Torgersen et al. (2000) reported on the largest twin study to date (N = 221 twin pairs) that examined BPD. Results suggested a genetic liability for BPD of 69%, though this heritability estimate must be considered approximate due to the small number of twins, the ascertainment method (sampling those who were treated



for mental disorder) and the fact that the zygosity and diagnostic status of co-twins was not hidden from the interviewers.

To extend the work of Torgersen et al. (2000), we initiated a twin study of BPD features in the general population. Specifically, we sought to assess a large number of community-based adult twins from a wide age range and from multiple countries. In this way, we were able to provide precise estimates of the genetic influence on BPD features, to test for quantitative and qualitative sex differences and to determine whether our estimates were consistent across the Netherlands, Belgium and Australia.

### **MFTHODS**

### **Participants**

Data were collected as part of an international project on BPD features in Dutch, Belgian and Australian twin cohorts. Protocols in all three countries were approved by their respective ethics committees.

### The Netherlands

72

In the Netherlands, this study is part of an ongoing study on health and lifestyle in twin families registered with The Netherlands Twin Register (NTR; Boomsma et al., 2002b, 2006a; Stubbe et al., 2005; Vink et al., 2004). Surveys on health and lifestyle were sent to the twin families every 2-3 years. For this study, data from the seventh survey were used which was sent in 2004-2005. A total of 12,785 twins from 6,764 families were approached of whom some individuals participated before (N = 7,712) and some never participated (N = 5,073). In total, 4,017 (31%) twins returned the survey. To examine reasons for not participating, we performed a non-response study by contacting by telephone two subgroups of non-respondents; non-respondents who had participated before and non-respondents who had never participated. Addresses proved incorrect in 23.8% and 42.0% of the two groups, respectively; thus a substantial group of targeted participants never received the questionnaire. After subtracting the estimated number of incorrect addresses from the number of sent questionnaires, the estimated 'true' response rates for the two groups were 52.2% and 13.6%, respectively. The pair-wise response rate of the targeted twins who had and had not participated before was 33.6% and 6.2%, respectively. Details on response rates and demographic characteristics of the sample can be found elsewhere (Distel et al., 2007). For a subsample of the Dutch participants retest data were available. At six months after the first questionnaire was sent, the retest survey was sent to 240 twins, siblings and parents (one per family) of whom 199 (83%) completed the questionnaire a second time.





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### Belgium

Dutch-speaking twins in Belgium were asked to take part in the Dutch health and lifestyle study. Belgian participants were recruited through the East Flanders Prospective Twin Survey (EFPTS), a population-based register of multiple births in the Belgian province of East Flanders which was started in 1964. Multiples are ascertained at birth. Basic perinatal data, chorion type and zygosity have been established (Derom et al., 2006; Loos et al., 1998). Young adult twins were contacted by mail and invited to complete a survey which was enclosed with the letter. A total of 3,979 twins were approached, of whom 932 (23%) twins returned the survey. As most targeted Belgian participants had not participated in a study of the EFPTS before, it is unknown to what extent addresses were correct. The pair wise response rate was 15.7%.

### Australia

Australian subjects were drawn from the Australian Twin Register (ATR) founded in 1978 (Jardine et al., 1984), as well as from a twin group previously recruited by the Queensland Institute of Medical Research (QIMR). Twins approached by the ATR were asked to participate in the Personality Features in Adulthood study; this was renamed Health, Lifestyle and Personality study for the QIMR approach. Targeted participants included Australian twins born between 1972 and 1987 and were invited by mail to participate in the study. A total of 155 complete ATR twin pairs' (310 twin individuals) contact details were forwarded to QIMR for approach with details for completing the survey either online or on paper; 268 of the 310 twins (86.4%) completed the survey. Of the 808 twins approached directly by QIMR, 431 (53.3%) completed the survey, resulting in a total of 699 completed surveys (493 online, 206 paper). The pair wise response rate was 50.6%.

### **Demographics**

The mean age of the Dutch twins was 34.9 years (SD = 11.6, range 19-86 years), of the Belgian twins 28.4 years (SD = 6.9, range 18-67 years) and of the Australian twins 23.1 years (SD = 3.74, range 18-33 years). Triplets (N = 51), twins with unknown zygosity (N = 55) or age (N = 9) and twins without a valid score on the Personality Assessment Inventory-Borderline Features scale (PAI-BOR) (N = 37) were excluded. This resulted in a total sample for analysis of 5,496 participants from 3,644 families.

# Zygosity

In the Netherlands, the zygosity of 3,135 same sex twins was determined either from DNA polymorphism (N = 1,203) or from self report answers to survey questions on physical twin resemblance and confusion of the twins by family members and strangers (N = 1,932). Based on the answers to these items from all available surveys, zygosity was assigned. When there were inconsistencies over time or persons reporting, the majority

73

of the zygosity judgements determined the final outcome. A total of 783 twins were of opposite sex and therefore classified as DZ (see Willemsen et al., 2005).

In Belgium, twin zygosity was determined through sequential analysis based on sex, fetal membranes, umbilical cord blood groups and placental alkaline phosphatase until 1985. After that time, DNA fingerprinting was used. In case of missing or insufficient DNA information, the zygosity of the same-sex DZ twins was based on survey items on physical twin resemblance and confusion of the twins (see Derom & Derom, 2005).

In Australia, the zygosity of 674 twins was determined either from self report answers to standard questions (N = 299), because the twins were of opposite sex (N = 91), or from DNA testing (N = 284) (see Nyholt, 2006).

### Measures

Borderline personality features were measured by the Personality Assessment Inventory-Borderline Features scale (PAI-BOR; Morey, 1991). PAI-BOR items tap features of severe personality pathology that are clinically associated with BPD. Based on a review of the historical conceptualizations of BPD, as well as on empirical studies of borderline patients, potential PAI-BOR items were generated to reflect core factors of the construct (affective instability, identity problems, negative relationships, and self-harm/ impulsivity) (Morey, 1991). Final selection of items was guided by both the conceptual nature of the items as well as the items' psychometric properties. The final version of the PAI-BOR consists of 24 items that are rated on a four-point scale (0 to 3: false; slightly true; mainly true; very true). Preliminary studies have supported the reliability and the validity of total PAI-BOR scores in indexing the degree to which borderline personality features are present (Morey, 1988, 1991; Trull, 1995, 2001b). Kurtz & Morey (2001) for example showed that PAI-BOR scores correlated 0.78 with a structured interview-based assessment of BPD, indicating high convergent validity. Morey (1991) also presented data supporting the validity of the four PAI-BOR subscales, and the PAI-BOR has been used in a number of studies of nonclinical participants as well (Trull, 1995, 2001b). The PAI-BOR was scored according to Morey's test manual (Morey, 1991), which states that at least 80% of the items must be answered to calculate a sum score and that missing and ambiguous answers should be substituted by a zero score. In the Netherlands and Belgium, the Dutch adaptation of the PAI-BOR was used. The English PAI-BOR was translated into Dutch and translated back into English by a native English speaking translator. The Dutch translation of the PAI-BOR was reviewed and approved by the test author and publishing company (Psychological Assessment Resources).

### Statistical Analysis

Twin studies make use of the genetic relatedness of twins and their family members. MZ twins are genetically identical while DZ twins share on average 50% of their segre-



gating genes, like other siblings (Boomsma et al., 2002a). Comparing the resemblance in BPD features within MZ twin pairs with the resemblance in BPD features within DZ twin pairs provides information of how to explain individual differences in BPD features.

Additive genetic effects (A) are suggested if the correlation in MZ twins is larger than the correlation in DZ twins. When the DZ correlation is more than half the MZ correlation, there is evidence for environmental effects shared by twins from the same family (C) but when the DZ correlation is less than half the MZ correlation, there is evidence for non-additive genetic effects (dominance; D). Differences in BPD feature scores within MZ twin pairs are due to unique environmental influences (E), which also include measurement error. The observed variance in BPD features can thus be decomposed in four possible sources of variance; A, D, C and E (Neale & Cardon, 1992) but the observed variances and covariances only provide enough information to model either an ACE model or an ADE model. Based on the pattern of twin correlations (see Results section), A, D and E were modelled in this study.

Statistical analyses were performed using structural equation modelling as implemented in the software package Mx (Neale et al., 2006). The raw data full information maximum likelihood approach in Mx was used to fit different models to the data. Testing of submodels was done by means of likelihood-ratio tests, by subtracting the negative log-likelihood (-2LL) for the more restricted model from the -2LL for the more general model. This yields a statistic that is distributed as  $\chi^2$  with degrees of freedom (df) equal to the difference in the number of parameters in the two models. If the  $\chi^2$ -test yields a p value higher than 0.01, the constrained model is deemed not significantly worse than the previous model and is kept as the most parsimonious model to which the next model will be compared. In addition, Akaike's Information Criterion (AIC; Akaike, 1987) ( $\chi^2$ - 2df) was evaluated because it reflects both the goodness of fit and the parsimony of the model. The lower the AIC value, the better the fit of the model relative to the number of parameters estimated.

We first fitted a saturated model for each country separately in which variances, covariances and means were estimated. Zygosity groups were separated by sex and both age and sex were included in the means model as a covariate. We tested for homogeneity of means and variances for MZ twins and DZ twins and for fixed effects of age and sex on BPD features. Finally we tested for quantitative sex differences by constraining the correlations between men and women within zygosity to be equal, and for qualitative sex differences by constraining the DZ same-sex correlation to equal the DZ opposite-sex twin correlations, which implies that the genetic correlation for both DZ same-sex and DZ opposite-sex twins is 0.5. For each country the most parsimonious model was retained for simultaneous analysis of data from the three countries. We tested for differences in means, standard deviations and correlation structure between the three countries.

75

To obtain the estimated proportion of variance explained by A, D and E, simultaneous genetic analyses of the data from the three countries were carried out. The first model decomposed the variance of BPD features into A, D and E with different parameter estimates for each country. Next, we tested the significance of A and D separately by constraining these parameters to zero in each country. Finally, we constrained the standardized estimates to be equal across the countries to obtain pooled estimates of the variance components explaining individual differences in BPD features.

### **RESULTS**

The six-month test-retest correlation of the Dutch PAI-BOR was 0.78 and the internal consistencies (Cronbach's  $\alpha$ ) of the PAI-BOR items in the Dutch and Belgian samples were both 0.84, suggesting that the Dutch translation of the PAI-BOR is a reliable measure. The internal consistency of the PAI-BOR items in the Australian sample was 0.87.

According to Morey, a total PAI-BOR score of 38 or more indicates the presence of significant BPD features, whereas a score of 60 or more indicates a likely Diagnostic and Statistical Manual of mental disorders (DSM)-IV BPD diagnosis. The sample prevalence of significant borderline features was 2.2% in The Netherlands, 4.0% in Belgium and 5.3% in Australia, while a BPD diagnosis was suggested for 0.03% in The Netherlands, 0.1% in Belgium and 0.7% in Australia. The somewhat higher prevalence in Australia could be due to the younger age range of the Australian sample as the prevalence rates of BPD are known to be highest among young adults (Stone, 1990; Paris et al., 1987; Coid et al., 2006; American Psychiatric Association, 2000; Samuels et al., 2002; Bernstein et al., 1996; Johnson et al., 2000).

Because the data showed a somewhat skewed distribution, a square root data transformation was performed. Table 5.1 displays the twin correlations using the transformed data. The mean borderline scores for males and females (corrected for age), the standard deviations and age regression effects in Table 5.1 were based on the raw, untransformed data.

Results of the tests performed in the saturated models for each country are shown in Table 5.2. In each country mean borderline scores did not differ significantly between MZ and DZ twins. Standard deviations were equal between males and females and DZ and MZ twins. Sex effects on the means were significant in the Dutch sample, where women scored on average 1.94 points higher than men. The same direction of effect was observed in the other two samples, but due to the smaller sample size these effects were not significant. The age regression coefficients on the means were negative in all samples, indicating that BPD features decrease with age. The age effect was significant in The Netherlands and in Belgium but not in Australia. For all three countries, the

Table 5.1. Number of participants from complete and incomplete twin pairs in each zygosity group, the maximum likelihood estimates of twin correlations<sup>a</sup> (95% Cls) and estimates for mean borderline scores for males and females, standard deviations and age regression

	Dutch Twins	Belgian Twins	Australian Twins
Monozygotic males		208	
N, From complete (incomplete) twin pairs	374 (189)	118 (45)	100 (36)
Maximum likelihood estimate (95% CI)	0.46 (0.34 - 0.56)	0.48 (0.23 - 0.64)	0.28 (-0.02 - 0.50)
Dizygotic males			
N, From complete (incomplete) twin pairs	154 (151)	32 (33)	(58) 18
Maximum likelihood estimate (95% CI)	0.27 (0.05 - 0.45)	0.19 (-0.25 - 0.53)	0.12 (-0.36 - 0.50)
Monozygotic females			
N, From complete (incomplete) twin pairs	1120 (396)	242 (73)	170 (23)
Maximum likelihood estimate (95% CI)	0.42 (0.35 - 0.48)	0.43 (0.28 - 0.56)	0.49 (0.32 - 0.62)
Dizygotic females			
N, From complete (incomplete) twin pairs	476 (275)	86 (59)	96 (12)
Maximum likelihood estimate (95% Cl)	0.11 (-0.03 - 0.24)	0.12 (-0.21 - 0.40)	0.32 (-0.03 - 0.55)
Dizygotic opposite sex			
N, From complete (incomplete) twin pairs	410 (373)	142 (74)	126 (35)
Maximum likelihood estimate (95% Cl)	0.24 (0.12 - 0.35)	0.12 (-0.11 - 0.33)	0.16 (-0.07 - 0.36)
All monozygotic twins <sup>b</sup>			
Maximum likelihood estimate (95% CI)	0.43 (0.37 - 0.48)	0.45 (0.32 - 0.55)	0.43 (0.28 - 0.55)
All dizygotic twins <sup>b</sup>			
Maximum likelihood estimate (95% CI)	0.19 (0.11 - 0.27)	0.13 (-0.05 - 0.29)	0.22 (0.05 - 0.32)
Mean score males, untransformed (transformed) <sup>c</sup>	16.04 [3.83]	21.01 [4.44]	21.43 [4.52]
Mean score females, untransformed (transformed) <sup>c</sup>	17.98 [4.09]	22.30 [4.58]	22.94 [4.63]
Standard deviation, untransformed (transformed) <sup>c</sup>	8.41 [1.07]	8.94 [1.07]	9.86 [1.10]
Regression of age per year, untransformed (transformed) <sup>c</sup>	-0.07 [-0.01]	-0.25 [-0.03]	-0.31 [-0.03]

CI = Confidence interval.



<sup>&</sup>lt;sup>a</sup> Correlations were estimated from the square root-transformed data.

<sup>&</sup>lt;sup>b</sup> After constraining these correlations to be equal.

<sup>&</sup>lt;sup>c</sup> Estimates are given for the untransformed data and using square root-transformed data.

Table 5.2. Saturated model-fitt	ing resu	lts for b	orderline	personality
disorder features in the Dutch.	Belgian	and Au	stralian ty	vin data

	Test	-2 LL	df	χ²	Δdf	р	AIC
The Netherlands							
0. Saturated model		11467.75	3899				
I. Mean MZ = mean DZ	I vs 0	11469.78	3900	2.02	1	0.16	0.02
2. SD males = females and							
SD MZ = DZ	2 vs I	11474.49	3909	4.72	9	0.86	-13.28
3. Sex effect on mean	3 vs 2	11519.22	3910	44.73	1	0.00	42.73
4. Age effect on mean	4 vs 2	11509.78	3910	35.29	- 1	0.00	33.29
5. Correlation MZM=MZF, DZM=DZF	5 vs 2	11476.66	3911	2.17	2	0.34	-1.83
6. Correlation DZM=DZF=DOS	6 vs 5	11477.79	3912	1.13	1	0.29	-0.87
Belgium							
0. Saturated model		2627.95	885				
I. Mean MZ = mean DZ	I vs 0	2632.98	886	5.03	1	0.03	3.03
2. SD males = females and SD MZ = DZ	2 vs I	2642.71	895	9.74	9	0.37	-8.26
3. Sex effect on mean	3 vs 2	2645.70	896	2.99	1	0.08	0.99
4. Age effect on mean	4 vs 3	2672.31	897	26.61	- 1	0.00	24.61
5. Correlation MZM=MZF, DZM=DZF	5 vs 3	2645.93	898	0.23	2	0.89	-3.77
6. Correlation DZM=DZF=DOS	6 vs 5	2645.97	899	0.04	- 1	0.84	-1.96
Australia							
0. Saturated model		1993.63	655				
I. Mean MZ = mean DZ	I vs 0	1996.17	656	2.53	1	0.11	0.53
2. SD males = females and SD MZ = DZ	2 vs I	2007.14	665	10.97	9	0.28	-7.03
3. Sex effect on mean	3 vs 2	2008.64	666	1.50	1	0.22	-0.50
4. Age effect on mean	4 vs 3	2015.22	667	6.58	1	0.01	4.58
5. Correlation MZM=MZF, DZM=DZF	5 vs 4	2017.81	669	2.59	2	0.27	-1.41
6. Correlation DZM=DZF=DOS	6 vs 5	2018.26	670	0.45	1	0.50	-1.55

Note. -2LL = -2 log-likelihood; df = degrees of freedom; AIC = Akaike's Information Criterion; SD = standard deviation; MZ = monozygotic; DZ = dizygotic; MZM = monozygotic male; MZF = monozygotic female; DZM = dizygotic male; DZF = dizygotic female; DOS = dizygotic opposite sex.







	Test	-2 LL	df	Χ²	Δdf	р	AIC
0. Saturated model		1,6130.90	5478				
I. Means NL = BE = AU	1 vs 0	1,6207.03	5480	76.12	2	0.00	72.12
2. SD NL = BE = AU	2 vs 0	1,6131.81	5480	0.91	2	0.64	-3.09
3. Twin correlations NL = BE = AU	3 vs 2	1,6132.52	5484	0.71	4	0.95	-7.29

Note.  $-2LL = -2 \log likelihood$ ; df = degrees of freedom; AIC = Akaike's Information Criterion; NL = The Netherlands; BE = Belgium; AU = Australia; SD = standard deviation. <sup>a</sup> Effects of sex and age are modelled for each country separately.

Table 5.4. Genetic model-fitting results including the data from three countries<sup>a</sup>

Countries							
	Test	-2 LL	df	Χ²	Δdf	р	AIC
0. ADE		1,6130.90	5,478				
I. AE for each country	1 vs 0	1,6132.29	5,481	1.382	3	0.71	-4.62
2. E for each country	2 vs 1	1,6356.16	5,484	223.87	3	0.00	217.87
3. Standardized estimates A and E equal							
$NL = BE = AU^b$	3 vs 1	1,6132.30	5,485	0.01	4		-7.99

Note. -2LL = -2 log likelihood; df = degrees of freedom; AlC = Akaike's Information Criterion; A = additive genetic factors; D = non-additive genetic factors (dominance); E = unique environmental factors; NL = The Netherlands; BE = Belgium; AU = Australia. <sup>a</sup> Effects of sex and age are modelled for each country separately. <sup>b</sup> Best-fitting model.

Table 5.5. Maximum likelihood estimates of proportions of variance explained by additive genetic and unique environmental effects

, ,		
	Α	E
The Netherlands (%)	42.3	57.7
Belgium (%)	42.5	57.5
Australia (%)	41.6	58.4
Estimates constrained to be equal (%)	42.2	57.8

Note. A = additive genetic effects; E = unique environmental effects.



twin correlations for MZ males and MZ females were equal as were the twin correlations for DZ males, DZ females and DZ opposite-sex twins. This indicates that there is no sex difference in the heritability of BPD features and that the same genes influence BPD features in males and females.

Table 5.3 shows the results of the simultaneous modelling of the data from the three countries. Mean scores differed between the three countries, but standard deviations could be equated. The lowest mean score (corrected for age) was found in The Netherlands (16.04 for males and 17.98 for females). The correlations for MZ twins were equal for The Netherlands, Belgium and Australia and the same was true for DZ twins.

In the full genetic model without sex differences the variance components A, D and E were estimated for the three countries, explaining 34.3, 8.4 and 57.3% of the variance in BPD features in the Dutch sample, 6.7, 37.8 and 55.5% in the Belgium sample and 33.6, 5.3 and 58.1% in the Australian sample, respectively. Model-fitting results are shown in Table 5.4. Removing D from the full model did not give a significant worsening of the goodness of fit (p = 0.71) of the model but removing A did (p = 0.00), resulting in model 3 as the best-fitting model. In addition, the AIC of model 3 was lower than the AIC of model 0, 1 and 2, indicating that model 3 was the most parsimonious model. Table 5.5 shows the estimates of the proportion of variance explained by A and E for each country and the three countries pooled.

### DISCUSSION

The present study is a large-scale multinational twin study specifically focusing on BPD symptoms and features in community samples. The aim of this study was to examine the genetic liability to BPD features in a large sample drawn from general populations, to test quantitative and qualitative sex differences, and for differences between The Netherlands, Belgium and Australia.

We found that BPD features are genetically influenced (42%) and that this genetic influence is similar across the three countries, does not differ between men and women and acts in an additive manner. Environmental factors unique to an individual accounted for the remaining 58% of the variance in BPD features. Torgersen et al. (2000) reported a higher heritability estimate (69%), though this estimate is probably too high due to methodological limitations.

Although BPD is more often diagnosed in women than in men (American Psychiatric Association, 2000; Gunderson & Zanarini, 1987; Widiger & Weissman, 1991), research findings about the sex difference in the prevalence of BPD are inconclusive. Several clinical studies have tested for sex differences in DSM personality disorders (Carter et al., 1999; Golomb et al., 1995; Grilo et al., 1996, 2002a; Jackson et al., 1991) but only one





(Carter et al., 1999) found a sex difference, the prevalence being unexpectedly higher in men. Results from non-clinical studies are also inconsistent; some reported higher prevalence rates in women (Zimmerman & Coryell, 1989), others in men (Coid et al., 2006; Samuels et al., 2002), while the only large representative population based study (Torgersen et al., 2001) did not find sex differences. In our study, mean scores on the PAI-BOR did not significantly differ between men and women in Belgium and Australia while in The Netherlands women scored higher than men. However, this sex difference was relatively small with a mean difference of 1.97 points (on a scale ranging from 0 to 72).

Generally BPD symptoms appear by early adulthood, and the disorder occurs less frequently with increasing age (Coid et al., 2006; Paris et al., 1987; Stone, 1990; American Psychiatric Association, 2000; Samuels et al., 2002; Bernstein et al., 1996; Johnson et al., 2000). In the present study, all age regression coefficients on the mean borderline features score were negative, indicating that BPD features decrease with increasing age, although the effects were small. In the Australian cohort this age effect was not significant, probably due to the narrow age range in the Australian sample (18 to 33 years) and the smaller sample size. The young age of the Australian cohort may also explain why the number of subjects scoring > 60 is higher in the Australian sample than in the Dutch and Belgian sample.

Recently, the nature of personality disorders and its relation to normal personality has received extensive attention (Widiger & Trull, 2007). The DSM-IV-R defines personality disorders within a categorical system, but the inclusion of a dimensional model of personality, is increasingly recommended (Trull et al., 1990, 2007; Livesley, 2007; Widiger & Trull, 2007). Three proposed dimensional models of personality are Livesley's 18-factor model of personality pathology (Livesley, 1986, 1987), which distinguishes four higher-order factors (emotional dysregulation, dissocial behavior, inhibitedness, compulsivity), Cloninger's psychobiological model (Cloninger et al., 1993), which distinguishes four dimensions of temperament (novelty seeking, harm avoidance, reward dependence and persistence) and three dimensions of character (self-directedness, cooperativeness and self-transcendence), and the Five Factor Model (FFM) of personality (Costa & McCrae, 1992), which distinguishes five personality traits (neuroticism, extraversion, openness to experience, agreeableness and conscientiousness).

Livesley's trait model of personality pathology is operationalized through a self-report questionnaire, the Dimensional Assessment of Personality Pathology - Basic Questionnaire (DAPP-BQ; Livesley, 2006). A series of small-sample twin studies (Livesley et al., 1993, 1998; Jang et al., 1996a, 1996b), provided support for the heritability of most of the 18 lower-order DAPP-BQ traits and of all of the four higher-order factors. According to Livesley, the emotional dysregulation factor and its first-order traits resemble, but are broader than, the diagnostic construct of BPD. For example, the correlation

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between DAPP-BQ emotional dysregulation scores and the number of BPD symptoms has been estimated to be 0.47 in clinical (Pukrop et al., 2001) and 0.62 in non-clinical (Bagge & Trull, 2003) samples. The heritability for emotional dysregulation has been reported at 53% and for the primary traits making up emotional dysregulation at 44% to 53% (Jang et al., 1996b; Livesley et al., 1998).

Concerning traits from the FFM and Cloninger's psychobiological model, heritability estimates between 41% and 55% have been reported for the big five factor neuroticism (Jang et al., 1996a; Johnson et al., 2004), and for Cloninger's novelty seeking scale (Keller et al., 2005a), both higher-order personality traits believed to be associated with BPD (Saulsman & Page, 2004; Morey, 1991; Korner et al., 2007). These findings support the present finding of moderate genetic effects on the manifestation of traits related to BPD features.

In the present study, the PAI-BOR questionnaire was used to measure BPD features. The PAI-BOR does not diagnose BPD per se, but assesses features related to the BPD syndrome which are also common to other personality disorders (Morey, 1991). In addition, a high score on the PAI-BOR is associated with higher prevalence rates for several Axis I disorders (Trull, 1995). The co-morbidity between BPD and other personality disorders as well as Axis I disorders is also well documented by studies using clinical samples (Zanarini et al., 1998; McGlashan et al., 2000; Grilo et al., 2002b; Becker et al., 2000; Zimmerman & Mattia, 1999). Several prior studies have shown the PAI-BOR to be a reliable and valid measure of BPD features, and support the usefulness of the PAI-BOR in assessing BPD features in the general population as well as BPD in clinical setting (Kurtz et al., 1993; Trull, 1995). BellPringle et al. (1997) and Stein et al. (2007), for example, showed that the PAI-BOR differentiates between patients diagnosed with BPD and patients without borderline personality pathology or unscreened controls with 75% to 80% accuracy. In addition, Jacobo et al. (2007) administered the PAI-BOR to patients diagnosed with BPD and found a significant correlation of 0.58 between the total number of BPD SCID-II criteria and the PAI-BOR scale.

Several issues should be kept in mind when interpreting the results of this study. First, when non-response influences the data collected in survey research, this may seriously limit the validity of the findings. While clinical studies tend to sample the most severe cases, non-response bias might cause affected individuals to be under-represented in population studies. Because BPD has a familial component, twin-family studies can study this possible non-response bias by using data from respondents as a proxy for the data of their non-responding family members. Distel et al. (2007) compared borderline personality scores from highly cooperative families (i.e. many of invited family members participate) with data provided by the participating members of less cooperative families (i.e. few invited family members participate). As expected, the participating members of less cooperative families showed somewhat higher scores on the PAI-BOR scale, suggest-



ing non-response will be higher among subjects with more BPD features. However, the difference between participants from less cooperative and highly cooperative families was relatively small, with a mean difference of less than I point on a scale ranging from 0 to 72. This suggests that although there is a difference, questionnaire data on BPD features are relatively unbiased, at least in the Dutch sample, which constituted the largest sample in the present study. Second, we did not find evidence for non-additive genetic effects though the twin correlations suggested a contribution of non-additive genetic influence. The heritability estimate of 42% may include some non-additive effects, but these are unlikely to be large. In the future we will collect and include data of siblings and parents of twins in the model to increase statistical power, needed to address this issue more thoroughly.

In addition, several other lines of future research on BPD are suggested. First, although our findings were consistent across three samples, suggesting no significant cultural role in BPD features, it will be important to try to replicate these findings in other samples and with other measures of BPD. Second, further phenotypic and genetic analyses of PAI-BOR items may be informative as these analyses may point to cohesive, genetically influenced, factors that could be used in future aetiological studies. Finally, our results and future studies using the PAI-BOR may aid in the evaluation of endophenotypes that have been proposed for this disorder, including laboratory tasks, neuroimaging findings, and psychophysiological indicators.







# FAMILIAL RESEMBLANCE OF BORDERLINE PERSONALITY DISORDER FEATURES: GENETIC OR CULTURAL TRANSMISSION?

Marijn A. Distel, Irene Rebollo-Mesa, Gonneke Willemsen, Catherine A. Derom, Timothy J. Trull, Nicholas G. Martin & Dorret I. Boomsma (2009). Familial resemblance of borderline personality disorder features: Genetic or cultural transmission? *PLoS ONE* 4(4):e5334,doi: 10.1371/journal.pone.0005334.

### **ABSTRACT**

ORDERLINE PERSONALITY DISORDER is a severe personality disorder for which genetic research has been limited to family studies and classical twin studies. These studies indicate that genetic effects explain 35 to 45% of the variance in borderline personality disorder and borderline personality features. However, effects of non-additive (dominance) genetic factors, non-random mating and cultural transmission have generally not been explored. In the present study an extended twin-family design was applied to self-report data of twins (N = 5,017) and their siblings (N = 1,266), parents (N = 3,064) and spouses (N = 939)from 4,015 families, to estimate the effects of additive and non-additive genetic and environmental factors, cultural transmission and non-random mating on individual differences in borderline personality features. Results showed that resemblance among biological relatives could completely be attributed to genetic effects. Variation in borderline personality features was explained by additive genetic (21%; 95% CI 17-26%) and dominant genetic (24%; 95% CI 17-31%) factors. Environmental influences (55%; 95% CI 51-60%) explained the remaining variance. Significant resemblance between spouses was observed, which was best explained by phenotypic assortative mating, but it had only a small effect on the genetic variance (1% of the total variance). There was no effect of cultural transmission from parents to offspring.



### INTRODUCTION

ORDERLINE PERSONALITY DISORDER (BPD) is characterized by emotional lability, impulsivity, interpersonal difficulties, identity disturbances, and cognitive impairments (American Psychiatric Association, 2000). BPD is associated with a number of negative outcomes, including suicidal behavior, frequent emergency room admissions, substance abuse, impaired occupational functioning, and poor quality of interpersonal relationships. Individuals with BPD are well-represented in treatment settings, accounting for 10% of all outpatients and 15-20% of all inpatients (Skodol et al., 2002a). Recent estimates from general population of the United States suggest that approximately 1% of adults meet diagnostic criteria for this disorder. BPD is equally prevalent among men and women and more likely to be diagnosed in early adulthood (Lenzenweger et al., 2007).

To date, genetic research on individual differences in BPD has been limited to non-twin family studies and classical twin studies. Family studies have consistently shown increased rates of BPD in family members of BPD patients (Zanarini et al., 2004; White et al., 2003; Bandelow et al., 2005), and twin studies of BPD reported heritability estimates around 40% (Distel et al., 2008a; Kendler et al., 2008; Torgersen et al., 2008). Classical twin studies are important to detect whether there are genetic influences on BPD features. By including siblings, spouses and parents of twins in the study several additional research questions can be answered.

Firstly, adding data from siblings to the classical twin model results in a considerable increase in power to detect non-additive genetic effects (Posthuma & Boomsma, 2000). Non-additive genetic effects can consist of interactions between alleles within a locus (dominance) or across different loci (epistasis). In this study, non-additive genetic effects are modelled as dominance. Using extended twin family designs, dominant genetic effects have been detected for many personality traits (Keller et al., 2005a; Rettew et al., 2008; Eaves et al., 1998, 1999; Rebollo & Boomsma, 2006). Lake et al. (2000), for example, examined individual differences for neuroticism in 45,850 members of extended 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 empirical studies have found strong associations between BPD and neuroticism (Widiger et al., 2002; McCrae et al., 2001). We therefore hypothesize that dominant genetic effects may also influence BPD features.

Secondly, the effect of assortative mating, meaning that spouses are more similar for a trait or disorder than expected under random mating (Merikangas, 1982; Garrison et al., 1968), can be detected and accounted for by including data from parents and spous-



es of twins. Some degree of assortative mating is often found for psychiatric disorders and related phenotypic traits. For depressive disorders, a meta-analysis reported marital resemblance for depression in twelve of seventeen studies (Mathews & Reus, 2001). Studies on the etiology of spousal similarity for psychiatric disorders were carried out by Maes et al. (1998) and Van Grootheest et al. (2008) in population-based samples. Several psychiatric diagnoses were examined, including generalized anxiety disorder, major depressive disorder, obsessive compulsive disorder, panic disorder and phobias. Moderate spousal correlations were seen for most psychiatric diagnoses. Social homogamy, marital interaction and phenotypic assortment are possible explanations for spousal similarity. Social homogamy refers to the tendency of spouses to have similar social backgrounds. Marital interaction means that spouses living together experience mutual influences which make them resemble each other, or that there are active influences of one spouse's phenotype on the other spouse's phenotype. Phenotypic assortment refers to the tendency of individuals to select their partner based on the partner's phenotype. The three mechanisms for spousal similarity have different implications for genetic analysis. Data of spouses of monozygotic and dizygotic twins provide information on which mechanism of assortment is most likely and should be included in the genetic analyses (Heath & Eaves, 1985; Van Grootheest et al., 2008; Penrose, 1944; Maes et al., 1998).

Although the classical twin design offers information about the influence of shared environment, it is not informative about how much of the shared environment is transmitted from parents to offspring. By adding phenotypic data from parents to the classical twin design vertical cultural transmission, reflecting the non-genetic influence of the parents' BPD features on their offspring can be tested. Because BPD features have a heritable component (Distel et al., 2008a) vertical cultural transmission will lead to genotype-environment correlation (Heath et al., 1985b; Eaves et al., 1978).

In this study, we examine the genetic and environmental influences on individual differences in BPD features using an extended twin-family design. We collected data on BPD in twins, their spouses, siblings and parents. Analyzing the data from family members simultaneously in one model allows for testing of additive and dominant genetic effects, individual specific environmental influence, assortment and cultural transmission (Boomsma & Molenaar, 1987; Fulker, 1982).

### **METHOD**

### **Participants**

Twins and their parents, siblings and spouses registered with the Netherlands Twin Register (Boomsma et al., 2006a) and the East Flanders Prospective Twin Survey





Table 6.1. Number of twins, siblings, parents and spouses and their mean age (standard deviation) and age range							
	N	Mean age (SD)	Age range				
Twins							
Monozygotic males	757						
Dizygotic males	389						
Monozygotic females	1,894						
Dizygotic females	932						
Dizygotic opposite sex males	417						
Dizygotic opposite sex females	628						
Total	5,017	33.7 (11.0)	18-86				
Siblings							
Brother	472						
Sister	794						
Total	1,266	38.1 (12.3)	18-90				
Parents							
Fathers	1,357						
Mothers	1,707						
Total	3,064	57.5 (6.5)	34-87				
Spouses							
Male spouses	595						
Female spouses	344						
Total	939	38.0 (12.2)	19-80				

(Derom et al., 2006) were approached by mail and invited to participate in the study by completing a questionnaire. The total sample for analysis consisted of 5,017 twins and 1,266 siblings, 3,064 parents and 939 spouses of twins from 4,015 families. An overview of the sample characteristics is given in Table 6.1.

Zygosity of 3,282 same sex twins was determined either from DNA typing (N = 1,907)or from self-report answers to eight survey questions on physical twin resemblance and confusion of the twins by family members and strangers. Based on the answers to these items from all longitudinal surveys, zygosity was assigned. A total of 1,045 twins were of opposite sex and therefore classified as dizygotic. Agreement between zygosity based on survey questions and zygosity based on DNA typing was 97% (Willemsen et al., 2005). Details on response rates, demographic characteristics and zygosity procedures can be



found elsewhere (Derom & Derom, 2005; Distel et al., 2007, 2008a). The study was approved by the Central Ethics Committee on Research involving human subjects of the vu University Medical Center, Amsterdam, an Institutional Review Board certified by the US Office of Human Research Protections (IRB number IRB-2991 under Federal wide Assurance-3703; IRB/institute codes, NTR 03-180). All subjects provided written informed consent.

### Measures

BPD features were measured by a Dutch translation of the 24-item Personality Assessment Inventory-Borderline Features scale (PAI-BOR) (Morey, 1991, 2003). The PAI-BOR consists of 24 items that are rated on a four-point scale (0 to 3; false, slightly true, mainly true, very true). The items consist of statements concerning, for example, stability of mood and affects, emotionally responsiveness, anger control, self image, feelings of emptiness, intense and unstable relationships, loneliness, impulsivity, self harm and recklessness. Several studies have supported the reliability and the validity of PAI-BOR scores in indexing the degree to which BPD features are present (Morey, 1988, 1991; Stein et al., 2007; Jacobo et al., 2007; Trull, 1995). Receiver operating characteristic analyses showed that the PAI-BOR discriminates well between BPD patients and patients with major depression disorder or dysthimia (area under the curve = 0.78). When interpreting the continuous PAI-BOR score as a categorical measure of BPD, at the best cut-off point of a score of 42, the sensitivity (proportion of individuals correctly classified as BPD) was 71% and the specificity 69% (1-specificity reflects the proportion of individuals falsely classified as BPD) (Distel et al., 2008b). Multigroup confirmatory factor analysis showed that the PAI-BOR is measurement invariant across sex and age (De Moor et al., 2009). The test-retest reliability and internal consistency (Cronbach's  $\alpha$ ) of the Dutch version of the PAI-BOR are 0.78 and 0.84, respectively (Distel et al., 2008a). The PAI-BOR was scored according to the manual, which states that at least 80% of the items must be answered to calculate a sum score and that missing and ambiguous answers should be substituted by a zero score (Morey, 1991).

### Genetic modelling

90

The classical twin design makes use of the different genetic relatedness of monozygotic (MZ) and dizygotic (DZ) twins to disentangle genetic and environmental influences on the variance in a trait. MZ twins are genetically (nearly) identical while DZ twins share on average 50% of their segregating genes, like non-twin siblings. The more similar MZ twins are relative to DZ twins, the more variability in a trait is caused by genetic effects. When there is no difference in resemblance between MZ and DZ twins, shared environmental influences are most likely the cause of the resemblance between twins. Genetic effects can act in an additive (A) or non-additive, or dominant (D; dominance) manner.



05/08/09 11:14:16

Environmental effects can be common to members of the same family (C) or unique to an individual (E).

Adding data from siblings, spouses and parents of twins to the classical twin study has several advantages. Firstly, it provides the information and statistical power to distinguish between A and D, which is poorly achieved with the classic twin design (Keller & Coventry, 2005b; Martin et al., 1978).

Secondly, the effects of assortative mating can be examined. In the classical twin design these may be confounded with the effects of the shared environment (Eaves et al., 2005). Information on the process of assortment (phenotypic assortment, marital interaction or social homogamy) can be deduced from the MZ and DZ co-twin spouse correlations. By comparing these correlations, a distinction can be made between phenotypic assortment and social homogamy. If assortment is primarily based on phenotypic assortment, the correlation between an MZ twin and their co-twins' spouse must be higher than the correlation between a DZ twin and their co-twins' spouse (Reynolds et al., 2006; Heath & Eaves, 1985a). If the trait is heritable, assortative mating increases genetic variance in the offspring generation because genetic effects in the parental generation are correlated. The correlation between the genotypes of parents will also increase the resemblance between parents and their offspring and among siblings (Falconer & Mackay, 1996). When assortative mating for a heritable trait is not explicitly modelled, heritability estimates may become biased. For example, in the classical twin study, heritability estimates will be biased downwards and spurious evidence for shared environment may be found (Maes et al., 1998). If assortment results from marital interaction, the spouse correlation increases as a function of duration of marriage and in general the correlation between parents of twins will be higher than between twins and their spouses (Van Grootheest et al., 2008).

Thirdly, including parents of twins into a study can provide information about cultural transmission from parents to offspring. Cultural transmission increases the parent-offspring correlation as well as the correlation among their offspring. In the classical twin design, cultural transmission will be accounted for as C. In an extended twin design cultural transmission can be distinguished from other forms of C, assuming that vertical cultural transmission from parents to offspring is based on the measured phenotype of the parents (Eaves et al., 2005). Factors that contribute to cultural transmission may be 'taught' from parents to their offspring in the form of imitation, customs or preferences, and have direct effects on behavioral phenotypes through processes of social learning or modelling. In contrast, non-transmittable shared-environment comprises environmental conditions shared by relatives reared together within a generation (Cloninger et al., 1979). Importantly, if parents transmit both genes and environment, this induces a gene-environment correlation, as a consequence of the contribution of

05/08/09 11:14:16



Note. A = additive genetic variance; a = factor loading of A; D = dominant genetic variance; d = factor loading of D; E = unique environmental variance; e = factor loading of E; F = vertical cultural transmission; f = factor loading of F; g = additive genetic variance; r = variance due to cultural transmission; s = genotype environment correlation (g, r and s are constrained as a function of offspring generation parameters); i = assortment. For clarity reasons only one non-twin sibling is drawn, although more are used in the analyses.

the parental phenotype, which is partly genetic in origin, to the offspring's environment (Eaves et al., 2005).



### Resemblance among relatives

In a first step, the resemblances between pairs of family members with different degrees of genetic relatedness were summarized by correlations. Correlations were estimated conditional on sex, for MZ and DZ twins, parent and offspring, sibling pairs, and for spouses (parents of twins and twins with their spouse). Simultaneously, means, variances and regression of BPD scores on age and sex were estimated. We tested for differences in correlations between DZ twins and sibs, for sex effects on twin and parentoffspring correlations and for regression effects of sex and age on the PAI-BOR scores. Next, the contribution of genetic and environmental factors to the variation in BPD features was estimated. Genetic modelling of the data was based on a re-parameterization of the model proposed by Fulker (1982), of mixed genetic and cultural transmission described by Neale and colleagues (1994a). The analysis of a univariate phenotype does not provide sufficient information to estimate the contribution of dominance, cultural transmission and shared environment. Based on the correlation structure of the data and prior analyses (Distel et al., 2008a) we assumed that C beyond cultural transmission did not contribute to the variance in BPD features. Figure 6.1 presents the path diagram of a model in which the phenotypic variance is explained by additive (A) and dominant (D) genetic variation, unique environmental variation (E), vertical cultural transmission (F) and genotype- environment covariance (s). The use of parental data entails the assumption that assortative mating, genetic and cultural transmission and gene-environment correlation remain constant from generation to generation (Heath & Eaves, 1985a). Therefore, the parameters g (genetic variance), r (variance due to vertical cultural transmission) and s (gene-environment covariance) in the parental generation are constrained in the model fitting as a function of the parameters in the offspring generation.

The additive genetic variance is perfectly correlated in MZ twins. For DZ twins and siblings the correlation between the latent A factors is 0.5. These coefficients are based on the assumption of random mating in the population (Falconer & Mackay, 1996). They imply that, if h<sup>2</sup> is the heritability of a trait, the correlation (due to A) between parents and offspring and between siblings equals ½h². Under assortative mating, there is an increase in the genetic variance, which will increase the resemblance between parents and offspring as well as between siblings, i.e.  $r_{\rm g}$  > 0.5 (Crow & Kimura, 1970). The effect of phenotypic assortment is included in the model as represented by the co-path i. The copath represents an extrinsic correlation that influences the covariance structure of the spouses' latent variables but does not contribute to their variance (Cloninger, 1980). Dominant genetic variation results from the interaction or combination of alleles at a particular locus. Offspring receive only one allele from each parent and not a combination of two alleles, thus assuming outbred mating the chance that two siblings receive the same allele is 0.5×0.5 resulting in a correlation of 0.25 between the latent D factor for DZ twins and a correlation of zero between parents and offspring. Variance due to



D is not expected to change as a product of assortative mating, since BPD characteristics are assumed to be influenced by a large number of genes (Falconer & Mackay, 1996; Crow & Kimura, 1970).

### Model fitting

Several models of familial resemblance were fitted to the data. We first estimated correlations between relatives and then fitted a series of genetic models to the data. In the first model (model I), A, D, E, cultural transmission and resulting genotype environment correlation are specified. Model II tests the significance of cultural transmission and genotype environment correlation, model III the significance of D and model V the significance of assortment. Finally, model IV tests the significance of A. Because the data showed a somewhat skewed distribution with a tail to the right, a square root transformation was applied. All analyses were performed in the software package Mx (Neale et al., 2006), using the raw-data full-information maximum-likelihood approach. The fit of the different models was evaluated by means of hierarchical log-likelihood ratio test (LRT) to select the simplest model that best explains the data among a set of possible models. The difference between the negative log likelihood (-2LL) of the two models has a  $\chi^2$  distribution and the degrees of freedom (df) for this test equals the difference in the number of estimated parameters in the two models. A non-significant pvalue means that the constrained model is not significantly worse than the model and is kept as the most parsimonious and best fitting model. Because of the large sample size a p-value of 0.01 was chosen.

### RESULTS

Table 6.2 gives the estimates for the intercept and regression coefficients for sex and age and estimates of the PAI-BOR score for 18 year old men. The sex and age regression coefficients represent the deviation per increasing age year and the deviation for women. The upper part of Table 6.3 shows the results of the tests on the regression coefficients and the variances. Both the age and sex regression coefficients on the mean PAI-BOR score were significant, with younger women showing most BPD features (both p < 0.001). The effects of sex and age on the PAI-BOR scores were therefore included in all genetic models as a regression coefficient. Variances were equal for men and women.

The bottom part of Table 6.3 shows the results of the tests on the correlations. There were no sex differences in twin and sibling correlations (all p > 0.01), indicating that there were no sex differences in the heritability of BPD features, the same genes influence BPD features in men and women (test not shown in Table 6.3) and there is no specific twin environment (all p > 0.01). The MZ twin correlation was 0.45 and the DZ/

94

Table 6.2. Estimates for borderline personality intercept (estimated for men at age 18), regression coefficients for sex (deviation in women) and age (per year) from the regression equation and standard deviations for untransformed data and square root transformed data (estimates plus 95% confidence intervals)

	Untransformed data	Transformed data
Intercept	18.00 (17.24,17.77)	4.10 (4.03,4.17)
$oldsymbol{eta}_{age}$	-0.07 (-0.09,-0.05)	-0.008 (-0.009,-0.007)
$oldsymbol{eta}_{sex}^{\circ}$	1.57 (1.14,2.01)	0.21 (0.16,0.25)
Standard deviation	8.02 (7.86,8.18)	1.00 (0.99,1.01)

sib correlation was 0.19 suggesting that around 50% of the variance in BPD features can be attributed to genetic factors and that part of the genetic variance might be dominant. Resemblance between mothers and their offspring was equal to the resemblance between fathers and their offspring (p = 0.014). The parent-offspring correlation (r = 0.13) was somewhat lower than the DZ/sibling correlation which is consistent with the presence of dominance. There was a significant association between the PAI-BOR scores of twins and the score of their spouses (r = 0.19). The correlation between MZ twins and their co-twins spouse (r = 0.18) was higher than the correlation between DZ twins and their co-twins' spouse (r = 0.08) which suggests that non random mating is primarily based on phenotypic assortment. The spouse correlation in the parental generation was

Table 6.3. Tests of variances, means and correlations								
Model	vs	-2LL	df	Χ²	$\Delta df$	Р		
1. Saturated model		26,025.096	9,329					
2. Variance males = variance females	-	26,025.149	9,330	0.053		0.818		
3. Sex effect on mean = 0	2	26,120.790	9,331	95.641	- 1	< 0.00		
4. Age effect on mean = 0	2	26,155.259	9,331	130.110	- 1	< 0.00		
5. rDZM = rBrother - brother = rDZF = rSister - sister = rDOS =	2	2/020.052	0.225	F 700	_	0.227		
rBrother - sister		26,030.852	9,335	5.703	5	0.336		
6. rMZM = rMZF	5	26,031.040	9,336	0.188		0.665		
7. rFather - mother = 0	6	26,091.713	9,337	60.673	- 1	< 0.00		
8. rFather - son = rFather - daughter = rMother - son = rMother - daugh- ter	6	26,041.683	9,339	10.643	3	0.014		

Note. vs = versus;  $-2LL = -2 \log likelihood$ ; df = degrees of freedom; p = p-value. The best fitting model is printed in bold.





05/08/09 11:14:17

Table 6.4. Maximum likelihood parameter estimates and goodness of fit
indices from the extended twin design for borderline personality (95%
confidence intervals in parentheses for the best fitting model)

	- 1	II	III	IV	٧
Additive genetic path (a)	0.593	0.447 (0.39, 0.50)	0.545	-	0.465
Dominant genetic path (d)	0.336	0.487 (0.42, 0.54)	-	-	0.480
Specific envi- ronment path (e)	0.741	0.738 (0.71, 0.76)	0.820	0.996	0.738
Assortment (i)	0.251	0.251 (0.21, 0.30)	0.240	0.246	-
Additive genetic variance (g)	1.088	1.056 (1.04, 1.07)	1.084	1.000	1.000
Variance due to cultural transmission (r)	0.013	_	_	_	_
A-C covariance (s)	-0.054		-	-	-
Cultural trans- mission (f)	-0.073	-	-	-	-
-2 LL	26,041.683	26,042.184	26,089.204	26,382.414	26,104.180
Degrees of freedom	9,339	9,340	9,341	9,342	9,341
X <sup>2</sup>	-	0.501	47.521	340.731	62.497
$\Delta$ degrees of freedom	-	- 1	2	3	2
P Medal la sultura	-	0.480	<0.001	<0.001	<0.001

Model I: cultural transmission model

Model II: dominance model; no cultural transmission

Model III: as model II, no dominance

Model IV: as model III, no additive genetic effects

Model V: as model II, no assortment Best fitting model printed in bold.

0.24 indicating that in addition to phenotypic assortment, there may be some influence of marital interaction. The estimates for the familial correlations for pairs of family members with different degrees of genetic relatedness are summarized in Figure 6.2.

## Genetic modelling

Table 6.4 shows the result of genetic model fitting. Model I specifies effects of A, D and E, assortment and cultural transmission. The model is just identified, meaning that





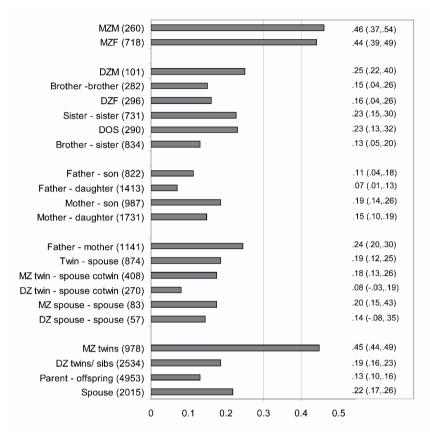


Figure 6.2. Correlations for BPD features between family members of different degrees of relatedness (number of pairs) and 95% confidence intervals. The bottom 4 bars collapse across categories above.

the number of free parameters in the model equals the number of peaces of information, and provides the same fit to the data as the correlation model (model 8) in Table 6.3. From the estimates for the path coefficients, the influence of A on individual differences in BPD features can be obtained by the product of the additive genetic path coefficient squared and the additive genetic variance divided by the total variance (A =  $a^{2}*g$  / total variance). The influence of assortment on A can be calculated by A - a<sup>2</sup> showing that in this model 3.0% of the additive genetic variance (38.5%) is explained by assortment. Non additive genetic effects ( $d^2$ / total variance) explained 11.4% of the variance. Unique environmental effects (e<sup>2</sup>/ total variance) explained 55.3% and negative cultural transmission (r) explained 1.3% of the variance. Genotype-environment covariance (as\*sa / total variance) was estimated to be negative, resulting in a negative contribution of 6.4% of the variance in BPD features. In model II (dominance model without cultural transmission), additive genetic effects explained 21.3% (1.1% due to assortment) and dominant

genetic effects explained 23.9% of the variance in BPD features. The remaining variance was accounted for by unique environmental influences. The fit of model II is not significantly worse than the fit of model I ( $\chi^2_{(1)}$  = 0.50, p = 0.480) which indicates that there is no significant effect of cultural transmission and resulting genotype environment correlation. Comparing the fit of model II with the fit of model III shows that removing D from the model results in a significant deterioration in the fit of the model ( $\chi^2_{(1)}$  = 47.0, p < 0.001). Model IV (versus model III), shows that the influence of A is highly significant since removing it from the model results in a considerable worsening of fit  $(\chi^2)$ = 293.2, p < 0.001). Finally, comparing model V with model II ( $\chi^2_{(1)}$  = 62.0, p < 0.001) shows that there is significant effect of assortment. Comparing the fit of the different models showed that the ADE model best explained the data.

### DISCUSSION

This is the first study that analyzes borderline personality data from twins and their family members simultaneously providing a powerful design to distinguish between additive and dominant genetic effects and to detect non-random mating, cultural transmission and genotype-environment correlation. A genetic model in which additive genetic effects (21.3%; 95% CI 16%-26%), dominant genetic effects (23.9%; 95% CI 17%-31%) and unique environmental influences (54.9%; 95% CI 51%-60%) explained the variance in BPD features best explained the data. There was no evidence for shared environmental influences, which is a common finding for a range of personality traits and personality disorders. The effect of phenotypic assortment was included in the genetic model, but it had only a small effect on the genetic variance.

The presence of significant dominant genetic effects is in line with what is often suspected for personality traits, but not detected due to a lack of statistical power in relatively small twin studies. Our results showed that BPD features are genetic in origin but only partly transmitted from parents to offspring because dominant genetic effects influence borderline personality only in combination with other genes. These combinations are not shared by parents and offspring. Keller et al. (2005a) used a twin-sibling design to estimate genetic and environmental effects on Eysenck's and Cloninger's personality dimensions using data from over 12,000 twins and siblings. They found that 0 to 34% of the variance in these personality dimensions was explained by additive genetic effects and 11 to 35% was explained by dominant genetic effects.

The finding of dominance for personality traits is not uncommon, but there may be alternative explanations for these data. The parent-offspring correlation for BPD features was lower than the DZ/sibling correlation which is indicative of the presence of dominance but might also suggest genotype by age interaction, i.e. the expression of differ-

ent genes at different ages or a change in genetic variance as a function of age. Gene by age interaction can inflate estimates of dominance because it will decrease the correlation between parents and offspring as a result of their differences in age. To investigate this alternative we first divided the twin sample into a group with roughly the same age as the parents in the total sample (N = 968, mean age 52.7 years) and a group with roughly the same age as the offspring in the sample (N = 4,047, mean age 29.1 years). The total variance did not differ between the two groups ( $\chi^2_{(i)}$  = 0.011, p = 0.916). The MZ and DZ twin correlations of the younger and older age groups were 0.472 versus 0.247, and 0.459 versus 0.095, suggesting that broad-sense heritability might be larger in the older generation. However, constraining the MZ and DZ twin correlations to be equal across age groups did not lead to a significant worsening of model fit ( $\chi^2$ ) = 0.051, p = 0.821 and  $\chi^2_{(1)}$  = 2.618, p = 0.106). Thus, heritability may not change as a function of age. Secondly, to investigate whether different genes are expressed at different ages, we selected a group of siblings less then 4 years (190 pairs) and a group of siblings 4 years or more apart in age (212 pairs). The PAI-BOR correlations for siblings in these groups were 0.208 and 0.327 and the resemblance between siblings thus does not decrease as the age difference between them increases. The correlations in the two sibling groups could be constrained to be equal ( $\chi^2_{(1)}$  = 1.69, p = 0.194) This suggests that the same genes influence BPD features at different ages.

The largest part of the variance in borderline personality was explained by unique environmental influences (54.9%). Several studies demonstrated that traumatic life events such as sexual and physical abuse, parental divorce or illness or parental psychopathology are important risk factors for the development of BPD (Machizawa-Summers, 2007; Zanarini et al., 2002; Trull, 2001a; Westen et al., 1990). The interaction, however, between the influences of genes and environment on the development of BPD has not been studied. Gene by environment interaction implies that genes determine the degree to which an individual is sensitive to an environment. In the presence of geneenvironment interaction, individuals with a 'sensitive' genotype will be at greater risk of developing BPD if an undesirable environment is present, than individuals with an 'insensitive' genotype. In the present study, gene-environment interaction would be included as part the unique environmental variance. Future research should focus on possible sources of unique environmental effects and gene-environment interaction to develop a comprehensive model of the development of BPD.

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# **GENETIC COVARIANCE**

# STRUCTURE OF THE FOUR MAIN

# FEATURES OF BORDERLINE

# PERSONALITY DISORDER

Marijn A. Distel, Gonneke Willemsen, Lannie Ligthart, Catherine A. Derom, Nicholas G. Martin, Michael C. Neale, Timothy J. Trull & Dorret I. Boomsma. Genetic covariance structure of the four main features of borderline personality disorder. *Journal of Personality Disorders*, in press.

### **ABSTRACT**

HE PATIENT POPULATION of borderline personality disorder (BPD) is heterogeneous; many different combinations of BPD symptoms can lead to a BPD diagnosis. We investigated to what extent the covariance among four main components of BPD is explained by shared genetic and environmental factors. Using an extended twin design, multivariate genetic models were applied to the scales of the PAI-BOR, a self-report questionnaire tapping four main features of BPD (affective instability, identity problems, negative relationships, and self-harm). Data on the four BPD scales were available for 5,533 twins and 1,202 siblings from the Netherlands, Belgium and Australia. The correlations among the scales ranged from 0.23 to 0.50 and were best explained by a genetic common pathway model. This model specifies that genes and environment influence the covariance between four main features of BPD in qualitatively similar ways, through a single latent factor representing the BPD construct. The heritability of the latent BPD factor was 51% and the remainder of its variance was explained by unique environmental influences. For each BPD scale, except self-harm, around 50% of its variance was explained by the latent BPD factor. The remaining variance for each of the four scales was explained by genetic (4% for affective instability to 20% for self-harm) and environmental (38% for negative relationships to 67% for selfharm) factors that were specific to each scale.





### INTRODUCTION

ORDERLINE PERSONALITY DISORDER (BPD) is one of the most studied personality disorders (Blashfield & Mcelroy, 1987; Blashfield & Intoccia, 2000). However, when compared to research on disorders such as depression or other psychiatric disorders, studies on the genetic factors that influence the development of BPD are surprisingly sparse (Crowell et al., 2009). BPD is complex, as symptoms contributing to a BPD diagnosis are very heterogeneous. The Diagnostic and Statistical Manual for mental disorders (American Psychiatric Association, 2000) describes nine symptoms of BPD of which at least five must be present to warrant a BPD diagnosis. The presence of five or more out of nine symptoms, however, results in many possible combinations of symptoms leading to a BPD diagnosis.

At the population level, the clustering of symptoms of BPD has frequently been studied. Results of factor analytic studies of the DSM-III (Clarkin et al., 1993; Rosenberger & Miller, 1989; Sanislow et al., 2000; Becker et al., 2006) and DSM-IV (Fossati et al., 1999; Blais et al., 1997; Johansen et al., 2004; Benazzi, 2006; Taylor & Reeves, 2007) criteria for BPD of show evidence for two (Rosenberger & Miller, 1989; Benazzi, 2006), three (Clarkin et al., 1993; Blais et al., 1997; Sanislow et al., 2000; Taylor & Reeves, 2007) or four (Becker et al., 2006) underlying factors. Important similarities between the structures identified in clinical and non-clinical samples were found (Taylor & Reeves, 2007). The factor structure found depends on the sample and instrument used. In our own study using data from twins and siblings from three countries and using the *Personality* Assessment Inventory Borderline features scale (Morey, 1991) to assess BPD features, we found that a four-factor structure best described the data (De Moor et al., 2009). These four components of BPD are: affective instability, identity problems, negative relationships and self-harm. Affective instability refers to the highly reactive moods of individuals with BPD in response to stimuli from the individual's environment. The basic mood often shifts between periods of anger, panic, anxiety or despair and is rarely relieved by periods of well-being or satisfaction. *Identity problems* involve a poorly defined concept of self. The self-image of persons with BPD may shift a lot, including sudden changes in opinions, sexual identity, types of friends, or career plans. The third factor, impulsivity, often results in self-damaging behavior. Common forms of impulsive behavior are excessive spending, reckless driving, binge eating, substance abuse and promiscuity. Unstable and stormy relationships and feelings of loneliness reflect the fourth factor of the PAI-BOR: negative relationships. This four factor structure resembles the four scales of the PAI-BOR as proposed by Morey (1991).

In the present study we explore why these features of BPD, represented by the four scales of the PAI-BOR, co-occur in the population by conducting genetic factor analyses. We test two models that represent different ways in which genes and environment





might affect the four scales of the PAI-BOR. The first model, the independent pathway model, specifies direct paths from one or more genetic factors and one or more environmental factors common to all PAI-BOR scales as well as paths from unique genetic and environmental factors specific to each scale. In this model, genes and environment can influence the covariance between the four scales through different pathways. The second model, the single factor common pathway model, is based on the assumption that the covariation among the four BPD scales is determined by a single latent factor (the BPD construct) whose variance is determined by genetic and environmental influences. In this model, genes and environment influence the covariance between the four scales in similar ways. In both models, there may be genetic and environmental influences specific to each scale, but these influences do not affect the co-occurrence of the four scales (Neale & Cardon, 1992; Kendler et al., 1987).

Data from twins and their siblings were available from the Netherlands Twin Register (Boomsma et al., 2006a), the East Flanders Prospective Twin Survey (Derom et al., 2006) and the Australian Twin Register (Jardine et al., 1984). Data from twins allow the identification of genetic and environmental factors, as monozygotic (MZ) twins share (nearly) 100% of their genetic material and dizygotic (DZ) twins and non-twin siblings share on average 50% of their segregating genes. By comparing the covariance structure in MZ and DZ twins, the relative influence of genetic and environmental factors on the variance in the four scales and on the covariance between them can be estimated and different multivariate genetic factor models can be tested.

### **METHOD**

### **Participants**

Data were collected as part of an international project on BPD features in Dutch, Belgian and Australian twin cohorts. Twins and siblings were approached by mail and invited to participate in the study by completing a questionnaire. The Dutch sample consisted of 3,951 twins (1,209 complete pairs) and 1,202 siblings from 2,931 families registered with the Netherlands Twin Register (Boomsma et al., 2006a). The Belgian sample consisted of 908 twins (242 complete pairs) from 595 families recruited through the East Flanders Prospective Twin Survey (Derom et al., 2006). A total of 674 twins (275 complete pairs) from 399 families were drawn from the Australian Twin Register (Jardine et al., 1984). Six months after the first questionnaire was sent 199 twins, siblings and parents (1 per family) from the Netherlands completed a retest survey. Details on response rates, demographic characteristics of the samples and zygosity determina-



tion procedures can be found elsewhere (Derom & Derom, 2005; Distel et al., 2008a; Nyholt, 2006).

### Measures

BPD features were measured by the 24-item Personality Assessment Inventory-Borderline Features scale (PAI-BOR; Morey, 1991). The PAI-BOR consists of four subscales each composed of six items that are rated on a four-point scale (o to 3; false, slightly true, mainly true, very true). The four subscales are affective instability (AI; e.g. stability of mood and affect, emotionally responsiveness and anger control), identity problems (IP; e.g. self image, concept of self and feelings of emptiness), negative relationships (NR; e.g. intense and unstable relationships and loneliness) and self harm (SH; e.g. impulsivity, self-harm and recklessness). Several studies have shown the PAI-BOR to be a reliable and valid measure of BPD features, and support the usefulness of the PAI-BOR in assessing BPD features in the general population as well as BPD in clinical settings (Kurtz et al., 1993; BellPringle et al., 1997; Stein et al., 2007; Trull, 1995). For example, Stein et al. (2007) showed that the PAI-BOR differentiates between patients diagnosed with BPD and patients without borderline personality pathology with 73% accuracy. Receiver operating character analysis showed that the PAI-BOR performs reasonably well in discriminating BPD patients and non-BPD depressed psychiatric patients, supporting the validity of PAI-BOR scores (Distel et al., 2008b). In the Netherlands and in Belgium, the Dutch translation of the PAI-BOR was used. The English PAI-BOR was translated into Dutch and translated back into English by a native English speaking translator. The Dutch translation of the PAI-BOR was reviewed and approved by the test author and publishing company (Psychological Assessment Resources). Multigroup confirmatory factor analysis showed that the Dutch version of the PAI-BOR is measurement invariant across sex and age (De Moor et al., 2009). The PAI-BOR was scored according to the test manual, which states that at least 80% of the items must be answered to calculate a sum score and that missing and ambiguous answers should be substituted by a zero score (Morey, 1991).

### **Analyses**

In twin-family studies, the different degree of genetic relatedness of monozygotic (MZ) and dizygotic (DZ) twin pairs and other first-degree relatives such as siblings is used to identify the relative contribution of genes and environment to the phenotypic variation of a trait. MZ twins share (nearly) all their genes while DZ twins and siblings share on average 50% of their segregating genes (Boomsma et al., 2002a). For a (univariate) phenotype (P) in a single individual we can express P as:

$$P_{i} = aA_{i} + dD_{i} + cC_{i} + eE_{i},$$
 (1)

where i refers to an individual and A, D, C and E represent additive genetic, non-additive genetic, common environmental and unique environmental factor scores respec-



105

tively. A refers to the additive effects of alleles at all genomic loci contributing to the phenotype, D to non-additive (dominance) effects of alleles, C to the effects of common environment shared by individuals growing up in the same family and E to non-shared environment (which also includes measurement error). The lower case letters a, d, c and e are regression coefficients on the latent variables A, C, D and E which are assumed to be independent of (uncorrelated with) each other. The expectation for the phenotypic variation may be written as:

$$V_{(P)} = V_{(A)} + V_{(D)} + V_{(C)} + V_{(E)}$$
 (2)

Broad-sense heritability (h²) is the proportion of phenotypic variance that is attributable to genotypic variance ( $h^2 = (V_{(A)} + V_{(D)}) / V_{(P)}$ ); narrow-sense heritability is the proportion of variation explained by additive genetic factors  $(h_n^2 = V_{(A)}/V_{(P)})$ . Based on data from only MZ and DZ twins and siblings, this model is not identified and a choice for an ADE or ACE model needs to be made. This choice may be based on the pattern of correlations in MZ and DZ twins. When the DZ correlation is more than half the MZ correlation, there is evidence for environmental effects shared by twins from the same family (C) but when the DZ correlation is less than half the MZ correlation, there is evidence for non-additive genetic effects (D). In the present study an ADE model was fitted to the data (see results section). Identification of the ADE model is achieved because, based on quantitative genetic theory, the correlation among the latent factors influencing the phenotype are known. For MZ twin pairs correlations between A, and A, (where A, and A, refer to the additive genetic factor score in twin 1 and twin 2) and between D<sub>1</sub> and D<sub>2</sub> is one. For DZ pairs, these correlations are 0.5 and 0.25, respectively. Correlations between E<sub>1</sub> and E<sub>2</sub> are zero in MZ and DZ pairs (e.g. Falconer & Mackay, 1996; Boomsma & Molenaar, 1986).

Multivariate genetic analyses can be applied to determine to what extent the covariation between traits can be explained by genetic and environmental factors. The comparison of MZ and DZ cross-twin cross-trait correlations provides a first indication about the shared etiology between traits. If a significant cross-twin cross-trait correlation is present it suggests that there is a familial influence on the etiology of the correlation between the two traits. If the MZ cross-twin cross-trait correlation exceeds the DZ cross-twin cross-trait correlation it suggests that the familial influence on the correlation is at least partly genetic in origin. Equations 1 and 2 can be generalized to multivariate phenotypes by writing:

 $P_{ij} = a_i A_i + d_j D_i + c_j C_i + e_j E_i$ , (3), where i refers to individual and j to trait.

 $\Sigma_{(P)} = \Sigma_{(A)} + \Sigma_{(D)} + \Sigma_{(C)} + \Sigma_{(E)}$  (4), where  $\Sigma$  has dimension j×j and consists of variances on the diagonal and covariances on the off-diagonal. If, for example,  $\Sigma_{(E)}$  is a diagonal matrix, then environmental correlations among traits are zero and the traits are only influenced by trait specific environmental factors (Martin & Eaves, 1977; Polderman et al., 2007; Boomsma et al., 1990).

106

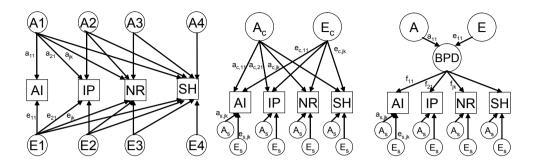


Figure 7.1. Graphical representations of the Cholesky, independent pathway and the common pathway models

Note. Al = affective instability; IP = identity problems; NR = negative relationships; SH = self harm; BPD = borderline personality disorder; Al through A4 = additive genetic factors, El through E4 = unique environmental factors, A<sub>c</sub> = additive genetic factor common to multiple traits; E<sub>c</sub> = unique environmental factor common to multiple traits; A<sub>s</sub> = specific genetic factors; E<sub>s</sub> = specific unique environmental factors; a, e and f = factor loadings; k = latent factor A or E; j = phenotype Al, IP, NR or SH. All latent A and E factors have unit variance.

Qualitative and quantitative sex differences in genetic architecture can arise in all parameters of the model. A first impression of such differences is obtained by inspection of twin correlations in male and female MZ and DZ twin pairs. If, for example, heritability is larger in men, we expect MZ males > MZ females and DZ males > DZ females. Qualitative sex differences are suggested if correlations in DZ twins of opposite sex (DOS) cannot be predicted based on the pattern of correlations in same-sex twin pairs. Testing for quantitative sex differences in the importance of A, D/C and E can be achieved by testing the equality of correlations in male-male and female-female twin pairs by constraining the correlations between men and women within zygosity to be equal. To test whether the same genes influence BPD features in men and women (qualitative differences) DOS correlations are predicted from DZ same-sex correlations.

We first fitted a saturated multivariate model that estimated means, variances and covariances (among family members and among scales). Data from the three countries were analyzed simultaneously in a multi-group analysis. For each scale an effect of sex and age was modelled and tested for significance. These effects were included as a regression of sex (coded as 0 for males and 1 for females) and age (in years) on each scale. By constraining the regression coefficients to equal zero and examining the change in log-likelihood we tested the significance of these effects. Significant effects of sex and age were retained in subsequent genetic analyses.



All correlations between MZ and DZ twin and sibling pairs within and between scales were initially estimated as a function of zygosity and sex. By constraining within-scale and cross-scale correlations to be equal for men and women within the zygosity groups qualitative and quantitative sex differences were tested.

We fitted three multivariate genetic models to the data (Figure 7.1 provides graphical representations of the three models):

- I. A Cholesky (or triangular) decomposition (model 1) decomposes the covariance matrix among the four scales into genetic and environmental covariance matrices (e.g.  $\Sigma_{(A)}$  and  $\Sigma_{(E)}$ ). The Cholesky decomposition is a fully parameterized, descriptive model and yields the best fit of a variance components model to the data. It imposes no underlying structure on the genetic and environmental influences and can be fitted to the data as depicted in Figure 7.1 for an AE model, i.e. if there are four scales there are four A and four E factors. The order of the variables in a Cholesky decomposition is arbitrary in that either order would produce the same fit to the data. However, with sex limitation this is not the case. It is therefore important to explore whether qualitative and quantitative sex differences are present before fitting a Cholesky model to the data (Neale et al., 2006b). The full Cholesky model serves as a baseline model to which more restricted factor models can be compared; in our case the independent pathway and the common pathway models.
- 2. The independent pathway model (model 2) specifies direct paths from genetic and environmental factors common to all scales as well as paths from genetic and environmental factors specific to each scale. Loadings on the common genetic factor contribute to the within-person cross-scale and to the cross-person cross-scale correlations. Loadings on the common environmental factor contribute to the within-person cross-scale correlation but not to the cross-person cross-scale correlation. The same genetic and environmental factors thus influence scores on all four scales of the PAI-BOR, although the magnitude of the effects can differ per scale. Loadings on the scale specific genetic factors contribute to the correlation between persons for a specific scale, but not to correlations across scales. Loadings on the scale specific environmental factors do not contribute to correlations between scales or between family members. Based on the results of the saturated model, parameter estimates were constrained to be equal between the countries, when possible.
- 3. The common pathway model (model 3) is a more stringent version of the independent pathway model and tests the assumption that the covariation among the scales is determined by one or more latent factors ('common pathways') whose variance is determined by a genetic and an environmental factor. However, under the common pathway model, genetic and environmental factors affect the trait by both acting on the same latent variable (Neale & Cardon, 1992).

Table 7.1. Number (N) of participants from complete/incomplete twin pairs, mean age, standard deviation (SD) and age range per zygosity in each country

Zygosity	N	Mean age	SD	Range
Dutch MZ males	378/190	35.8	13.0	19-76
Dutch DZ males	156/151	35.0	11.6	19-75
Dutch MZ females	1,146/384	35.7	12.2	19-86
Dutch DZ females	484/273	35.0	10.9	19-74
Dutch males from DZ opposite-sex pairs	209/107	33.4	10.5	20-75
Dutch females from DZ opposite-sex pairs	209/264	32.9	9.5	19-75
Dutch brothers	449	38.7	14.2	18-90
Dutch sisters	753	38.2	11.3	18-84
Belgian MZ males	118/45	27.5	6.1	18-40
Belgian DZ males	32/33	28.3	5.7	18-40
Belgian MZ females	246/72	29.7	6.9	18-48
Belgian DZ females	88/58	29.1	7.2	18-46
Belgian males from DZ opposite-sex pairs	71/14	25.5	6.1	18-39
Belgian females from DZ opposite-sex pairs	71/60	27.2	6.7	18-40
Australian MZ males	100/36	23.2	3.7	18-33
Australian DZ males	58/18	22.2	2.6	18-29
Australian MZ females	170/23	23.4	3.9	18-33
Australian DZ females	96/12	24.5	4.0	18-32
Australian males from DZ opposite-sex pairs	63/15	22.1	3.6	18-32
Australian females from DZ opposite-sex pairs	63/20	22.2	3.6	18-32
Note M7	. D7 – diti-			

Note. MZ = monozygotic; DZ = dizygotic





Model fitting was performed using the structural equation modelling software package Mx (Neale et al., 2006a). Comparison of models was done by means of likelihoodratio tests, by subtracting the negative log likelihood (-2LL) for the more restricted models (models 2 and 3) from the -2LL for the general model (model 1). This yields a statistic that is distributed as  $\chi^2$  with degrees of freedom (df) equal to the difference in the number of parameters in the two models. If the  $\chi^2$ -test yields a p-value higher than 0.01, the constrained model is deemed not significantly worse than the unconstrained model and is therefore the most parsimonious model. In addition, Akaike's Information Criterion (AIC; Akaike, 1987), calculated as  $\chi^2$ - 2df, was evaluated because it reflects both the goodness of fit and the parsimony of the model. The lower the AIC value, the better the fit of the model relative to the number of parameters estimated (Lubke & Neale, 2006; Markon & Krueger, 2004). Finally, Bayesian information criterion (BIC; Schwarz, 1978), calculated as 0.5(-2LL-df-ln(N)), is reported.

Because the data on all four scales showed a somewhat skewed distribution, a square root transformation was performed.

### RESULTS

### Descriptives

Table 7.I shows the number of participants from complete and incomplete twin pairs, mean age, standard deviation and age range per zygosity in each country. In total, 5,533 twins (1,879 complete twin pairs) and 1,202 siblings from 3,925 families took part in the study. The six-month test-retest correlation of the Dutch PAI-BOR scales were 0.75, 0.69, 0.60 and 0.53 for AI, IP, NR and SH, respectively. The internal consistencies (Cronbach's α) of the scales AI, IP, NR and SH were 0.71, 0.62, 0.56 and 0.64 in the Dutch sample, 0.66, 0.67, 0.59 and 0.67 in the Belgian sample and 0.78, 0.68, 0.70 and 0.73 in the Australian sample, respectively.

### Tests of fixed effects on mean structure

Sex effects on the means were significant in the Dutch sample for AI ( $\chi^2 = 66.5$ , p < 0.00I), IP ( $\chi^2 = 64.I$ , p < 0.00I), and NR ( $\chi^2 = 28.2$ , p < 0.00I); with women scoring higher than men. The same direction of effect was seen for AI ( $\chi^2 = 2.5$ , p = 0.II2), IP ( $\chi^2 = 4.0$ , p = 0.045), and NR ( $\chi^2 = 1.3$ , p = 0.26I) and SH ( $\chi^2 = 0.4$ , p = 0.530) in the Belgian data and for AI ( $\chi^2 = 5.3$ , p = 0.022), IP ( $\chi^2 = 4.9$ , p = 0.026), and NR ( $\chi^2 = 4.5$ , p = 0.034) in the Australian data, but these effects were not significant. Men from the Netherlands ( $\chi^2 = 0.13$ , p = 0.720) and Australia ( $\chi^2 = 3.9$ , p = 0.049) had higher scores on the subscale SH than women, but these effects were not significant. BPD features de-

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Table 7.2. MZ and DZ male and female within person, within-scale and cross nstability (AI), Identity Problems (IP), Negative Relationships (NR) and Self Within scale (diagonal) and cross scale (diagonal) and cr	e and female within person, within-scale and cross-scale oblems (IP), Negative Relationships (NR) and Self-Harn Within scale (diagonal) and cross scale (off correlation Male pairs Female SH AI IP NR SH AI IP 0.30 DZ 0.09 0.16	e and female within person, within-scale and cross-scale correoblems (IP), Negative Relationships (NR) and Self-Harm (SH)  Within scale (diagonal) and cross scale (off diagonal) are cross-scale correctly and Self-Harm (SH)  National Al IP NR SH Al IP NR  Al MZ 0.30 0.30 0.36 0.16	ion, within-scale and cross-scale correlations for Affeedationships (NR) and Self-Harm (SH)  hin scale (diagonal) and cross scale (off diagonals) correlations  Male pairs  Female pairs  Opposite  NR SH AI IP NR SH AI IP  O36  O16  O25  O32	con, within-scale and cross-scale correlations for elationships (NR) and Self-Harm (SH) hin scale (diagonal) and cross scale (off diagonals) correlations Male pairs IP NR SH AI IP NR SH AI  0.36 0.16 0.08
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egative Relationships (NR) and Self Within scale (diagonal) and cross sca  Male pairs  AI IP NR SH AI  MZ 0.30  0.36  0.70	egative Relationships (NR) and Self-Harn Within scale (diagonal) and cross scale (off cross scale pairs  Male pairs  NR SH AI IP	egative Relationships (NR) and Self-Harm (SH)  Within scale (diagonal) and cross scale (off diagonal)  Male pairs  AI IP NR SH AI IP NR  MZ 0.30  0.30  0.36  0.16	con, within-scale and cross-scale correlations for Afference lationships (NR) and Self-Harm (SH)  hin scale (diagonal) and cross scale (off diagonals) correlations  Male pairs  Female pairs  Opposite  ONR  ONR  ONR  ONR  ONR  ONR  ONR  ON	con, within-scale and cross-scale correlations for Afference lationships (NR) and Self-Harm (SH)  hin scale (diagonal) and cross scale (off diagonals) correlations  Male pairs  Female pairs  Opposite  ONR  ONR  ONR  ONR  ONR  ONR  ONR  ON
person, within-scale and cross re Relationships (NR) and Self Within scale (diagonal) and cross sca Male pairs Al IP NR SH AI 0.30 0.30 0.36	person, within-scale and cross-scale re Relationships (NR) and Self-Harn Within scale (diagonal) and cross scale (off or Male pairs AI IP NR SH AI IP  0.30  0.30  0.36	person, within-scale and cross-scale correct Relationships (NR) and Self-Harm (SH) Within scale (diagonal) and cross scale (off diagonal)  Male pairs  AI IP NR SH AI IP NR  0.30  0.30  0.36	con, within-scale and cross-scale correlations for Afference (NR) and Self-Harm (SH)  hin scale (diagonal) and cross scale (off diagonals) correlations  Male pairs  Opposite  IP NR SH AI IP NR SH AI IP  0.36  0.08	con, within-scale and cross-scale correlations for Afference (NR) and Self-Harm (SH)  hin scale (diagonal) and cross scale (off diagonals) correlations  Male pairs  Opposite  IP NR SH AI IP NR SH AI IP  0.36  0.08
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hin-scale and cross hips (NR) and Self diagonal) and cross sca pairs NR SH AI 0.36	nin-scale and cross-scale hips (NR) and Self-Harn diagonal) and cross scale (off c pairs Female NR SH AI IP  0.36 0.16	nin-scale and cross-scale correhips (NR) and Self-Harm (SH) diagonal) and cross scale (off diagonal pairs  NR SH AI IP NR  0.36  0.16	lations for Affe	lations for Affe
lle and cross  VR) and Self  I) and cross sca  SH AI  0.36  0.16	le and cross-scale NR) and Self-Harn l) and cross scale (off o Female SH AI IP 0.36 0.16	le and cross-scale corre NR) and Self-Harm (SH) ) and cross scale (off diagonal Female pairs SH AI IP NR  0.36  0.16	lations for Affe	lations for Affe
d cross nd Self ross sca Al 0.36 0.16	I cross-scale nd Self-Harn ross scale (off c Female Al IP 0.36 0.16	I cross-scale corre  Ind Self-Harm (SH)  I cross scale (off diagonal  Female pairs  Al IP NR  0.36  0.16	lations for Affe	lations for Affe
	-scale -Harn -Harn lle (off c Female	Scale corre Harm (SH) Ile (off diagonal Female pairs IP NR	lations for Affe	lations for Affe
correlation n (SH) liagonals) corre pairs NR SH	s) corre		Affe pposi	Affe pposi
lations for some state of the second	lations for some state of the second	s for Jations Ol		sex pai

relation explained by genetic and environmental factors (95% confidence intervals) Table 7.3. Estimates of phenotypic  $(r_p)$ , genetic  $(r_p)$  and environmental  $(r_p)$ , correlations and the percentage of cor-

% of correlation explained		% of correlation explained
by genetic factors	, o	by environmental factors
0.77 (0.76-0.84) 48% (42%-55%)	0.37 (0.33-0.41)	52% (45%-57%)
0.81 (0.75-0.88) 54% (48%-60%)	0.34 (0.30-0.38)	46% (39%-52%)
0.43 (0.32-0.54) 49% (36%-62%)	0.18 (0.14-0.22)	51% (38%-64%)
0.67 (0.59-0.74) 48% (40%-54%)	0.36 (0.33-0.40)	52% (46%-59%)
0.37 (0.25-0.48) 45% (30%-59%)	0.18 (0.15-0.22)	55% (41%-70%)
0.46 (0.35-0.56) 55% (42%-68%)	0.16 (0.12-0.20)	45% (37%-58%)
	% of correlation explained by genetic factors .84) 48% (42%-55%) .88) 54% (48%-60%) .54) 49% (36%-62%) .74) 48% (40%-54%) .74) 45% (30%-59%) .74) 45% (30%-59%) .76) 55% (42%-68%)	% of correlation explained by genetic factors



creased significantly with age (all p < 0.01) except for NR in the Dutch sample ( $\chi^2$  = 5.5, p = 0.019) and AI ( $\chi^2$  = 1.01, p = 0.313) and NR ( $\chi^2$  = 1.1, p = 0.290) in the Australian sample.

### Correlation structure

Phenotypic correlations (within-person, cross-scales) and twin and sibling correlations (cross-persons, within-scale) did not differ significantly across the three countries. Cross correlations (cross-persons, cross-scales) also did not differ significantly. Based on these results, in subsequent analyses all correlations were constrained to be equal between countries. Table 7.2 summarizes the correlation structure for males, females and opposite-sex pairs. The first four columns show the phenotypic correlations for men and women. Constraining the phenotypic correlations to be equal for men and women did not result in a significant deterioration of model fit ( $\chi^2$  = 14.28, p = 0.027). The diagonals of the other 4×4 correlation matrices show the within-scale correlations, the off-diagonals show the cross-scales correlations. The within-scale and cross-scales correlations did not differ significantly between MZ male and female twin pairs ( $\chi^2$ <sub>(1)</sub> = 3.57, p = 0.467 and  $\chi^2_{(6)}$  = 4.41, p = 0.622), nor between DZ twin and sibling male and female pairs ( $\chi^2_{(4)}$  = 7.25, p = 0.123 and  $\chi^2_{(6)}$  = 8.95, p = 0.177). This indicates that the heritability for the four scales of the PAI-BOR is the same for men and women and that the same genetic structure explains the covariance between the four scales in men and women. The within-scale and cross-scales correlations for opposite-sex DZ twin and sibling pairs did not differ from same-sex DZ twin and sibling pairs ( $\chi^2_{(a)} = 4.62$ , p = 0.328 and  $\chi^2_{(6)} = 5.59$ , p = 0.471) indicating that the same set of genes influences BPD features in men and women. All correlations were thus equal across sex. Estimates of the MZ and DZ twin/sibling correlations were 0.34 and 0.12 for AI, 0.33 and 0.13 for IP, 0.37 and 0.14 for NR and 0.31 and 0.08 for SH. All MZ twin correlations were more than twice as large as those for DZ twins and siblings, suggesting that the genetic effects that contribute to individual differences may be partly non-additive. All MZ cross-scales correlations exceeded the DZ cross-scales correlations, suggesting that factors influencing all four scales of the PAI-BOR are at least partly genetic. Based on the correlation structure, ADE models were fitted in subsequent analyses. The absence of evidence for sex-limitation in these data circumvents the problems with the Cholesky model noted by Neale et al (2006b).

# Multivariate genetic modeling

In the multivariate genetic models non-additive genetic effects could be removed from the model without a significant deterioration in the fit of the model ( $\chi^2_{(10)} = 20.1$  p = 0.029). Thus, variance in AI, IP, NR and SH and their covariance can be explained by additive genetic and unique environmental factors. Results of the Cholesky decomposition are depicted in Table 7.3. In addition to the phenotypic correlations between scales, the genetic and environmental correlations are given. Their impact on the phenotypic





Table 7.4. Percentage of variance accounted for by the genetic and environmental factors common and specific to each variable in the independent and common pathway model

	Indep	endent p	athway n	nodel	Cor	mmon pa	thway mo	odel
	A <sub>c</sub>	E <sub>c</sub>	A <sub>s</sub>	E <sub>s</sub>	A <sub>c</sub>	E <sub>c</sub>	A <sub>s</sub>	E <sub>s</sub>
Al	28%	25%	3%	44%	27%	26%	4%	43%
IP	20%	27%	1%	42%	23%	23%	10%	44%
NR	24%	26%	9%	41%	24%	23%	10%	43%
SH	6%	6%	20%	68%	6%	6%	20%	68%
BPD	-	-	-	-	51%	49%	-	-

Note. Al = affective instability; IP = identity problems; NR = negative relationships; SH = self-harm; BPD = borderline personality disorder;  $A_c$  = common genetic factor;  $E_c$  = common unique environmental factor;  $A_s$  = specific genetic factor;  $E_s$  = specific unique environmental factor.

correlation is weighted by the heritability's (h²) and environmentalities (e²) of the scales. The heritability estimates for AI, IP, NR and SH were 31% (95% CI 27%-35%), 31% (95% CI 26%-35%), 35% (95% CI 31%-39%) and 26% (95% CI 22%-30%), respectively and the remainder of the variance was explained by e². The genetic risk factors for AI, IP and NR were strongly correlated ( $r_{\rm g}$  0.67 to 0.81) while the genetic risk factors for SH and the other three scales were moderately correlated ( $r_{\rm g}$  0.37 to 0.46). The same pattern was seen for the environmental correlations. The phenotypic correlations between the four scales were explained half by genetic effects and half by unique environmental effects.

Next we fitted two models with different theoretical implications on this pattern of covariances: the independent pathway and the common pathway model. The estimated path coefficients of these models are depicted in Figure 7.2. The path coefficients were standardized and squared to calculate the proportion of variance accounted for by the latent predictor variables A and E, shown in percentages in Table 7.4. For example, the total variance in AI in the independent pathway model is 0.63 (0.40<sup>2</sup> + 0.42<sup>2</sup> + 0.14<sup>2</sup> + 0.532). The variance in AI accounted for by the common genetic factor divided by the total variance gives the proportion of variance in AI accounted for by the common genetic factor  $(0.42^2 / 0.63 = 0.28)$ . The independent pathway model shows that around 20% to 28% of the variance in AI, IP and NR can be explained by a common genetic factor while only 6% of the variance in SH can be explained by the common genetic factor. However, SH did load significantly on the common genetic factor since this path could not be left out of the model without a significant deterioration of the fit of the model. To calculate the percentage of variance accounted for by the latent predictor variables A and E in the common pathway model, a similar procedure is followed. For example, the total variance in IP is  $0.50 (0.48^2 + 0.22^2 + 0.47^2)$ . The variance in IP accounted for





### $\mathsf{A}_\mathsf{c}$ $E_c$ 0.36 0.37 (0.32-0.40)(0.33-0.41) 0.20 0.20 (0.16-0.25)(0.15-0.20) 0.31 0.37 (0.28-0.35)(0.33-0.41) 0.42 0.40 (0.38-0.47)(0.36-0.44) IΡ NR SH ΑI

0.22 0.47 (0.17-0.26)(0.46-0.49)

 $\mathsf{E}_\mathsf{s}$ 

0.36 0.66 (0.31-0.40)(0.65-0.67)

 $\mathbf{E}_{\mathsf{s}}$ 

### Common pathway model

0.24 0.46 (0.20-0.27)(0.43-0.48)

 $\mathsf{E}_\mathsf{s}$ 

0.14 0.53 (-0.20-0.21) (0.51-0.56)

 $\mathsf{E}_\mathsf{s}$ 

Independent pathway model

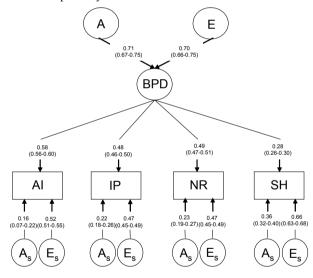


Figure 7.2. Graphical representation and path coefficients (95% confidence intervals) of the independent pathway model and the common pathway model.

Note. Al = affective instability; IP = identity problems; NR = negative relationships; SH = self harm; BPD = borderline personality disorder; A = genetic factor common to multiple traits; E = unique environmental factor common to multiple traits; A = specific genetic factors; E = specific unique environmental factors. All latent A and E factors have unit variance.



Table 7.5. Genetic tries	mod	el fitting	results i	includi	ing data	a from	the t	hree coun-
	vs	-2 LL	df	Χ²	$\Delta df$	Р	AIC	BIC
I Cholesky		55,284.2	26,589					
2. Independent path- way model	I	55,287.5	26,593	3.3	4	0.51	-4.7	-82,315.092
3. Common pathway model	I	55,291.8	26,596	7.7	7	0.36	-6.3	-82,333.577

Note. Vs = versus; -2 LL = -2 log likelihood; df = degrees of freedom; AIC = Akaike's information criterion; BIC = Bayesian information criterion.

by genetic variation in the common factor can by calculated by dividing the product of the additive genetic variance of the latent predictor variable and the variance in IP accounted for by the latent predictor variable by the total variance in IP ((0.71²\*0.48²) / 0.50 = 0.23). In the common pathway model all scales load significantly on the latent BPD factor, but SH the least strongly (6% for SH and 27%, 23% and 24% for AI, IP and NR respectively). Genetic model fitting results are summarized in Table 7.5. Both the independent pathway and the common pathway model did not fit the data significantly worse than the Cholesky decomposition. Based on the principle of model parsimony (the least complex model which gives an adequate account of the data), the common pathway model explained the data best. The four main features of BPD thus co-occur as a result of genetic and environmental factors that influence the four component in similar ways, through a latent predictor variable (the BPD construct).

## DISCUSSION

The aim of the present study was to examine the relationship between the four scales of the PAI-BOR, reflecting four main features of BPD, in terms of genetic and environmental risk factors. Because BPD is a complex disorder with various manifestations, exploring the main features of BPD may lead to a better understanding of the etiology of BPD. We first established that there is a substantial association among the four scales. We then applied a series of multivariate genetic factor models, including the independent pathway and the common pathway models, to investigate the etiology of this association between the scales at the level of genetic and environmental influences. The common pathway model was the most parsimonious. This model tests the assumption that the covariation among the four scales is determined by a single latent factor. Genetic and environmental factors thus influence AI, IP, NR and SH through the same mecha-

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nism. Additive genetic factors explained 51% of the variance in the latent BPD factor and unique environmental factors explained the remaining 49%. This heritability estimate is somewhat higher than the estimate we obtained for the total PAI-BOR score (h2= 0.42; Distel et al., 2008a), which was based on a sum score of all items and on data of twins only. In the present study, the four scales AI, IP, NR, and SH were moderately heritable with estimates ranging from 26% (SH) to 35% (NR). These estimates were equal for men and women and the same genes influenced variation in men and women. Thus, although BPD is more often diagnosed in women than in men, there is no evidence for gender differences in genetic and environmental effects on BPD. In addition, there was no support for a different factor structure for men and women. All scales load substantially on the latent BPD factor except for SH of which only 12% of the variance is explained by the common factor. Each scale was also influenced by specific genetic factors, which do not overlap with each other. These genetic factors specific to each scale explained a much smaller amount of variance than the common genetic factor, except for SH (4% versus 27% for AI, 10% versus 23% for IP, 10% versus 24% for NR and 20% versus 6% for sH). Thus there is support for a genetic factor which makes individuals vulnerable to all four main features of BPD. In addition, genetic effects specific to each scale contribute modestly to individual differences in each of the four scales.

Though the twin correlations suggested a contribution of non-additive genetic influence, non-additive genetic effects were not significant. This may be partly due to the low statistical power of the classical twin study to resolve the effects of genetic non-additivity (Martin & Eaves, 1977; Neale et al., 1994b; Visscher, 2004). The heritability estimate in this study is thus likely to include some non-additive effects.

An interesting finding of our study is the strong unique environmental covariance between the four scales of the PAI-BOR. This means there are environmental factors which simultaneously increase the risk for AI, IP, NR and SH. Many studies into the etiology of BPD focused on the environmental determinants of BPD and demonstrated that traumatic life events such as sexual or physical abuse and parental divorce, loss or illness are generally 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). Also, the total number of negative life events to which BPD patients have been exposed is higher than for control subjects (Horesh et al., 2008; Jovev & Jackson, 2006). Based on this study it is likely that these life events influence all four main features of BPD. However, not all individuals who have experienced a traumatic event develop BPD, thus a genetic vulnerability in addition to the influence of environment is a likely requirement. Also, gene-environment interaction in which the effect of exposure to environmental factors depends on a person's genotype may play a role. In the presence of gene-environment interaction, individuals with

a 'sensitive' genotype will be at greater risk if the predisposing environment is present, than individuals with an 'insensitive' genotype (Boomsma & Martin, 2002c; Rutter, 2007). If gene by environment interaction is present for BPD, this will have increased the estimates for E. In addition, certain life events may be a consequence, rather than a cause, of BPD features.

Several limitations should be kept in mind when interpreting the results of this study. First, some selection bias may have been present in the sample. The Dutch sample, which constituted the largest in the present study, was shown to be representative of the general population with regard to a number of variables such as socioeconomic status, smoking behavior, and religion (Boomsma et al., 2002b). However, individuals from less cooperative families (i.e., families in which only some individuals participate) show slightly more borderline personality features than individuals from highly cooperative families (i.e., families in which most individuals participate) (Distel et al., 2007). Second, while the four scales of the PAI-BOR are all important clinical characteristics of the disorder, one (Fossati et al., 1999), two (Rosenberger & Miller, 1989) and three (Clarkin et al., 1993; Sanislow et al., 2000, 2002) factor structures have also been reported when different measures are used.

In conclusion, the results of this study suggest that genetic and environmental effects influence affective instability, identity problems, negative relationships, and self-harm through an intermediate phenotype, the BPD construct. A single genetic factor underlies most of the genetic variance in this latent variable and thus in most symptoms, although genetic effects specific to each components are also present, particularly for SH. This is important for future studies trying to find the causative genes for BPD features.









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# CHROMOSOME 9: LINKAGE FOR BORDERLINE PERSONALITY DISORDER FEATURES

Marijn A. Distel, Jouke J. Hottenga, Timothy J. Trull, & Dorret I. Boomsma (2008). Chromosome 9: Linkage for borderline personality disorder features. *Psychiatric Genetics*, 18, 302-307.

### **ABSTRACT**

Objective A large-scale twin study implicated genetic influences on borderline personality disorder (BPD) features, with a heritability estimate of 42%. To date, no genome-wide linkage study has been conducted to identify the genomic region(s) containing the quantitative trait loci that influence the manifestation of BPD features.

*Methods* We conducted a family-based linkage study using Merlin-regress. The participating families were drawn from the community-based Netherlands Twin Register. The sample consisted of 711 sibling pairs with phenotype and genotype data, and 561 additional parents with genotype data. BPD features were assessed on a quantitative scale.

*Results* Evidence for linkage was found on chromosomes 1, 4, 9 and 18. The highest linkage peak was found on chromosome 9p at marker D9S286 with a logarithm of odds score of 3.548 (empirical p = 0.0001).

Conclusion To our knowledge, this is the first linkage study on BPD features and shows that chromosome 9 is the richest candidate for genes influencing BPD. The results of this study will move the field closer to determining the genetic etiology of BPD and may have important implications for treatment programs in the future. Association studies in this region are, however, warranted to detect the actual genes.





### INTRODUCTION

ORDERLINE PERSONALITY DISORDER (BPD) is characterized by emotional lability, impulsivity, interpersonal difficulties, identity disturbances, and cognitive impairments (American Psychiatric Association, 2000). BPD is often comorbid with other personality and mood disorders and is associated with poor short-term treatment outcomes (Skodol et al., 2002b). Individuals with BPD are well represented in treatment settings, accounting for 10% of all outpatients and 15-20% of all inpatients (Skodol et al., 2002a). BPD is associated with a number of negative outcomes, including suicidal behavior, frequent emergency room admissions, substance abuse, impaired occupational functioning, and poor quality of interpersonal relationships. Recent estimates from the us general population suggest that approximately 1% of adults meet diagnostic criteria for this disorder. BPD is equally prevalent among men and women and more likely to be diagnosed in early adulthood (Lenzenweger et al., 2007).

A recent, multi-national, large-scale twin study implicated genetic influence on BPD features, with a heritability estimate of 42% (Distel et al., 2008a). A study into the genetic covariance structure between four main features of BPD suggested that a single genetic factor underlies most of the genetic variance in BPD symptoms (Distel et al. 2009c), and this is the optimal case for the goal of the present study: to conduct a genome-wide linkage analysis to help identify chromosomal regions that may harbor the gene(s) that influence the development of BPD. To date, we know of no linkage study that has been conducted to help identify the genomic region(s) that contain the quantitative trait loci that influence the manifestation of BPD features.

### **MFTHODS**

### **Participants**

This study is part of an ongoing study on health and lifestyle in twin families registered with the Netherlands Twin Register (NTR; Boomsma et al., 2006a). Surveys on health and lifestyle were sent to the twin families every 2-3 years. For this study, data from the seventh survey, which was sent in 2004-2005, were used. Details on response rate and demographic characteristics of the sample have been described elsewhere (Distel et al., 2007, 2008a).

Survey data from 5,234 twins and siblings were available of whom a subsample was also invited to provide DNA through buccal swab or whole blood (Boomsma et al., 2000, 2006b; Middeldorp et al., 2006). Phenotype and genotype data were available for 1,032

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siblings from 505 nuclear twin families of which 10 families were also related at second degree (and analyzed as such). There were 300 dizygotic male twins and brothers and 510 dizygotic female twins and sisters (in total 711 sibling pairs). There were 87 families consisting of at least one sibling plus a monozygotic twin pair and two families with only a monozygotic twin pair. Monozygotic twin status was specified in Merlin and phenotype and genotype data from both monozygotic twins were included in the analysis. Monozygotic twin pairs do not provide information for linkage, but data from monozygotic twins give information on the total genetic contribution to trait variance. To estimate identity by descent, genotype data from 561 additional parents were included. All participants gave their informed consent and the study was approved by the appropriate ethical committees.

For receiver operating character (ROC) analysis, Personality Assessment Inventory-Borderline Features scale (PAI-BOR) data were collected from an independent sample of 62 BPD outpatients and a control group of 45 psychiatric participants without BPD but with current major depressive disorder (MDD) or dysthymia (DYS). All patient data were obtained from an ongoing experience sampling study of affective instability (Trull et al., 2008b). After diagnostic interviewing to establish eligibility for the study, patients completed the PAI-BOR and other questionnaires before starting the experience sampling phase of the study. Psychiatric diagnoses were established with Axis I and Axis II interviews, and reliability of the assigned diagnoses was checked by independent raters who reviewed audiotapes of a random sample of the 14 participants. Agreement was excellent for a diagnosis of MDD/DYS ( $\kappa$  = 1.0), a diagnosis of BPD ( $\kappa$  = 0.85), and the number of BPD symptoms present (intraclass correlation coefficient = 0.96). For the entire sample of patients, the average age of participants was 33.69 (SD = II.73), and the majority of participants were women (86.9%), white non-hispanic (87.9%), single/divorced/separated (67.3%), and reported a family income of \$25000 or less (72.0%). Fifty percent of the sample reported being currently employed full or part time. Most participants reported at least one previous psychiatric hospitalization (52.3%).

### Measures

BPD features were measured by the PAI-BOR (PAI-BOR; Morey, 1991, 2003). PAI-BOR items tap features of severe personality pathology that are clinically associated with BPD. The PAI-BOR consists of 24 items that are rated on a four-point scale (0 to 3; false, slightly true, mainly true, very true). The items consist of statements concerning, for example, stability of mood and affects, emotionally responsiveness, anger control, self-image, feelings of emptiness, intense and unstable relationships, loneliness, impulsivity, self-harm and recklessness. Several studies have supported the reliability and the validity of total PAI-BOR scores in indexing the degree to which BPD features are present (Morey, 1988; 1991; Trull, 1995, 2001b). Kurtz & Morey (2001), for example, showed that PAI-





BOR scores correlated 0.78 with a structured interview-based assessment of BPD. The PAI-BOR was scored according to Morey's test manual, which states that at least 80% of the items must be answered to calculate a sum score and that missing and ambiguous answers should be substituted by a zero score (Morey, 1991, 2003).

### Statistical analysis

To evaluate the accuracy of the PAI-BOR to identify individuals with BPD, ROC analyses were conducted among participants in the BPD patient group and the MDD/DYS psychiatric control group. ROC analyses plot the proportion of individuals correctly classified as BPD (true positive rate; sensitivity) by the proportion of individuals falsely classified as BPD (false positive rate; I- specificity) at different PAI-BOR score cutoff points. This plot is used to examine the ability of the PAI-BOR to discriminate between individuals with and without BPD. The area under the curve indicates how well the PAI-BOR performs. A value of 0.50 indicates no discrimination (chance level) and a value of 1.0 indicates perfect discrimination between BPD patients and non-BPD patients (Swets, 1996; Mcfall & Treat, 1999). The positive predictive value was calculated by dividing the number of true positives by the sum of the number of true positives and false positives; the negative predictive value was calculated by dividing the number of true negatives by the sum of the number of true negatives and false negatives. ROC analyses were carried out in SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Earlier genetic analysis of the PAI-BOR scores of 5,496 male and female twins from the Netherlands, Belgium and Australia showed a heritability of 42% (Distel et al., 2008a). There was no evidence that different genes influence BPD features in men and women, as same-sex and opposite-sex twin and sibling correlations were the same. The results of the genetic analyses were the same across three different countries. As women and younger participants tend to have higher scores on the PAI-BOR, scores were adjusted for sex and age before linkage analysis, using linear regression in the entire sample.

DNA from the siblings and their parents was extracted from either whole blood or buccal swabs following standard protocols (Miller et al., 1988; Distel et al., 2008a; Meulenbelt et al., 1995). Genotyping was performed by the Mammalian Genotyping Service in Marshfield and the Molecular Epidemiology Section, Leiden University Medical Centre (Sullivan et al., 2006). The genotype data from these screens were aligned with their allele calling and binning and then combined using approximately 30 duplicate samples. In case there were inconsistencies, the data were set to unknown for tested markers (binning and allele calling inconsistencies), and persons (genotyping errors). Sex and zygosity measured earlier were confirmed with the marker data. Pedigree relations were checked with the GRR program (Abecasis et al., 2001). Errors of Mendelian inheritance were detected with Pedstats (Abecasis et al., 2002). Markers and samples were removed if their total error rate was more than 1%, in all other cases





genotypes were set to unknown. Unlikely recombinants were detected with Merlin and erroneous genotypes were removed with pedwipe (Abecasis et al., 2002). After cleaning, only sibling pairs that had at least 200 autosomal markers genotyped for each individual were selected. The average heterozygosity of autosomal markers was 76.1% with an average spacing of 9.7 cM. The Haldane function was used for the statistical analysis; all reported values are in Kosambi cM. The marker positions were interpolated through locally weighted linear regression from the National Center for Biotechnology Information build 35.1 physical map positions and the Rutgers genetic map (Duffy, 2006; Kong et al., 2004).

The linkage analysis was performed with the full families; however, most information for linkage is obtained from sibling pairs. If a pair of siblings has received the same combination of alleles from a parent at a certain marker locus of the genome, the pair is said to share the parent's alleles at the locus identical by descent (IBD; Haseman & Elston, 1972). As offspring receive the alleles from two parents, the pair can share 0, 1 or 2 alleles IBD at a locus. If the marker locus is close to a causal gene, then IBD status at the marker locus reflects IBD status at the causal locus (Haseman & Elston, 1972). IBD status will then be associated with trait resemblance in sibling pairs. When the parents are homozygous at the marker locus or when the parents are not genotyped, IBD status can not be determined exactly. In this case, the probabilities of the pair being 0, 1 or 2 IBD are estimated, making use of the population allele frequencies. IBD estimation for all family pairs and linkage analysis were done with Merlin regress (Abecasis et al., 2002). Allele frequencies were calculated from the data in the whole genotyped sample (N = 1,593). Regression analysis implemented in Merlin regress is based on a modified method initially proposed by Haseman & Elston (1972). The multipoint IBD sharing is regressed on trait-squared sums and squared differences, for all pairs of relatives (Sham et al., 2002). The trait squared sums and differences indicate the resemblance and difference between relatives. The method takes into account incomplete IBD information, but requires the population mean, variance and heritability to be specified. The heritability of BPD features was specified at 42%, based on Merlin calculations after correction of age and sex. The same estimate was found in earlier genetic analyses of the PAI-BOR scores (Distel et al., 2008a). Linkage was made on the residual BPD scores corrected for sex and age and had values of 0.0 for the mean BPD score and 68.1 for the variance. Logarithm of odds (LOD) scores were calculated with a grid of I cM on the genome.

Empirical p values for the LOD scores were estimated with 2,500 replicates that were simulated under the null hypothesis of no linkage using the simulate option in Merlin. These replicates were analyzed under the same analysis conditions as the original data set. Point-wise empirical p-values were calculated for each location that showed evidence for linkage to determine the probability of the observed LOD score at a given position.

Table 8.1. Mean age and mean BPD score on the PAI-BOR for th	е
genotyped sample and for the total sample	

		Genotyped sa	ample		Total :	sample
	Ν	Mean age (SD)	Mean BPD score (SD)	Ν	Mean age (SD)	Mean BPD score (SD)
Male	369	38.6 (12.7)	13.2 (7.4)	1,663	36.4 (12.8)	14.5 (7.8)
Female	663	37.8 (11.2)	16.2 (8.7)	2,686	35.9 (11.3)	16.6 (8.4)
Total	1,032	38.1 (11.8)	15.1 (8.4)	5,234	36.1 (11.8)	16.0 (8.3)

Note. BPD = borderline personality disorder; PAI-BOR = Personality Assessment Inventory-Borderline Features scale.

Genome-wide empirical p-values were calculated to determine the probability of a certain LOD score given all LOD scores of 2,500 replicates genome-wide.

### RESULTS

Mean age and mean BPD score on the PAI-BOR for the genotyped sample (N = 1,032)and for the total sample (N = 5,234) are shown in Table 8.1. The participants in the genotyped sample were slightly older (38.1 vs. 36.1 years) and had slightly lower BPD scores (15.1 vs. 16.0), but the differences were small. Corrected for age, the difference in mean BPD score between the genotyped and total sample was even smaller; 1.12 and 0.28 for men and women, respectively, on a scale ranging from 0 to 72.

ROC analysis showed an area under the curve of 0.78 (95% confidence interval: 0.70-0.87) indicating that the PAI-BOR discriminates between BPD patients and MDD/DYS patients reasonably well. At the best cutoff point of 42, the sensitivity was 71% and the specificity 69%. The positive predictive value and negative predictive value were 76 and 64%, respectively.

Table 8.2. Ma	rkers and positions	of possible	QTLs		
Chromosome	Marker	Position cM Kosambi	LOD score	Point-wise p-value	Genome- wide p-value
1q31.1	D1S518	198	1.602	0.0048	0.0054
4p16.1	D4S2935 - DS403	19.6	1.491	0.0060	0.0069
9p24.1	D9S2169 - D9S286	15.7	3.548	0.0004	0.0001
18q23	D18S462	117.6	1.441	0.0116	0.0077

Note. LOD = logarithm of odds; QTL = quantitative trait loci.

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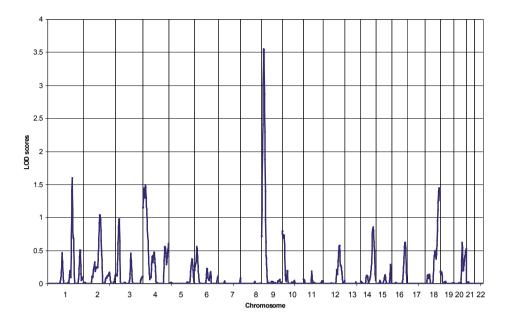


Figure 8.1. Results of the genome-wide linkage analysis of borderline personality disorder.

The results of the genome wide linkage scan for BPD features are shown in Figure 8.1. The strongest evidence of linkage was found on chromosome 9 at 15.7 Kosambi cM with a LOD score of 3.548 (empirical p = 0.0004, genome-wide p = 0.0001) (Figure 8.2). Suggestive linkage peaks were found on chromosomes 1, 4 and 18 with LOD scores of 1.602, 1.491 and 1.441, respectively. Table 8.2 provides an overview of the chromosome regions that may harbor genes influencing the development of BPD.

### DISCUSSION

BPD is a common psychiatric disorder associated with many negative outcomes. This is the first study aiming to detect the location of quantitative trait loci for BPD features as measured by the PAI-BOR. ROC analysis showed that the PAI-BOR performs reasonably well in discriminating BPD patients and non-BPD depressed psychiatric patients, supporting the validity of PAI-BOR scores. For this linkage analysis genotype and phenotype data from 1,032 offspring, and genotype data from 561 parents were used. Significant linkage was found on chromosome 9 near marker D9S286, with a LOD score of 3.548 and a genome-wide empirical p value of 0.0001. In addition, suggestive linkage signals were found on chromosomes 1q31 (p = 0.0054), 4p16 (p = 0.0069) and 18q23 (p = 0.0077).





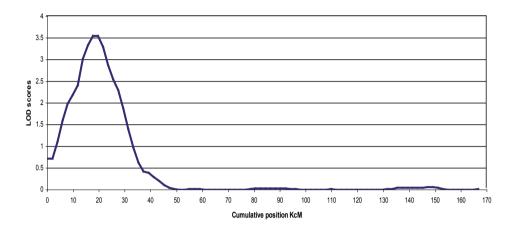


Figure 8.2. Results of the genome-wide linkage analysis for chromosome 9 with the position of the markers in cM (Kosambi) on the x-axis.

There were six families in the sample that included individuals with very high PAI-BOR scores. These families had a relatively large contribution to the LOD score on chromosome 9 in the Merlin regress analysis. We examined the PAI-BOR scores and additional information of these individuals more closely and found some to being diagnosed with BPD and some using antidepressive medication.

To evaluate if our linkage results are also associated with other psychiatric disorders we consulted the search engine designed by P. Sullivan: Sullivan Lab Evidence Project: psychiatric genetics-vo9 (SLEP; https://slep.unc.edu/evidence). Our most pronounced linkage result, the region on chromosome 9p24, has been associated with other psychiatric disorders before in linkage studies. A genome-wide linkage scan for bipolar disorder obtained a linkage signal on chromosome 9p24 (D9S286), but it did not reach significant evidence for linkage [non-parametric linkage (NLP) 1.55, p = 0.063] (Fallin et al., 2004). Although BPD and bipolar disorder are distinct disorders, the symptoms (especially relating to affective instability) do show considerable overlap (Deltito et al., 2001). A genome wide linkage scan for schizophrenia also showed suggestive evidence for linkage on 9p24, but at another marker close by (D9S288; NPL 1.70, p = 0.05) (Faraone et al., 1998).

We found some evidence of a relationship of BPD with the region surrounding D1S238/D1S518 (1q31.1), which was also reported by Garver et al. (2001) (D1S518; NLP 1.56, p = 0.029) for schizophrenia. In the surrounding area of our linkage signal on chromosome 4p15-16, a signal for schizophrenia was detected by Lerer et al. (2003) (D4S394;





NPL 2.18, p = 0.02). The 18q23 region is also mentioned by two other studies for bipolar disorder. The NIMH Genetics Initiative Bipolar Group reported that the D18S70 marker showed allele sharing with nominal p < 0.05 in a genomic survey of 97 families with multiple cases of bipolar illness (Nurnberger et al., 1997). McInnis et al. (2003) found a NLP peak at D18S878 (18q22) of 2.9 (p = 0.004) for bipolar disorder.

To determine the importance of chromosomes I, 4, 9 and I8 in the development of BPD it is essential that the results of the present study are replicated by others. If the results are replicated in other samples, candidate genes under the peaks can be considered for association analysis. Localizing and identifying the genes that influence the development of BPD will not only be important for scientific purposes, but will also have clinical implications. A better insight into the etiology of BPD may have great implications for the development of both pharmacologic and psychosocial treatment programs in the future.









129

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# THE FIVE FACTOR MODEL OF PERSONALITY AND BORDERLINE PERSONALITY DISORDER: A GENETIC ANALYSIS OF COMORBIDITY

Marijn A. Distel, Timothy J. Trull, Gonneke Willemsen, Jacqueline M. Vink, Catherine A. Derom, Michael T. Lynskey, Nicholas G. Martin & Dorret I. Boomsma. The Five Factor Model of personality and borderline personality disorder: A genetic analysis of comorbidity. *Biological Psychiatry*, in press.

### **ABSTRACT**

*Background* Recently, the nature of personality disorders and their relationship with normal personality traits has received extensive attention. The five factor model (FFM) of personality, consisting of the personality traits neuroticism, extraversion, openness to experience, agreeableness and conscientiousness, is one of the proposed models to conceptualize personality disorders as maladaptive variants of continuously distributed personality traits.

*Methods* The present study examined the phenotypic and genetic association between borderline personality and FFM personality traits. Data were available for 4,403 monozygotic twins, 4,425 dizygotic twins and 1,661 siblings from 6,140 Dutch, Belgian and Australian families.

Results Broad-sense heritability estimates for neuroticism, agreeableness, conscientiousness, extraversion, openness to experience and borderline personality were 43%, 36%, 43%, 47%, 54%, and 45%, respectively. Phenotypic correlations between borderline personality and the FFM personality traits ranged from 0.06 for openness to experience to 0.68 for neuroticism. Multiple regression analyses showed that a combination of high neuroticism and low agreeableness predicted borderline personality best. Multivariate genetic analyses showed the genetic factors that influence individual differences in neuroticism, agreeableness, conscientiousness and extraversion account for all genetic liability to borderline personality. Environmental effects on borderline personality however, were not completely shared with those for the FFM traits (33% is unique to borderline personality).

*Conclusions* Borderline personality shares all genetic variation with neuroticism, agreeableness, conscientiousness and extraversion. The unique environmental influences specific to borderline personality may cause personality traits to develop into borderline personality.

### INTRODUCTION

EVERAL RESEARCHERS HAVE proposed to conceptualize personality disorders as maladaptive variants of continuously distributed normal personality traits (Livesley & Jang, 2005; Clark, 2007; Widiger & Lowe, 2008; Trull & Durrett, 2005). Such a dimensional approach provides quantitative estimates of the degree to which relevant personality traits are present in each individual. This representation of personality disorders has several advantages. Firstly, a dimensional representation helps to explain symptom heterogeneity and the lack of clear boundaries between different categorical diagnoses. Secondly, important information is retained about subthreshold traits and symptoms which may be of clinical and empirical interest. Finally, dimensional models allow us to integrate scientific findings concerning the distribution of personality traits and associated maladaptivity into a classification system (Trull et al., 2007).

A number of dimensional models of personality and personality disorders have been suggested. Some are based on personality traits that underlie personality disorders; others are designed to measure normal personality. Within the first category fall Livesley's Dimensional Assessment of Personality Pathology (DAPP; Livesley, 2006) inventory which identifies four higher order dimensions underlying personality pathology or Clark's Schedule for Nonadaptive and Adaptive Personality (SNAP; Clark, 1993) model which specifies 12 dimensions of maladaptive personality function. The second category contains for instance Cloninger's seven factor model (Cloninger et al., 1993), which distinguishes four dimensions of temperament, and three dimensions of character, or the Five Factor Model (FFM; Costa & McCrae, 1992) of personality which distinguishes five domains of personality. This last, FFM of personality is the most popular one and is often promoted for inclusion in the fifth edition of the Diagnostic and Statistical Manual (DSM) for mental disorders (Widiger & Lowe, 2008).

In this study we investigate the association between borderline personality disorder (BPD) features and FFM personality traits (neuroticism versus emotional stability, extraversion versus introversion, openness versus closeness to experience, agreeableness versus antagonism and conscientiousness versus irresponsibility). BPD is characterized by disturbances in emotional regulation, impulse control, interpersonal relationships, and identity. Until now, studies into the relationship between FFM personality traits and BPD focused on analyses at the phenotypic level. Widiger and Costa (2002) reviewed 56 studies into the association between DSM-IV personality disorders and the FFM and showed that borderline patients (measured in 35 studies) tend to score high on neuroticism and low on agreeableness and conscientiousness. Two meta-analytic studies of FFM personality disorder research confirmed this association (Saulsman & Page, 2004; Samuel & Widiger, 2008).





The heritability of the FFM personality traits has been studied intensively, showing broad-sense heritability estimates ranging from 33% to 65% (Jang et al., 1996c; Riemann et al., 1997; Vernon et al., 2008; Loehlin et al., 1998; Waller, 1999). In studies with sufficient statistical power the influence of both additive and non-additive genetic factors is suggested. Genetic studies of BPD are scarce. Only three large scale studies so far investigated the genetic liability for BPD and BPD features reporting broad-sense heritability estimates around 40% (Distel et al., 2008a, 2009a; Torgersen et al., 2008). Applying a multigenerational design to the data, Distel et al. (2009a) established that additive and non-additive genetic factors explain familial resemblance in BPD features.

If an association between normal personality traits and BPD is also found at the genetic level, this provides further evidence in favor of a dimensional model of personality disorders. Multivariate genetic analysis can address this issue (Martin & Eaves, 1977; Boomsma & Molenaar, 1986; Middeldorp et al., 2005a; Kendler et al., 2008). In multivariate genetic analysis the comorbidity or covariance between traits is decomposed into a genetic and an environmental part. The genetic contribution to the covariance between traits is a function of the genetic correlation between the traits and the square root of the heritabilities; likewise the environmental contribution is a function of the environmental correlation weighted by the square root of the proportions of variance explained by environmental factors. The phenotypic, genetic and environmental covariance structures among a set of variables is not necessarily the same: for example, the phenotypic correlation among traits can be low while the genetic correlation is high, meaning that the overlap that is there is predominantly explained by an overlap in genes.

In this paper we explore the genetic etiology of the relationship between border-line personality and the FFM personality traits. Data on borderline personality and FFM personality traits were available for 10,489 twins and siblings from Dutch, Belgian and Australian twin registries. We first analyze the phenotypic variance in these traits in a series of univariate genetic analyses to determine the genetic and environmental contributions to variation. The large sample size and the inclusion of data of siblings in the analyses allows for the investigation of additive and non-additive genetic effects (Posthuma & Boomsma, 1999). Next, the association between borderline personality and the FFM personality traits is explored with correlational and multiple regression analysis. Finally, multivariate genetic analyses are applied to determine to what extent the phenotypic association is due to genetic and environmental associations among traits.

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### **METHODS**

### **Participants**

Data were collected as part of a project on borderline personality in Dutch, Belgian and Australian twin family cohorts. Twins and siblings were approached by mail and invited to participate in the study by completing a questionnaire. In total there were 11,050 twins and siblings registered with the Netherlands Twin Register (Boomsma et al., 2006a), the East Flanders Prospective Twin Survey (Derom et al., 2006), and the Australian Twin Register (Jardine et al., 1984) who completed the questionnaire. Twins with unknown zygosity (N = 247), individuals with unknown age (N = 27), individuals under the age of 18 (N = 37), half-siblings (N = 17), individuals without a borderline score (N = 35), scores on the FFM personality traits (N = 106) or neither (N = 42) were excluded. A maximum of two brothers and two sisters per family were included in the analyses; remaining siblings were excluded (N = 50). This resulted in a total sample for analysis of 1,336 monozygotic male twins, 773 dizygotic male twins, 3,067 monozygotic female twins, 1,751 dizygotic female twins, 778 males from dizygotic opposite sex pairs, 1,123 females from dizygotic opposite sex pairs and 609 brothers and 1,052 sisters from 6,140 families. The mean age of the total sample was 33 years (SD = 9.97, range 18-90).

Zygosity of same-sex twins was determined from DNA polymorphisms or from selfreport answers to validated survey questions on physical twin resemblance and confusion of the twins. Further details on response rates, demographic characteristics of the sample and zygosity determination procedures can be found elsewhere (Nyholt, 2006; Distel et al., 2007, 2008a; Derom & Derom, 2005).

### Measures

Borderline personality was assessed with the 24-item Personality Assessment Inventory-Borderline Features scale (PAI-BOR; Morey, 1991, 2003). The PAI-BOR consists of 24 statements concerning, for example, stability of mood and affects, anger control, self image, feelings of emptiness, intense and unstable relationships, loneliness, impulsivity and self-harm, that are to be rated on a four-point scale (0 to 3; false, slightly true, mainly true, very true). Several studies have supported the reliability and the validity of total PAI-BOR scores in indexing the degree to which main personality characteristics of borderline personality disorder are present (Stein et al., 2007; Morey, 1991; Trull, 1995). Receiver operating characteristic analysis showed that the PAI-BOR discriminates reasonably well between borderline patients and patients with major depression disorder or dysthymia (AUC = 0.78). At the best cut-off point of 42 the sensitivity was 71% and the specificity 69% (Distel et al., 2008b). Multigroup confirmatory factor analysis showed that the PAI-BOR is measurement invariant across sex and age (De Moor et al., 2009). The test-retest





reliability and internal consistency (Cronbach's α) of the Dutch version of the PAI-BOR are 0.78 and 0.84, respectively (Distel et al., 2008a). The PAI-BOR was scored according to the test manual, which states that at least 80% of the items must be answered to calculate a sum score and that missing and ambiguous answers should be substituted with a zero score (Morey, 1991).

FFM personality traits were measured by the *NEO Five Factor Inventory* (NEO-FFI), a shortened version of the NEO-PI-R (Costa & McCrae, 1992). The NEO-FFI contains 60 items which are to be rated on a five point scale (1 to 5; *totally disagree, disagree, neutral, agree, totally agree*) and derives scores for the personality traits neuroticism, extraversion, openness to experience, agreeableness and conscientiousness. A score was calculated if no more than 9 items in total or 3 items per subscale were left unanswered. Missing and ambiguous answers were substituted with the neutral option.

### Genetic modelling

Twin family studies make use of the different degree of genetic relatedness of pairs of family members to estimate the relative contribution of genes and environment to the variance in a trait (Boomsma et al., 2002a). Monozygotic (MZ) twins are genetically (nearly) identical while dizygotic (DZ) twins share on average 50% of their segregating genes, like non-twin siblings. Quantitative genetic modelling is based on the fact that the phenotypic variance is a function of genetic (G) shared (C), and non-shared environmental (E) variance. Genetic variance can be additive (A), indicating that the effects of multiple alleles are additive, or non-additive (dominance; D) meaning that alleles at a particular locus interact. Twin correlations provide a first impression of the relative contribution of A, C, D and E. The more similar MZ twins are in their phenotypes compared to DZ twins and non-twin siblings, the more variance in a trait is caused by genetic effects. When the DZ correlation is less than half the MZ correlation, there is evidence for D. Differences within MZ twin pairs are due to E which also include measurement error (Boomsma et al., 2002a; Martin & Eaves, 1977). In multivariate analyses, a significant cross-twin cross-trait correlation suggests that there is a familial influence on the etiology of the correlation between traits. If the MZ cross-twin cross-trait correlation exceeds the DZ cross-twin cross-trait correlation this suggests that the familial influence on the correlation is at least partly genetic in origin. A twin-sibling design only provides information to model either an ACE model or an ADE model, and the choice of the model is based on the pattern of MZ and DZ twin and sibling correlations.

# Statistical analyses

All analyses were carried out using structural equation modelling in Mx (Neale et al., 2006a). Because the PAI-BOR data showed a somewhat skewed distribution, a square root data transformation was performed for this variable. We first ran univariate satu-





rated models for the FFM personality traits and borderline personality. In these models, we tested for the significance of sex differences in standard deviations and the heterogeneity of correlations of males versus females and DZ twins versus non-twin siblings. Because we analyze data from male and female twins and siblings of varying age and from multiple countries we included effects of age, sex and country on the mean scores. With genetic models we estimated the extent to which A, D and E influence the variance in these variables.

Next, in a multivariate saturated model phenotypic correlations and cross-twin cross-trait correlations were estimated. These correlations show the association between BPD features and the FFM personality traits and the importance of genetic and environmental influences on this association. We tested whether the correlations differed for males and females and between the countries.

Comparison of different models was done by means of likelihood-ratio tests, by subtracting the negative log likelihood (-2LL) for a more restricted model from the -2LL for a more general model. This yields a statistic that is distributed as  $\chi^2$  with degrees of freedom (df) equal to the difference in the number of parameters in the two models. If the  $\chi^2$ -test yields a p-value higher than 0.01, the constrained model is deemed not significantly worse.

To determine which personality traits of the FFM predict the PAI-BOR score best and contributed most to the variance, multiple regression analysis was conducted. The FFM traits were included in the model as predictors and the PAI-BOR as dependent variable. Age, sex and country were also included in the model as predictors. Analyses were conducted using backward stepwise regression. In the first model all predictor variables were included in the regression equation:

PAI-BOR =  $\alpha$  + ( $\beta_{neu}$  \* Neu) + ( $\beta_{agr}$  \* Agr) + ( $\beta_{con}$  \* Con) + ( $\beta_{ext}$  \* Ext) + ( $\beta_{open}$  \* Open) + ( $\beta_{age}$  \* Age) + ( $\beta_{sex}$  \* Sex) + ( $\beta_{country}$  \* Country) +  $\epsilon$ , where  $\alpha$  and  $\epsilon$  stand for intercept and residual, respectively. As in the saturated model, a dummy coding was used for the effects on the mean of country. After fitting the full regression model, the predictor explaining the least variance (as reflected in the squared product of the regression coefficient multiplied by the variance of the predictor [i.e.,  $\beta^2$  \* Var<sub>pred</sub>]) was dropped from the model. This procedure was repeated until all predictor variables were tested.

Finally, to determine to what extent borderline personality and the FFM dimensions share genetic liability, a multivariate triangular decomposition (Cholesky model) was fitted to the data in which a 5×5 phenotypic covariance matrix (openness was not included in this analysis; see results section) was decomposed into genetic and environmental covariance matrices (Neale & Cardon, 1992). A Cholesky model is a factor model in which the first variable loads only on the first factor, the second variable loads on the first two factors, and so on, yielding a triangular factor loading matrix. From the estimated path coefficients of latent genetic and environmental effects on each trait, we can



Table 9.1. Number of	twins (from compl	ete/incomplete t	win pairs) and	sib-
lings and sample descri	riptives for the Dut	ch, Belgian and A	Australian sam	ples

	Total sample	The Netherlands	Belgium	Australia
Sample configuration				
Monozygotic males	930/406	472/205	122/41	336/160
Dizygotic males	438/335	208/171	28/36	202/128
Monozygotic females	2,292/775	1,376/403	146/172	770/200
Dizygotic females	1,220/531	578/304	94/55	548/172
Dizygotic opposite sex	1,068/833	506/430	148/74	414/329
Brother	609	509	6	94
Sister	1,052	892	17	143
Total	10,489	6,054	939	3,496
Sample descriptives				
Mean age (SD)	33.02 (9.97)	35.33 (11.81)	28.48 (6.92)	30.24 (4.61)
Age range	18-90	18-90	18-67	18-45
% females	67%	68%	66%	65%

calculate the standardized covariance and correlations for genetic and environmental overlap between the different traits.

### **RESULTS**

The sample configuration and the descriptive statistics of the sample are provided in Table 9.1. The upper part of Table 9.2 describes the mean structure (full model) of the FFM personality traits and borderline personality. The description includes a mean value for each trait in 18 year old men, and regression of these scores on sex (deviation for women), age (deviation per increasing age year) and country of origin. The personality traits extraversion versus introversion, agreeableness versus antagonism and conscientiousness versus irresponsibility are negatively associated with borderline personality. We therefore recoded the data of these three variables by multiplying each score by minus I, such that the associations between BPD and all five personality traits were positive. We therefore refer to introversion versus extraversion, antagonism versus agreeableness and irresponsibility versus conscientiousness. All mean scores were dependent on sex, except for introversion versus extraversion ( $\chi^2_{(i)}$  = 1.96, p = 0.161), and age (all p < 0.01). In the Belgian sample mean scores for irresponsibility versus agreeableness, introversion versus extraversion and openness versus closeness to experience were significantly different from the mean scores in the Dutch sample (all p < 0.001) and in the Australian sample mean scores for neuroticism versus emotional stability, antagonism versus agreeableness





males) and beta coefficients of the regression equation and standard deviations for males and females Table 9.2. Estimated twin and sibling correlations for the FFM personality traits and borderline personality, intercepts (mean score at age 18 for Neuroticism-Antagonism-Irresponsibility-Conscientiousness Introversion-Openness-closeness to

**Emotional stability** 

Agreeableness

Extraversion

experience

Borderline personality

Intercept	28.71	-42.36	-44.03	-43.35	37.06
βsex=female	3.05	-2.76	-0.85	0.19	0.39
βage	-0.05	-0.04	-0.03	0.08	-0.02
βAustralia	0.93	-I.34	-1.44	0.39	1.86
βBelgium	2.65	0.59	0.04	0.15	-0.08
SD males	7.59	5.18	5.89	6.04	6.06
SD females	8.03	4.89	5.63	6.13	5.82
Twin and sibling correlations	lations				
MZ males	0.48	0.39	0.49	0.47	0.53
DZ males	0.14	0.14	0.11	0.29	0.28
MZ females	0.43	0.38	0.43	0.47	0.55
DZ females	0.24	0.18	0.22	0.16	0.28
DZ opposite sex	0.18	0.14	0.16	0.12	0.25
Brother-Brother	0.21	0.13	0.18	0.06	0.27
Sister-Sister	0.21	0.19	0.18	0.19	0.28
Brother-Sister	0.13	0.11	0.16	0.16	0.27
All MZ	0.45	0.38	0.45	0.47	0.54
All DZ/sibling	0.19	0.15	0.17	0.16	0.26
Parameter estimates full genetic model	full genetic model	l		l	l
a²	0.31 (0.17 - 0.45)				) 1 - ) 7 - ) 7 - )
d <sup>2</sup>	0.14 (0.00 - 0.29)	0.22 (0.21 - 0.37)	0.24 (0.21 - 0.39)	0.17 (0.02 - 0.31)	0.51 (0.51 - 0.55)
,		0.22 (0.21 - 0.37)	0.24 (0.21 - 0.39) 0.21 (0.05 - 0.37)	0.17 (0.02 - 0.31) 0.31 (0.15 - 0.46)	0.51 (0.51 - 0.55)

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Table 9.3. Estimates of phenotypic correlations and monozygotic (MZ) and dizygotic/sibling (DZ,sib) cross trait correlations

	Phenotypic correlation						MZ/DZ,sib cross twin cross trait correlation					
	N/E	A/A	//C	I/E	O/C	R		A/A			O/C	В
Neuroticism/		, , , ,	0		0,0			, , , ,	0		0,0	
emotional												
stability	-						-					
Antagonism/												
agreeable-												
ness	0.32	-					0.14/0.08	-				
Irresponsibil-												
ity/conscien-												
tiousness	0.40	0.24	-				0.23/0.10	0.12/0.04	-			
Introversion/												
extraversion	0.50	0.27	0.35	-			0.29/0.11	0.13/0.05	0.21/0.08	-		
Openness/												
closeness to								-0.03/-		-0.02/-		
experience	0.01	-0.07	0.04	-0.10	-		0.04/-0.02	0.05	0.06/0.02	0.04	-	
Borderline												
personality	0.68	0.41	0.35	0.31	0.06	-	0.36/0.17	0.22/0.12	0.21/0.09	0.19/0.09	0.04/-0.01	-

Note. The variables agreeableness, conscientiousness and extraversion are recoded such that they reflect opposite traits which are positively associated with borderline personality features.

and irresponsible versus conscientiousness were significantly different from the mean scores in the Dutch sample. Thus, in subsequent genetic analyses the significant effects of sex, age and country of origin were included in the means model as a regression coefficient. Standard deviations were equal in males and females for introversion versus extraversion ( $\chi^2_{(1)}$  = 1.08, p = 0.298) but not for neuroticism versus emotional stability, for which the standard deviation was higher in females ( $\chi^2_{(1)} = 3.59$ , p < 0.001) and antagonism versus agreeableness ( $\chi^2_{(1)}$  = 15.76, p < 0.001), irresponsibility versus conscientiousness ( $\chi^2_{(1)}$  = 8.60, p = 0.003), and openness versus closeness to experience ( $\chi^2_{(1)}$ = 7.23, p = 0.007) for which the standard deviations were higher in males. The middle part of Table 9.2 shows the MZ and DZ twin and sibling correlations for males and females within each variable. Correlations were similar for DZ twins and siblings for all variables (all p > 0.01). For all variables, the correlations were equal for DZ males and females and for MZ males and females (all p > 0.01) suggesting that the heritability is the same for men and women. Additionally, the DZ and sibling same sex correlations were equal to the DZ and sibling opposite sex correlations (all p > 0.01) indicating that the same genes influence the variables in men and women. All MZ twin correlations were more than twice as large as the correlations for DZ twins and siblings indicating that the genetic effects that contribute to individual differences may be partly non-additive

Table 9.4. Regression coefficients and the	e proportions of ex	xplained variance
in borderline personality		

Predictor	β	β <sup>2</sup> *Var <sub>pred</sub>
Neuroticism/emotional stability	0.0832	0.4518
Antagonism/agreeableness	0.0456	0.0564
Irresponsibility/conscientiousness	0.0154	0.0079
Introversion/extraversion	-0.0148	0.0083
Openness/closeness to experience	0.0099	0.0035

(dominance) thus in subsequent analyses, A, D and E were modelled. Based on the results of the univariate model, variances for males and females were allowed to differ in all subsequent analyses for neuroticism versus emotional stability, antagonism versus agreeableness and irresponsibility versus conscientiousness by including a fixed scalar in the variance covariance model. The variance components for males were constrained to be equal to a scalar multiple (k²) of the female variance components. In this way, the standardized variance components were equal across sexes but the unstandardized variance components were allowed to differ (Neale & Cardon, 1992). Broad-sense heritability estimates ranged from 36% for antagonism versus agreeableness to 54% for introversion versus extraversion. Table 9.2 lists estimates of A, D, and E of the full models.

Next, phenotypic correlations and cross-twin cross-trait correlation for MZ and DZ twin and sibling pairs were estimated, which are shown in Table 9.3. Phenotypic correlations between borderline personality features and the FFM personality traits ranged from 0.06 (openness versus closeness to experience) to 0.68 (neuroticism versus emotional stability). BPD and openness versus closeness to experience thus do not share much etiological influences. Consistent with the expectation that the same genetic factors contribute to personality and personality pathology, all cross-twin correlations between the FFM personality traits and borderline features were stronger in MZ than in DZ twins.

Because the FFM personality traits are correlated among each other and 4 out of 5 scales are correlated with the PAI-BOR, stepwise backward multivariate regression analysis was run with the PAI-BOR scores as dependent variables, to investigate whether variance in borderline personality can be explained by FFM personality traits above and beyond neuroticism versus emotional stability. Even with a conservative p-value of p < 0.01, all variables significantly predicted the PAI-BOR score. However, openness versus closeness to experience explained less than 1% of the variance. In the regression model including all variables, neuroticism versus emotional stability best predicted the PAI-BOR score explaining 45% of the variance in borderline personality. Irresponsibility versus conscientiousness and introversion versus extraversion explained around 1% of the variance and antagonism versus agreeableness explained 6% of the variance. Regression coeffi-





Figure 9.1. Unstandardized path coefficients of the Cholesky model for the FFM personality traits and borderline personality. A1 through A5 = additive genetic factors; D1 through D5 = non-additive genetic factors; E1 through E5 = non-additive genetic factors have unit variance.



cients and the proportions of explained variance in borderline personality are shown in Table 9.4

To determine to what extent BPD and the FFM personality traits share genetic liability a multivariate model was fitted to the data. Openness versus closeness to experience was not included in these analyses since it does not correlate with borderline personality or the other FFM dimensions. A graphical representation of the model is depicted in Figure 9.1 (scalar not depicted). The path coefficients can be standardized and squared to calculate the proportion of variance accounted for by the latent predictor variables A, D and E. For example, the total variance in neuroticism is  $64.82 (4.55^2 + 2.85^2 + 6.0^2)$ . The variance in neuroticism versus emotional stability accounted for by the common genetic factor divided by the total variance gives the proportion of variance in neuroticism versus emotional stability accounted for by the common genetic factor (4.55<sup>2</sup>/ 64.82 = 0.32). Genetic and environmental correlations between the traits are shown in Table 9.5. Additive genetic correlations ranged from 0.18 to 0.95. The correlations between the environmental influences on the traits were moderate to high. Around 50% of the phenotypic correlation between borderline personality and the FFM traits can be explained by common genetic effects. The remaining variance can be explained by environmental effects common to borderline personality and the FFM personality traits. Based on the full model depicted in Figure 9.1, nearly all genetic variation is shared between the FFM traits and borderline personality and a substantial amount of environmental effects on borderline personality (33%) is specific to borderline personality. Testing the significance of the genetic factors (A+D) specific to borderline personality showed that these factors did not contribute significantly to variance in borderline personality ( $\chi^2$ <sub>(1)</sub> = 0.12, p = 0.944).

### DISCUSSION

In this study data from over 10,000 twins and siblings were analyzed to investigate the phenotypic and genetic association between five personality traits as assessed by the NEO-FFI, and borderline personality disorder as assessed with a quantitative scale (PAI-BOR).

Multivariate regression analysis showed that all FFM personality traits; neuroticism, agreeableness, conscientiousness, extraversion and openness to experience, significantly predict borderline personality scores. Borderline personality was positively associated with neuroticism and openness to experience and negatively with agreeableness, conscientiousness, and extraversion. Neuroticism (45%) and agreeableness (6%) explained the largest part of the variance, while conscientiousness and extraversion explained only 1% and openness to experience less than 1% of the variance. These findings are in line

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Table 9.5. Genetic and environmental correlations (left off diagonal) between the neuroticism, antagonism, irre-
sponsibility, introversion and borderline personality, estimates of A, D and E (right diagonal) and the proportion of
phenotypic correlation accounted for by A, D and E (right off diagonal)

	Additive §	Additive genetic correlation	rrelation			a <sup>2</sup> and %	a² and % of r, accounted for by A	unted for	by A	
	NE	A/A	NC	1/E	В	NE NE	A/A	1/2	I/E	В
Neuroticism/emotional stability	-					0.32				
Antagonism/agreeableness	09.0	-				0.50	0.22			
Irresponsibility/conscientiousness	0.59	0.18	_			0.41	0.17	0.24		
Introversion/extraversion	0.57	0.38	0.45			0.27	0.28	0.26	0.18	
Borderline personality	0.95	0.81	0.56	0.62	_	0.47	0.57	0.47	0.51	0.37
	Dominan	Dominant genetic correlation	orrelation			d² and %	d² and % of r, accounted for by D	unted for	by D	
Neuroticism/emotional stability	_					0.13	_			
Antagonism/agreeableness	-0.12	-				-0.05	0.16			
Irresponsibility/conscientiousness	0.40	0.44	_			0.16	0.34	0.22		
Introversion/extraversion	0.79	0.23	0.47			0.31	0.18	0.34	0.30	
Borderline personality	0.34	-0.07	0.28	0.18	_	0.05	-0.02	0.11	0.10	01.0
	Environm	Environmental correlation	elation			e <sup>2</sup> and %	and % of r accounted for by E	unted for	by E	
Neuroticism/emotional stability	_					0.55				
Antagonism/agreeableness	0.30	-				0.55	0.62			
Irresponsibility/conscientiousness	0.31	0.20	_			0.43	0.49	0.55		
Introversion/extraversion	0.39	0.26	0.26			0.42	0.54	0.40	0.53	
Borderline personality	0.59	0.32	0.27	0.22	_	0.47	0.45	0.42	0.39	0.54

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Note.  $a^2$  = proportion of variance explained by additive genetic factors;  $d^2$  = proportion of variance explained by dominant genetic factors;  $c^2$  = proportion of variance explained by unique environmental factors;  $c^2$  = phenotypic correlation.

with previous studies reporting the association between the FFM personality traits and BPD (Saulsman & Page, 2004; Samuel & Widiger, 2008).

Also in line with previous studies (Jang et al., 1996b; Riemann et al., 1997; Vernon et al., 2008; Loehlin et al., 1998; Waller, 1999) genes contributed significantly to the variance in personality traits, with broad-sense heritability estimates ranging from 36% for agreeableness to 48% for extraversion. Broad-sense heritability for borderline personality was estimated at 45%. Multivariate genetic analyses showed that dominant genetic effects explain 10% (borderline personality) to 30% (introversion versus extraversion) of the variance. The influence of non-additive genetic effects is not an uncommon finding for personality traits. In extended twin family designs Eaves (1998; 1999), Rettew et al. (2008) and Keller et al. (2005) found dominant genetic effects on extraversion and neuroticism in adults and adolescents.

Consistent with the idea that pathological personality traits are the extreme forms of normal personality traits, we found that 50% of the phenotypic association between borderline personality and the FFM traits can be explained by genetic effects. The genetic correlation was highest between neuroticism and borderline personality ( $r_{\rm ag}=0.95$ ), but high genetic correlations of 0.81, 0.56 and 0.62 were also found between borderline and agreeableness, conscientiousness and extraversion, respectively.

The most important finding from our study is that all genetic variation for borderline personality disorder is shared with normal personality traits. In contrast, a significant proportion of the environmental effects (33%) on borderline personality is not shared with the FFM personality traits. We hypothesize that environmental factors thus cause normal personality to develop into borderline personality. For example, it is often hypothesized that childhood neglect or traumatic life events are risk factors for the development of BPD (Crowell et al., 2009). In the context of this study these factors may serve as the environmental factor that leads to the development of BPD in individuals with a high (genetic) score on neuroticism and low scores on conscientiousness and agreeableness.

Our results show that *all* genetic variance in borderline personality is shared with FFM personality traits. This result is in line with, but more extreme than, findings for other psychiatric disorders (Kendler et al., 1993b, 2006; Hettema et al., 2006). For example Kendler et al. (2006) report that the association between neuroticism and major depression resulted largely from shared genetic risk factors, with a genetic correlation of 0.47, which is substantially lower than the genetic correlation between neuroticism and borderline personality found in our study ( $r_{ag} = 0.95$ ). Studies into the genetic architecture of normal personality traits may thus contribute to knowledge about the biological pathways leading to BPD. For many quantitative traits, disorders and diseases common genetic variants in the population are currently identified using genome wide association (GWA) analyses (Sanna et al., 2008; Willer et al., 2008; Wang et al., 2007,





145

05/08/09 11:14:23

2009). To date, two GWA studies for personality traits have been conducted, one on the Eysenck neuroticism scale (Shifman et al., 2008) and the other on all five FFM personality traits (Terracciano et al., 2009). For neuroticism and agreeableness, the two personality traits that showed the highest genetic correlation with borderline personality, association with SNPs in candidate genes have been suggested. For neuroticism some evidence exists for an association with the rs362584 polymorphism in the SNAP25 gene (Terracciano et al., 2009), which 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). Agreeableness may be associated with 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). Potential quantitative trait loci (QTL) for neuroticism also have been reported from genome-wide linkage scans although linkage signals often did not reach genome wide significance (Nash et al., 2004; Kuo et al., 2007; Gillespie et al., 2008; Wray et al., 2008; Neale et al., 2005; Fullerton et al., 2003). Using a sample of twins extremely discordant and concordant for neuroticism Fullerton et al. (2003) identified five loci (at 19, 49, 7p, 129 and 139) that exceeded the genome wide significance threshold. Of these loci the region 129 has been reported in multiple studies. Wray et al. (2008) found three chromosomal regions which exceeded empirically derived thresholds for suggestive linkage (10p 5 Kosambi centimorgan (cM), 14q 103 cM and 18q 117 cM), but only the 14q locus retained significance after correction for multiple testing. Linkage intervals for these regions all overlapped with regions identified in other studies of neuroticism or related traits and/or in studies of anxiety in mice. The genes reported in genome-wide linkage and association studies on normal personality traits, especially those on neuroticism, are thus likely also involved in the biological pathways leading to borderline personality.







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LIFE EVENTS AND BORDERLINE
PERSONALITY: THE INFLUENCE
OF GENE-ENVIRONMENT
CORRELATION AND GENEENVIRONMENT INTERACTION

Marijn A. Distel, Christel M. Middeldorp, Timothy J. Trull, Catherine A. Derom, Gonneke Willemsen & Dorret I. Boomsma. Life events and borderline personality: the influence of gene-environment correlation and gene-environment interaction. *Archives of General Psychiatry*, submitted.

## **ABSTRACT**

150

Context Traumatic life events are generally more common in patients with borderline personality disorder (BPD) than in non-patients or patients with other personality disorders.

Objective To test whether genes that influence BPD features increase the likelihood of exposure to life events (gene-environment correlation) and to test for moderation effects of exposure to life events on the genetic architecture of BPD features (gene-environment interaction).

Design Community based genetically informative sample of twin families.

Setting Gene-environment correlation and interaction were assessed with the cotwin control design, the intra-mz-pair sum-difference covariance method and structural equation modeling.

Participants A total of 5,083 twins (mean age 34.1, 5D = 10.9) and 1,285 additional non-twin siblings (mean age 38.6, SD = 12.2) from the Netherlands and Belgium.

Main Outcome Measurements Borderline personality was assessed by means of a selfreport questionnaire; the Personality Assessment Inventory-Borderline Features scale. Self-reported life events under study were divorce/break-up, traffic accident, violent assault, sexual assault, robbery and job-loss.

Results Both the self reported exposure to specific life events and the total number of experienced life events were associated with more BPD features. There was evidence for both gene-environment correlation and interaction. The genes that influence BPD features also increased the likelihood of being exposed to divorce/break-up, violent assault and job-loss. Additive genetic influences on BPD features interacted with the exposure to sexual assault, with estimated genetic variance being lower in exposed individuals. In individuals who experienced a divorce/break-up, sexual assault, violent assault or jobloss the estimate of the environmental variance for BPD was higher, leading to a lower heritability estimate of BPD in exposed individuals.

Conclusion To our knowledge, this study is the first to test the joint effect of genetic and environmental influences and the exposure to life events on BPD features in the general population. Our results indicate the importance of both genetic vulnerability and life events.





## INTRODUCTION

NITIALLY, RESEARCH IN behavioral and psychiatric genetics focused on disentangling the genetic and environmental influences on a trait or disorder. The findings of these studies were highly relevant in showing the influence of genetic factors in the etiology of almost all traits and disorders. Most of these studies assumed that the effects of genes and environment act independently, meaning that the effect of an environmental risk factor does not depend on the genotype. In a seminal paper, Kendler & Eaves (1986) presented two alternative models that represent how genes and environment jointly influence variation in a trait or disorder: genotype-environment correlation (rGE) and genotype-environment interaction (G×E). rGE occurs when genes that influence a trait also influence the exposure to an environmental risk factor. rGE can result when children are exposed to environments selected or shaped by their parents based on the genotypes of the parents (passive  $r_{GE}$ ), when individuals evoke reactions from other people based on their genotype (evocative or reactive rGE) or when individuals select their environment or interpret their environment based on their genotype (active rGE) (Plomin et al., 1977; Kendler & Eaves, 1986). G×E occurs when the effect of exposure to environmental factors depends on a person's genotype. In the presence of G×E, individuals with a 'sensitive' genotype will be of greater risk if the predisposing environment is present, than individuals with an 'insensitive' genotype (Boomsma & Martin, 2002c; Rutter, 2007).

The present study aimed to explore the influence of rgE and G×E on individual differences in borderline personality disorder (BPD) features. BPD is characterized by emotional lability, impulsivity, interpersonal difficulties, identity disturbance, and cognitive impairment (American Psychiatric Association, 2000). A combination of factors from various domains (e.g. biological, social) influence the risk to develop BPD. Many studies using clinical samples demonstrated that traumatic life events such as sexual or physical abuse and parental divorce, loss or illness are generally 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). Laporte & Guttman (1996) reviewed psychiatric records of patients diagnosed with BPD and found that 93% had experienced some type of loss or abuse in childhood, compared to 74% of patients with other personality disorders. In community samples of women who report having been abused as children, higher frequencies of BPD characteristics such as self harm (Romans et al., 1995) and relationship problems (Browne & Finkelhor, 1986) were found. Also, the total number of experienced negative life events is higher for BPD patients than for control subjects (Horesh et al., 2008; Jovev & Jackson, 2006). Although it seems reasonable to conclude that having experienced a traumatic life event increases

05/08/09 11:14:23

the risk for BPD, it is only found in a subgroup of the BPD population and not all individuals who have experienced a traumatic event develop BPD (Paris, 1997; Sabo, 1997). History of trauma is thus neither necessary nor sufficient for the development of BPD.

Recently, several twin and twin family studies provided evidence that genetic factors explain familial clustering of BPD with heritability estimates ranging from 35 to 45% and no evidence that shared environment contributes to resemblance among relatives (Torgersen et al., 2008; Kendler et al., 2008; Distel et al., 2008a). The etiology of BPD should thus be viewed in context of both traumatic life events and biological vulnerabilities, as is true for other psychiatric disorders. The joint influence of life events and genetic vulnerability on the development of BPD has not yet been investigated although many researchers and psychiatrists acknowledge the importance of both (Livesley, 2008; Distel et al., 2009b; Livesley & Jang, 2008; Paris, 2008).

In the present study, data from 5,083 twins and 1,285 non-twin siblings are analyzed to investigate the association between borderline personality and life events. Borderline personality was measured with the Personality Assessment Inventory-Borderline features Scale (Morey, 1991), a self report questionnaire designed to quantify features clinically associated with BPD. The self reported exposure to divorce/break-up, traffic accident, violent and sexual assault, robbery and job-loss was assessed at the same time. We investigated whether there was a main effect of these life events on BPD features and if the time-interval between the self reported exposure to these life events and the completion of the PAI-BOR influenced the PAI-BOR scores. The presence of  $r_{\rm GE}$  was investigated with the co-twin control design (Cederlof et al., 1977; Kendler et al., 1993d; Middeldorp et al., 2008). With this method, the association between the exposure to a life event and borderline personality is compared in a group of monozygotic (MZ) twins discordant for a life event, a group of dizygotic (DZ) twins discordant for a life event and a group of unrelated individuals discordant for a life event. Since life events can also be under genetic influence (Middeldorp et al., 2005b; Kendler et al., 1993c), it is possible that life events and BPD features are influenced by common genetic effects. Recently, Distel et al. (2009a) showed that passive rGE is unlikely for borderline personality, based on observations from multigenerational twin families. It is, however, important to explore whether  $r_{GE}$  may be present in other forms.

To investigate the presence of G×E interaction, we first tested whether genetic factors interact with non-shared environment (within family environmental influences) by means of a correlation between intrapair sum and difference scores in MZ twin pairs. Since MZ twin pairs share (nearly) all their genetic material, the only source of differences between two members of a MZ twin pair is environmental. The MZ intrapair sumscore will differ between twin pairs if twins from different families have different genotypes. Thus, if the genotype interacts with environmental factors, the intrapair difference score and the intrapair sumscore in MZ twins will be correlated (Jinks & Fulker, 1970). Next,

152



we tested whether genetic and environmental factors interact with the exposure to life events by using structural equation modelling (Eaves, 1984; Kendler & Eaves, 1986). The exposure to a life event was included as a moderator on the path coefficients from latent genetic and environmental factors to the observed phenotype (Purcell, 2002).

### **METHOD**

## **Participants**

Data were collected as part of an ongoing project on health, lifestyle and personality in twin families voluntarily registered with the Netherlands Twin Registry (Boomsma et al., 2006a) and the East Flanders Prospective Twin Survey (Derom et al., 2006). In this study we focus on data on BPD features and the exposure to life events which were collected in 2004-2005. The total sample available for analysis consisted of 5,083 twins, 477 brothers and 808 sisters from 3,688 families. The mean age of the twins and the siblings was 34.1 (SD = 10.9, range 18-86) and 38.6 years (SD = 12.2, range 18-90), respectively.

Zygosity of same-sex twins was determined by placental examination, blood groups and DNA typing for Belgian twins. In the Dutch sample zygosity was based on DNA typing or on self-report answers to a validated survey containing questions on physical twin resemblance. Agreement between the two last methods was 97% (Willemsen et al., 2005). There were 764 monozygotic male twins, 386 dizygotic male twins, 1,932 monozygotic female twins, 944 dizygotic female twins, 421 male dizygotic opposite sex twins and 636 female dizygotic opposite sex twins. Further details on response rates, demographic characteristics of the sample and zygosity determination procedures can be found elsewhere (Derom & Derom, 2005; Distel et al., 2008a).

#### Measures

Borderline personality was assessed by the *Personality Assessment Inventory—Borderline Features Scale* (PAI-BOR; Morey, 1991, 2003), a 24-item self report questionnaire tapping features of psychopathology that are clinically associated with BPD. The items concern for example, stability of mood and affects, emotionally responsiveness, anger control, self image, feelings of emptiness, intense and unstable relationships, loneliness, impulsivity, self harm and recklessness which are to be rated on a four-point scale (0 to 3; *false, slightly true, mainly true, very true*). Multigroup confirmatory factor analysis showed that the PAI-BOR is measurement invariant across sex and age (De Moor et al., 2009). Receiver operating character analysis showed that the PAI-BOR performs reasonably well in discriminating BPD patients and non-BPD depressed psychiatric patients, supporting the validity of PAI-BOR scores (Distel et al., 2009a). The test-retest reliability and inter-



nal consistency (Cronbach's α) of the Dutch version of the Pai-Bor are 0.78 and 0.84, respectively (Distel et al., 2008a). The Pai-Bor was scored according to the test manual, which states that at least 80% of the items must be answered to calculate a sum score and that missing and ambiguous answers should be substituted by a zero score (Morey, 1991). The exposure to life events was assessed by the Dutch life events scale (Schokverwerkings Inventarisatie Lijst; Van der Velden et al., 1992). The experience of the following life events was asked: divorce/break-off an intimate relationship, traffic accident, violent and sexual assault, robbery and job-loss. Response categories were: 'never experienced', '0-6 months ago', '6-12 months ago', '1-5 years ago' and 'more than 5 years ago'.

## Statistical analysis

154

#### Gene-environment correlation

Gene-environment correlation was investigated for each life event with the co-twin control design (Middeldorp et al., 2008; Kendler et al., 1993d; Cederlof et al., 1977). Toward this end, three groups of subjects were identified for each life event. The first group consisted of monozygotic (MZ) twins discordant for the life event (i.e. one member of the twin pair was exposed and the co-twin was not exposed). Subjects in this group are automatically matched for age, sex and genotype. The second group consisted of dizygotic (DZ) twins discordant for the life event. Subjects in this group are automatically matched for age and only same-sex DZ twins were included. DZ twins share on average 50% of their segregating genes. The third group consisted of pairs of genetically unrelated individuals discordant for the life event. Subjects in this group were matched for age and sex by creating pairs of men and women of the same age. Given the different degree of genetic relationship between the three groups (100%, 50% and 0% for the MZ, DZ and unrelated pairs, respectively), a distinct pattern for the difference scores between exposed and non-exposed individuals is expected in each group in the absence and presence of  $r_{GE}$ . In the absence of  $r_{GE}$ , the difference in PAI-BOR scores between the exposed and non-exposed subjects will be similar in the three groups. In other words, if the genes influencing borderline personality and the genes influencing exposure to a life event are not correlated, the difference between the PAI-BOR score of the exposed and non-exposed subject does not depend on the degree of genetic relationship between the exposed and non-exposed subject. In the *presence* of rGE, however, it is expected that non-exposed subjects from the unrelated group will score lower than the DZ non-exposed subjects who will score lower than the MZ non-exposed subjects. In other words, if the association between borderline personality and the exposure to a life event is caused by common genetic effects, non-exposed and exposed subjects who share all genetic make-up (i.e. MZ twins) will have more similar PAI-BOR scores than non-exposed subjects and exposed subjects who share half of their genetic make-up (i.e.





DZ twins) who in turn will have more similar scores than genetically unrelated subjects. Differences in scores of the non-exposed subjects across the three groups were tested by regression analyses for each life event with the PAI-BOR score in non-exposed subjects as the dependent variable and group membership (MZ, DZ and unrelated, coded as 0, -1 and -2, respectively) as the independent variable. In the presence of  $r_{\rm GE}$ , group membership will significantly predict the PAI-BOR score.

#### Gene-environment interaction

Two approaches were used to investigate gene-environment interaction. Firstly, we tested whether an interaction existed between genotype and within family environmental influences. Toward this end, a correlation between intrapair sum and difference scores in MZ twin pairs was calculated in SPSS. Since MZ twin pairs share all their genetic material, the only source of differences between two members of a MZ twin pair is environmental. Thus, with twins reared together, the difference scores (the score of the first twin minus the score of the second twin for every MZ twin pair) provide an estimate of the magnitude of environmental influences within families. If all twin pairs are affected to the same extent by environmental influences, then the difference scores are the same for each twin pair, within sampling error. However, the difference score will be different per twin pair, if twins in some families reacted differently from those in other families. On the other hand, the sum of the MZ twin scores will differ between MZ twin pairs if the twins belonging to different families have different genotypes. If there is any interaction between genotype and within family environment, then there should be a correlation between the MZ twin sums and differences (Jinks & Fulker, 1970).

Secondly, structural equation modelling was used to test whether genetic and environmental effects on the variance in borderline personality interact with the exposure to life events. Variance in a trait can be caused by genetic (G) or environmental (E) factors. It is assumed that many genes contribute to the variance in a complex disorder such as BPD. If the contribution of these genes to the variance in BPD is independent from each other, the genetic effects are additive (A). However, if alleles interact within a particular locus (D; dominance), or across different loci (epistasis) the genetic effects are said to be non-additive. In this study, non-additive genetic effects are modelled as dominance (Distel et al., 2009a). A series of interaction models was fitted for each life event. Figure 10.1 shows this model for a pair of relatives. MZ twins reared together share all genes and DZ twins and sibling pairs share on average 50% of their segregating genes, so the correlation between the genetic factors is fixed to I for MZ twin pairs and 0.5 for DZ and sibling pairs. Dominant genetic variation results from the interaction or combination of alleles at a particular locus. Because offspring receive only one allele from each parent and not a combination of two alleles, the chance that two siblings receive the same allele is 0.5×0.5 resulting in a correlation of 0.25 between the latent D factor for DZ twins





155

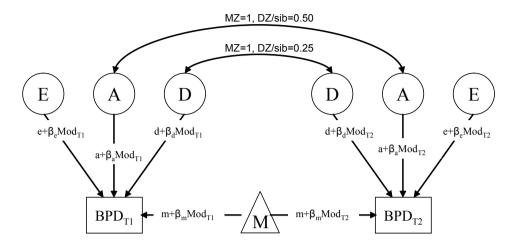


Figure 10.1. Gene-environment interaction model for borderline personality with the exposure to a life event included as a moderator in a pair of relatives (monozygotic twins (MZ), dizygotic twins (DZ) or non-twin siblings (sib)).

Note. BPD = borderline personality disorder; TI = twin one; T2 = twin two; m = mean PAI-BOR score; A = additive genetic variance; a = factor loading of A; D = dominant genetic variance; d = factor loading of D; E = unique environmental variance; e = factor loading of E; Mod = moderator.

and sibling pairs (Posthuma et al., 2003). The exposure to a life event was included as a moderator on the path from latent factors A, D and E. In Figure 10.1 this is represented as  $a+\beta_a^*Mod_{T_1}$  for the path from A to the phenotype. Here *a* represents the effect of A independent from the moderator, and  $Mod_{T_1}$  represents the exposure to a life event (o for non-exposed individuals and 1 for exposed individuals). If  $\beta_a$  is significantly different from zero, an interaction between the latent additive genetic factor and the life event is present. In the same way, interaction effects are tested by constraining  $\beta_d$  and  $\beta_e$  to equal zero. To make sure that possible *r*GE does not lead to spurious findings of G×E, the life event in question was included as a covariate on the mean PAI-BOR score to remove all variance shared between the moderator and borderline personality (Purcell, 2002).

Earlier analyses showed that the heritability of borderline personality is equal for men and women, that there is no shared environmental effect and that the same genes influence borderline personality in men and women ( $r_{MZ}$  males =  $r_{MZ}$  females = 0.43 and  $r_{DZ}$  males =  $r_{DZ}$  females =  $r_{DZ}$  opposite sex = 0.18) (Distel et al., 2008a). Therefore, in the present analyses, sex differences in variance components were not included in the model. Sex, age and country of origin were included in the analyses as fixed effects (regression on the mean PAI-BOR score).



Table 10.1. Prevalence of having experienced a divorce/break-up, traffic accident, violent or sexual assault, robbery and job-loss and the mean PAI-BOR score of the exposed and unexposed subjects for each life event

	Non-	exposed	E	kposed
	N (%)	BPD score (SD)	N (%)	BPD score (SD)
Divorce/ break-up	4,225 (72%)	15.4 (7.8)	1,655 (28%)	19.4 (9.4)
Traffic accident	5,451 (90%)	16.1 (8.3)	617 (10%)	18.4 (9.1)
Violent assault	5,622 (93%)	16.0 (8.2)	409 (7%)	20.3 (10.1)
Sexual assault	5,595 (93%)	15.9 (8.1)	433 (7%)	21.6 (10.3)
Robbery	4,346 (71%)	16.2 (8.3)	1,762 (29%)	16.7 (8.6)
Job-loss	5,010 (82%)	15.8 (8.0)	1,079 (19%)	19.2 (9.5)

All genetic analyses were performed in the software package Mx (Neale et al., 2006a). The fit of the different models was evaluated by means of hierarchical log-likelihood ratio test to select the simplest model that best explains the data among a set of possible models. The difference between the negative log likelihood of the two models has a  $\chi^2$  distribution and the degrees of freedom for this test equals the difference in the number of estimated parameters in the two models. A non-significant p-value (p > 0.01) means that the constrained model is not significantly worse than the less constrained model and is kept as the most parsimonious and best fitting model. Because the PAI-BOR data showed a somewhat skewed distribution with a tail to the right, a square root transformation was applied.

#### **RESULTS**

### Main effects

Table 10.1 shows the prevalence of exposure to each life event and the mean PAI-BOR score of the exposed and unexposed subjects. Prevalences ranged from 29% (robbery) to 7% (violent and sexual assault). For all life events, except for robbery ( $F_{(1)}$  = 3.834, p = 0.05) the exposed subjects had significantly higher mean PAI-BOR scores than the non-exposed subjects (all p < 0.001). To investigate if the strength of the effect of exposure to a life event on BPD features depends on the time interval between completing the PAI-BOR and the occurrence of life events and on the number of experienced life events, we separately analyzed the effect of life events experienced in the past five years and life events experienced more than five years ago. Both the number of experienced life events in the past five years and more than five years ago were associated with higher PAI-BOR scores, but the effect was strongest when the life events occurred more recent (r = 0.229,



157

p < 0.001 versus r = 0.095, p < 0.001). Figure 10.2 gives a graphical representation of the mean PAI-BOR scores of subjects who were exposed to zero, one or more life events in the past five years, longer than five years ago and ever.

#### Gene-environment correlation

Figure 10.3 gives a graphical representation of the pattern of PAI-BOR scores of subjects in the MZ discordant, DZ discordant and unrelated discordant subjects per life event. The difference between the exposed and non-exposed subjects was larger in the unrelated group for all life events. Also, the non-exposed subjects scored highest in the MZ discordant group and lowest in the unrelated discordant group. With regression analyses we tested whether the scores of the non-exposed subjects differed per group. In other words, we tested whether the degree of genetic relatedness with the exposed subject significantly predicted the PAI-BOR score. This was true for divorce/break-up ( $F_{(1)} = 7.36I$ , p = 0.007), violent assault ( $F_{(1)} = 8.265$ , p = 0.004) and job-loss ( $F_{(1)} = 8.122$ , p = 0.005). No differences were found for traffic accident ( $F_{(1)} = 0.009$ , p = 0.926), sexual assault ( $F_{(1)} = 3.070$ , p = 0.081) and robbery ( $F_{(1)} = 1.222$ , p = 0.269). Thus, based on these results there is strong evidence for  $F_{(2)} = 1.222$ ,  $F_{(3)} = 0.026$ , since the scores of the exposed and non-exposed MZ twins differ.

#### Gene-environment interaction

A correlation of 0.395 between the intrapair difference score and the intrapair sumscore in MZ twins indicated that genetic factors influencing BPD features interact with within family environmental factors. The positive correlation indicates that MZ pairs who have lower PAI-BOR scores (low sum score) have more similar PAI-BOR scores (low difference score). Environmental effects unique to an individual make MZ twins differ, and thus cause higher MZ difference scores. These results indicate that the environment might have a greater influence in genetically more vulnerable people.

The intra-mz-pair sum-difference approach does not specify the environmental influences that are responsible for possible G×E. In a next step, we used structural equation modelling to explore which life events moderate the genetic architecture of BPD features. The influence of the specific life events was considered as well as the total number of life events. A series of G×E models were fitted to the data. As more recent life events have a stronger effect on the borderline score, we gave life events from the past five years a higher weight (1.5) than life events from more than five years ago. Since rGE was present for some life events, the mean PAI-BOR score was corrected for the effect of the moderator by including it as a fixed effect in the mean model. Results of genetic model fitting are shown in Table 10.2. For each life event, the full model (model 1) contains all moderation effects on the paths from A, D and E to the phenotype. Models 2, 3 and

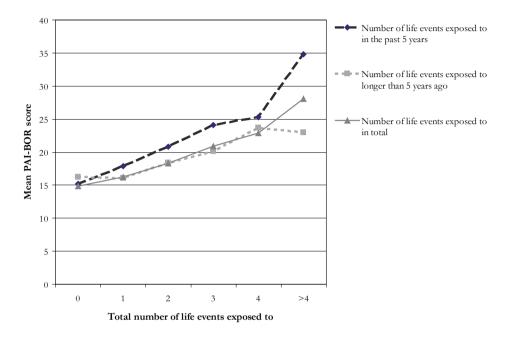


Figure 10.2. Graphical representation of the mean PAI-BOR scores of subjects who were exposed to zero, one or more life events in the past five years, longer than five years ago and ever.

4 subsequently constrained the effect of moderation on D, A, and E at zero and the model fit was then compared to the most parsimonious model at that point. For traffic accident and robbery all moderation effects could be dropped from the models without a significant deterioration in fit. The genetic and environmental effects on borderline personality thus do not interact with the exposure to these life events. Broad heritability (A+D) of BPD was estimated at 47%.

Removing the moderation effect of divorce/break-up, violent assault and job-loss on D and A resulted in a non-significant deterioration of model fit. However, the positive moderation effect of divorce/break-up, violent assault and job-loss on E could not be dropped from the model, indicating that unique environmental influences on BPD features are relatively more important in individuals who have experienced these life events. Note that although there is no moderation effect on the genetic factors, the relative contribution of A and D is lower in individuals exposed to divorce/break-up, violent assault or job-loss since the relative contribution of E is larger in these individuals. The broad heritability estimate (A+D) of BPD features is 46%, 45% and 47% in non-exposed

and 39%, 37% and 39% in individuals exposed to divorce/break-up, violent assault or job-loss, respectively.

For sexual assault a strong negative moderation effect on A was found, resulting in no significant contribution of A in individuals who have experienced sexual assault. Dominant genetic effects explained 20% of the variance. In addition, a significant positive moderation effect on E was found indicating that environmental influences explain relatively more variance in individuals who have experience sexual assault. The exposure to sexual assault leads thus to a lower heritability estimate for BPD features. More specifically, in exposed individuals, additive genetic effects do not influence BPD features, and as a result of the increased environmental variance, the influence of dominant genetic effects is slightly lower than in non-exposed individuals.

The total number of life events to which an individual has been exposed does not interact with genetic effects on BPD features but unique environmental influences are more important in individuals who have experienced more life events. The heritability estimate thus decreases as a function the number of experienced life events, from 46% in non-exposed subjects to 36% in those who experienced 6 life events. Figure 10.4 shows the absolute contribution of additive genetic and environmental factors to variation in BPD features for individuals non-exposed and exposed to divorce/break-up, violent or sexual assault, job-loss or any life event.

### COMMENT

This study corroborates previous findings in clinical and non-clinical studies that showed a strong relationship between having experienced (one or more) traumatic life events and (the severity of) BPD symptoms (Silk et al., 1995; Johnson et al., 1999; Jovev & Jackson, 2006; Horesh et al., 2008; Zanarini et al., 2002). We explored how genes and environment jointly affect BPD features. Gene-environment correlation was found for divorce/break-up, violent assault and job-loss. Genes influencing BPD features thus increase the likelihood of being exposed to these three life events through evocative or active *r*GE processes. Kendler et al. (2003) also found evidence for *r*GE for neuroticism, a personality trait strongly associated with BPD (McCrae et al., 2001), and marital problems, job-loss and problems getting along with people. For traffic accidents, robbery and sexual assault no evidence for gene-environment correlation was found.

Using the co-twin control design, we found that exposed MZ twins have relatively higher PAI-BOR scores than their unexposed co-twin, thus common genes are not the only explanation for the association. Having experienced a divorce/break-up, violent assault or job-loss may also increase BPD features either through a reciprocal or unidirectional causal mechanism. The following part of our study suggests that this effect is



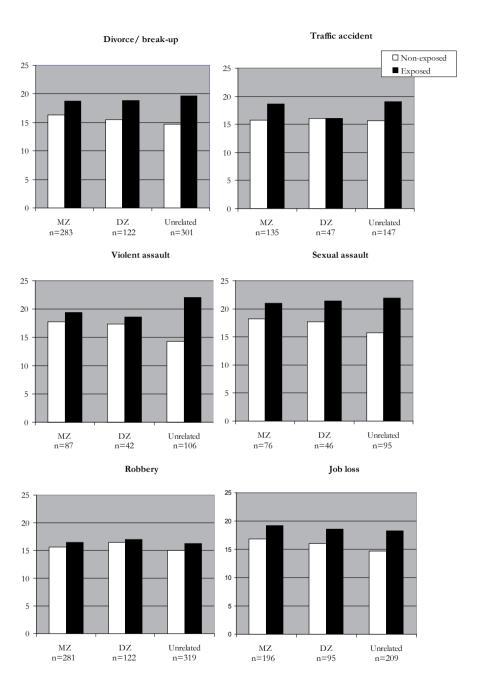


Figure 10.3. Graphical representation of the pattern of PAI-BOR scores of subjects in the monozygotic (MZ) discordant, dizygotic (DZ) discordant and unrelated discordant subjects per life event.





		vs	-2LL	df	Χ²	Δdf	р	A	D	E
Divorce/b	oreak-up									
Model I	Full model		16631.504	6003						
Model 2	Drop moderation D	- 1	16634.734	6004	3.230	- 1	.072			
Model 3	Drop moderation A	2	16634.751	6005	.016	- 1	.899			
Model 4	Drop moderation E	3	16652.677	6006	17.926	1	<.001			
Model 5	Drop D parameter	3	16639.128	6006	13.549	- 1	<.001			
Standardi	zed parameter estimate	es					exposed	.23	.23	.54 .61
Traffic accident										
Model I	Full model		16168.333	5773						
Model 2	Drop moderation D	- 1	16169.249	5774	.915	1	.339			
Model 3	Drop moderation A	2	16169.252	5775	.003	- 1	.956			
Model 4	Drop moderation E	3	16171.856	5776	2.604	I	.107			
Model 5	Drop D parameter	4	16177.220	5777	5.364	1	.021			
Standardi	zed parameter estimate	es		١	Von-expos	sed & e	xposed	.22	.25	.53
Violent ass	sault									
Model I	Full model		15918.102	5697						
Model 2	Drop moderation D	- 1	15920.368	5698	2.267	- 1	.132			
Model 3	Drop moderation A	2	15920.413	5699	.045	.045   .832				
Model 4	Drop moderation E	3	15929.504	5700	9.091	- 1	.003			
Model 5	Drop D parameter	3	15924.513	5700	4.145	- 1	.042			
Standardi	zed parameter estimate	26				Non-e	exposed	.23	.22	.55
Juli Idal di	zea pararrieter estimate					E	exposed	.19	.18	.63
Sexual ass	sault									
Model I	Full model		15874.010	5705						
Model 2	Drop moderation D	- 1	15874.057	5706	.047	- 1	.828			
Model 3	Drop moderation A	2	15880.437	5707	6.38	1	.012			
Model 4	Drop moderation E	2	15880.053	5707	5.996	1	.014			
Model 5	Drop D parameter	2	15878.989	5707	4.932	- 1	.026			
						Non-e	exposed	.23	.24	.52
Standardi	zed parameter estimate	es			Exposed			.00	.20	.80





# Table 10.2. Model fitting results for an interaction model of borderline personality with the life events as moderators. Standardized parameter estimates are given for the best fitting model.

		vs	-2LL	df	χ²	Δdf	р	A	D	E
Robbery										
Model I	Full model		16386.198	5839						
Model 2	Drop moderation D	- 1	16386.872	5840	.675	- 1	.411			
Model 3	Drop moderation A	2	16386.885	5841	.013	1	.909			
Model 4	Drop moderation E	3	16387.496	5842	.611	- 1	.434			
Model 5	Drop D parameter	4	16394.030	5843	6.534	1	.011			
Standardi	Standardized parameter estimates Non-exposed & exposed					xposed	.19	.28	.53	
Job-loss										
Model I	Full model		16170.494	5811						
Model 2	Drop moderation D	- 1	16171.196	5812	.701	1	.402			
Model 3	Drop moderation A	2	16171.530	5813	.334	- 1	.563			
Model 4	Drop moderation E	3	16187.862	5814	16.332	1	<.001			
Model 5	Drop D parameter	3	16177.382	5814	10.48	1	.001			
Standardi	Standardized parameter estimates Non-exposed					xposed	.20	.27	.53	
Exposed							.17	.22	.61	
Number of life events										
Model I	Full model		17483.684	6357						
Model 2	Drop moderation D	- 1	17484.817	6358	1.133	1	.287			
Model 3	Drop moderation A	2	17484.820	6359	.003	- 1	.956			
Model 4	Drop moderation E	3	17497.009	6360	12.189	- 1	<.001			
Model 5	Drop D parameter	3	17490.544	6360	6.465	1	.011			
Standardi	zed parameter estimate	es				Non-e	xposed	.21	.25	.54
					Exposed	to I lif	e event	.20	.24	.56
					Exposed	to 2 life	events	.19	.23	.58
					Exposed	to 3 life	events	.18	.22	.60
					Exposed	to 4 life	events	.17	.21	.61
					Exposed	to 5 life	events	.17	.20	.63
					Exposed	to 6 life	events	.16	.20	.64

Note. A = additive genetic variance; D = dominant genetic variance; E = unique environmental variance; vs = versus; -2LL = -2 log likelihood; df = degrees of freedom.

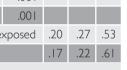


Figure 10.4. The absolute contribution of genetic (A, D) and environmental (E) factors to variation in borderline personality for non-exposed and exposed individuals.

not only additive to the genetic influences on BPD, but that gene-environment interaction also plays a role.

Significant gene-environment interaction was reflected by a positive correlation (r = 0.395) between intrapair sum and difference scores in MZ twin pairs. This indicates that within family environmental influences may have greater effects in genetically vulnerable individuals. We aimed to identify specific environmental influences that moderate the genetic and environmental influences on BPD features. Both additive genetic and unique environmental influences on BPD features were found to interact with the exposure to sexual assault. Additive genetic variance was smaller and environmental variance larger in exposed individuals. This suggests that sexual assault has such a large effect that even in less genetically vulnerable individuals it is associated with more BPD features. In other words, even stable individuals are at risk of developing BPD after a sexual assault. In addition, environmental influences explain relatively more variance in individuals who have experienced sexual assault which may point to the large individual differences



in the assault and the way individuals experiences such a life event. The influence of environmental factors is relatively larger in individuals who have experienced a divorce/break-up, violent assault or job-loss reflecting the wide range of variation in the impact of these life events. Also, the influence of environmental factors is larger when individuals have been exposed to more life events. As a result of the increase in environmental variance, the genetic effects become relatively less important. The broad heritability for BPD features decreases with 7%, 8%, 8% and 27% after exposure to divorce/break-up, violent assault, job-loss or sexual assault, respectively. The heritability decreases from 46% in non-exposed individuals to 36% in individuals exposed to 6 life events.

Several limitations of this study should be noted. First, some selection bias may have been present in the sample. In general, the Dutch sample, which constituted the largest sample in the present study, was shown to be representative of the general Dutch population with regard to a number of variables such as socioeconomic status, smoking behavior, and religion (Boomsma et al., 2002b). However, individuals from families in which only some individuals participate show slightly more borderline personality features than individuals from families in which most individuals participate (Distel et al., 2007). The second limitation concerns measurement. Features clinically associated with BPD were assessed in a large sample of subjects drawn from the general population. Although, the PAI-BOR is shown to discriminate well between BPD patients and patients with other personality disorders or non-patients, findings should be generalized to patients with caution. Life events are retrospectively assessed which is sometimes argued to cause reported life events to be in part due to biased memory. Since data on life events were also collected at a prior occasion it was possible to test whether individuals reported life events consistently. A total of 75% of the subjects who reported a life event on the first occasion also reported that life event on the second occasion. A third limitation concerns the investigated life events. We only assessed negative life events while positive life events or protective familial influences and social networks might also play a role. Positive life events may serve as a protective factor by buffering the effects of negative life events. Horesh et al. (2008) reported that not only BPD patients had experienced more negative life events but also less positive life events than control subjects.

We showed that the association between life events and BPD features can be explained by shared genetic influences, causal effects and/or an interaction between genes and environment depending on the type of life event. These findings hold several important implications for clinical settings and research. The fact that individuals with BPD features have a higher risk of experiencing a divorce/break-up, violent assault and job-loss, based on their genotype and that the exposure to these life events increases the number of BPD features, indicates how important it is during treatment to have attention for problems in relationships and at work. Further, although it has already been well known that sexual assault is highly associated with psychopathology, the finding that sexual as-

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sault can even increase BPD features in genetically invulnerable subjects emphasizes the impact of this kind of life event. Moreover, in future studies that aim to find genes that influence BPD features, individuals exposed to sexual assault and possibly other severe life events, could be excluded from the analyses, because the importance of genes in the development of BPD is much lower in individuals who experienced such life events compared to individuals who did not.









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# SUMMARY AND DISCUSSION





#### **SUMMARY**

orderline 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 data data and personality traits, life events and data data 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 though 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-





171

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; rGE) and if exposure to life events moderates the heritability of BPD features (gene-environment interaction; G×E). Analyses that involve rGE and G×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 rGE. 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-

172



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 6oT 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 II.I 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  $\geq$  48 for men and  $\geq$  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 (I-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 border-line personality disorder features

	Men (	N = 4,518)	Wome	en (N = 7,354)
T-score	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, 200I; 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 nonpatients 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 (1931.1, 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 (10p 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 19, 49, 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 Ip and IIq, 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-HTTlinked 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

179







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 I (dopamine active transporter, DATI) 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 III 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-



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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 eight 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.







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INDIVIDUELE VERSCHILLEN IN

**BORDERLINE** 

PERSOONLIJKHEIDSKENMERKEN

EEN GENETISCH PERSPECTIEF



N DE GEDRAGSGENETICA is relatief weinig onderzoek gedaan naar borderline persoonlijkheidsstoornis (BPS). Dit is opvallend omdat BPS duidelijk familiair is en een zware belasting vormt voor de persoon zelf, diens familieleden en de samenleving. BPS wordt gekenmerkt door sterke wisselingen in emoties, gedachten en gedrag. Mensen met BPS zijn impulsief, reageren extreem en hebben moeite met het onderhouden van relaties. Onderzoek naar het ontstaan van BPS richt zich vaak op sociale en omgevingsdeterminanten, zoals traumatische ervaringen, maar deze studies hebben niet geleid tot een duidelijk beeld over de etiologie. Dit proefschrift is een bijdrage aan het onderzoek naar het ontstaan van BPS vanuit een genetisch perspectief.

Voor dit onderzoek is gebruik gemaakt van gegevens van tweelingfamilies die ingeschreven staan bij het Nederlands Tweelingen Register. Elke 2 à 3 jaar ontvangen adolescente en volwassen tweelingen en hun familieleden per post een vragenlijst over gezondheid, leefgewoonten en persoonlijkheid. De gegevens die in dit proefschrift zijn geanalyseerd maken deel uit van de zevende vragenlijst die in 2004 en 2005 is verstuurd. In 2004 is de vragenlijst voor het eerst ook verstuurd naar Nederlandstalige Belgische tweelingen en hun ouders die ingeschreven staan bij het Oost Vlaams Meerlingen Register. Daarnaast zijn in de hoofdstukken 5, 7 en 9 ook gegevens van Australische tweelingen en hun familieleden die betrokken zijn bij het Australische Tweelingen Register geanalyseerd. In het totaal hebben meer dan 15.000 tweelingen en familieleden uit deze drie landen een vragenlijst ingevuld. De aanwezigheid van BPS kenmerken is bepaald met de door ons ontwikkelde vertaling van de Engelstalige Personality Assessment Inventory-Borderline features (PAI-BOR) schaal, een zelfbeoordelingvragenlijst waarmee borderline kenmerken op een continue schaal in kaart gebracht kunnen worden. De PAI-BOR bestaat uit 24 items die zijn ingedeeld in vier domeinen (zes items per domein). Elk domein weerspiegelt één van de hoofdkenmerken van borderline persoonlijkheid: affectieve instabiliteit, identiteitsproblemen, negatieve relaties en zelfbeschadiging. In hoofdstuk één van dit proefschrift worden de kenmerken van BPS besproken en wordt uiteengezet welke onderzoeken al werden uitgevoerd naar de genetische invloeden op BPS. Hoofdstuk twee beschrijft studies naar de betrouwbaarheid en validiteit van de PAI-BOR vragenlijst en geeft een overzicht van de gegevensverzameling voor dit proefschrift.

Bij een studie over persoonlijkheidseigenschappen in de normale populatie moet men rekening houden met een mogelijke invloed van non-respons op de resultaten. Wanneer personen met veel borderline kenmerken bijvoorbeeld minder geneigd zijn om een vragenlijst in te vullen kan dit de validiteit van de studie ondermijnen. In hoofdstuk drie is vastgesteld dat de PAI-BOR scores van mensen uit families waarvan weinig familieleden meededen aan het onderzoek enigszins hoger zijn dan de PAI-BOR scores van mensen uit families waarvan veel familieleden meededen aan het onderzoek. Het verschil was echter klein en zal waarschijnlijk een geringe invloed op de resultaten hebben gehad. Voor de validiteit van het onderzoek is het naast de afwezigheid van nonresponse bias belangrijk dat de PAI-BOR vragenlijst meetinvariant is, dat wil zeggen dat de vragenlijst hetzelfde werkt in verschillende groepen. Uit *hoofdstuk vier* blijkt dat de PAI-BOR vragenlijst wat betreft sekse en leeftijd meetinvariant is. Dat wil zeggen dat, gegeven een zekere mate van borderline kenmerken, mannen en vrouwen van verschillende leeftijden dezelfde kans hebben om een bepaald antwoord op een bepaald item te geven. De scores van mannen en vrouwen en van mensen van verschillende leeftijden kunnen dus betrouwbaar vergeleken worden.

In hoofdstuk vijf wordt onderzocht in hoeverre individuele verschillen in borderline kenmerken worden beïnvloed door genetische en omgevingsfactoren. Met behulp van gegevens van 5.496 tweelingen uit Nederland, België en Australië is vastgesteld dat 42% van de individuele verschillen in borderline persoonlijkheid verklaard wordt door genetische invloeden. Naast genetische factoren blijken omgevingsinvloeden die uniek zijn per individu bepalend te zijn voor de mate waarin mensen borderline kenmerken hebben. De erfelijkheidsschatting is gelijk in de drie landen en voor mannen en vrouwen en er zijn geen specifieke genen die borderline kenmerken alleen beïnvloeden in mannen of vrouwen. Door het tweelingmodel uit te breiden met informatie van broers, zussen en ouders van tweelingen kon in hoofdstuk zes worden vastgesteld dat de invloed van verschillende genen die borderline kenmerken beïnvloeden niet allemaal bij elkaar optellen maar dat er deels sprake is van interacties tussen verschillende allelen van een gen (dominantie). Ook werd gevonden dat de gelijkenis tussen ouders en kinderen volledig verklaard kan worden doordat ouders hun genen doorgeven aan hun kinderen; er is geen directe invloed van de borderline kenmerken van ouders op de omgeving waarin hun kinderen opgroeien. Met andere woorden, er is geen invloed van culturele transmissie; alle overeenkomsten tussen ouders en hun nageslacht wordt verklaard door genetische transmissie. In hoofdstuk zeven zijn de vier subschalen van de PAI-BOR onderzocht. Het model dat de data van de vier subschalen het beste weergaf was het 'common pathway model'. Dit model houdt in dat de samenhang tussen de vier schalen bepaald wordt door één latente factor die in dit geval het BPS construct representeert; genetische en omgevingsinvloeden beïnvloeden de vier schalen van de PAI-BOR daarmee via hetzelfde mechanisme. De erfelijkheidsschattingen voor affectieve instabiliteit, identiteitsproblemen, negatieve relaties en zelfbeschadiging varieren van 26% voor zelfbeschadiging tot 35% voor negatieve relaties.

BPS kenmerken worden dus in belangrijke mate beïnvloed door erfelijke factoren. In *hoofdstuk acht* is voor het eerst door middel van koppelingsonderzoek ('linkage') vastgesteld dat op een regio van chromosoom 9 mogelijk genen liggen die BPS kenmerken beïnvloeden. Een gen in dit gebied is het *protein tyrosine phosphatase receptor type delta* (PTPRD) gen welke ook van invloed lijkt te zijn op ADHD en nicotine verslaving. Aangezien zowel ADHD en nicotine verslaving vaak samen voorkomen met BPS zou dit

gen biologische processen in gang kunnen zetten die het risico op zowel BPS als ADHD en nicotine verslaving vergroten.

Er is in de afgelopen jaren veel aandacht geweest voor persoonlijkheidsstoornissen in relatie tot normale persoonlijkheid. De vraag of persoonlijkheidsstoornissen gezien kunnen worden als extremen van normale persoonlijkheid stond hierin centraal. De NEO persoonlijkheidsvragenlijst is ontwikkeld om normale persoonlijkheid te beschrijven en geeft aan in hoeverre iemand de persoonlijkheidseigenschappen neuroticisme, extraversie, openheid voor ervaringen, altruïsme, en consciëntieusheid bezit. In hoofdstuk negen wordt de fenotypische en genetische relatie tussen deze persoonlijkheidseigenschappen en BPS kenmerken onderzocht. BPS kenmerken konden het beste voorspeld worden door een hoge score op neuroticisme en een lage score op altruïsme. Dit is in overeenstemming met eerdere studies naar deze relatie in BPS patiënten. De genetische relatie is echter niet eerder onderzocht. Wij vonden dat de genen die BPS beïnvloeden in zijn geheel overlappen met de genen die normale persoonlijkheidseigenschappen beïnvloeden. Dit is een belangrijke bevinding die ons dichterbij de biologische mechanismen achter variatie in BPS kenmerken kan brengen. Omgevingsinvloeden op variatie in BPS kenmerken zijn wel in belangrijke mate specifiek voor BPS. Wij stellen dat deze omgevingsinvloeden mogelijk het verschil bepalen tussen extreme vormen van normale persoonlijkheidskenmerken en BPS.

Stressvolle gebeurtenissen worden gezien als belangrijke omgevingsfactoren die van invloed zouden kunnen zijn op de ontwikkeling van BPS. Een hoog percentage mensen met BPS geeft aan ooit traumatische gebeurtenissen meegemaakt te hebben. Hoewel het niet bewezen is dat traumatische gebeurtenissen verantwoordelijk zijn voor het ontstaan van BPS zijn mensen met BPS vaker dan mensen zonder BPS of mensen met andere persoonlijkheidsstoornissen slachtoffer geweest van een seksueel of geweldsmisdrijf. In hoofdstuk tien wordt de relatie tussen BPS kenmerken en het meemaken van een scheiding/verbreken van een relatie, verkeersongeval, gewelds- of seksueel misdrijf, diefstal en ontslag onderzocht vanuit een genetisch perspectief met als doel het samenspel tussen genen en omgeving in kaart te brengen. Uit dit onderzoek blijkt dat mensen met een genetische gevoeligheid om BPS te ontwikkelen op basis van die genetische gevoeligheid ook een groter risico lopen om een scheiding of het verbreken van een relatie, een geweldsmisdrijf of ontslag mee te maken. De kans op het meemaken van een verkeersongeval, seksueel misdrijf of diefstal wordt niet groter door een genetische gevoeligheid voor BPS. Daarnaast is er soms ook sprake van een oorzakelijk verband en bestaan er interacties tussen genetische invloeden op BPS en het meemaken van stressvolle gebeurtenissen. Bij mensen die een seksueel misdrijf hebben meegemaakt is de invloed van genen minder belangrijk bij het verklaren van individuele verschillen in BPS kenmerken dan bij mensen die geen seksueel misdrijf hebben meegemaakt. Dit geldt ook voor



mensen die een scheiding, ontslag of een geweldsmisdrijf hebben meegemaakt doordat een groter deel van de variatie verklaard wordt door omgevingsinvloeden.

Uit het onderzoek beschreven in dit proefschrift blijkt dat zowel genetische als omgevingsinvloeden van invloed zijn op het ontstaan van BPS, zoals geldt voor de meeste psychiatrische stoornissen. De beschreven resultaten kunnen belangrijke implicaties hebben voor de behandeling van BPS en voor verder onderzoek naar het ontstaan van BPS. Dit proefschrift draagt in de eerste plaats bij aan de kennis over het ontstaan van BPS. Voor patiënten en familieleden van patiënten kan inzicht in de stoornis het gevoel van controle over de ziekte vergroten wat bij kan dragen aan een hogere kwaliteit van leven. Een specifiek patroon van normale persoonlijkheidskenmerken, namelijk veel neuroticisme kenmerken en weinig altruïsme kenmerken, vergroot het risico op BPS. Het identificeren van deze patronen kan een bijdrage leveren aan de preventie van BPS. Mensen met dit persoonlijkheidsprofiel zouden bijvoorbeeld interventieprogramma's kunnen volgen die gericht zijn op het leren reguleren van emoties. Daarnaast is het bij deze mensen belangrijk dat stressvolle gebeurtenissen vermeden worden om zo de kans op het ontwikkelen van BPS te verkleinen. Het vermijden van stressvolle gebeurtenissen zou ook een belangrijk thema kunnen zijn in behandelingsprogramma's voor BPS aangezien mensen met BPS meer risico lopen op het meemaken van bepaalde stressvolle gebeurtenissen en het aantal BPS kenmerken vergroot na het meemaken van een stressvolle gebeurtenis.

Dit proefschrift laat zien dat genetische invloeden een belangrijke rol spelen in de ontwikkeling van BPS en dat genen in een regio op chromosoom 9 hier mogelijk verantwoordelijk voor zijn. Toekomstig onderzoek moet uitwijzen welke specifiek genen biologische processen in gang zetten die de kans op het ontwikkelen van BPS verhogen. In de nabije toekomst zullen wij een genoom brede associatie studie uitvoeren waarmee we deze specifieke genen hopen te identificeren. Zoals in dit proefschrift aangetoond spelen ook omgevingsfactoren, zoals negatieve levensgebeurtenissen, een rol in de etiologie van BPS. Vervolgonderzoek zal zich ook moeten richten op het verder in kaart brengen van de verschillende omgevingsinvloeden en de interactie met genetische aanleg. Hierbij is ook aandacht nodig voor positieve gebeurtenissen die mogelijk de kans op BPS verkleinen en zo dus een beschermende factor zijn. Men zou hierbij kunnen denken aan de invloed van een groot sociaal netwerk of de positieve invloed van familie. Op dit moment wordt voor de achtste keer een vragenlijst verstuurd naar tweelingen en hun familieleden die ingeschreven staan bij het Nederlands Tweelingen Register waarbij opnieuw gevraagd wordt naar BPS kenmerken en levensgebeurtenissen. Dit maakt het mogelijk om in de toekomst de invloed van levensgebeurtenissen op het ontwikkelen van BPS longitudinaal te onderzoeken. Deze toekomstige studies zullen een aanvulling zijn op de onderzoeksbevindingen beschreven in dit proefschrift en mogelijk leiden tot





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## NEDERLANDSE SAMENVATTING

een model voor de ontwikkeling van BPS waarin biologische en omgevingsinvloeden geïntegreerd zijn.







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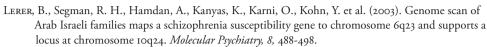
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NEDERLANDSE VERTALING VAN

DE PERSONALITY ASSESSMENT

INVENTORY- BORDERLINE

KENMERKEN SCHAAL (PAI-BOR):

NORMGEGEVENS,

**FACTORSTRUCTUUR EN** 

## BETROUWBAARHEID

Marijn A. Distel, Marleen H.M. De Moor & Dorret I. Boomsma (2009). Nederlandse vertaling van de Personality Assessment Inventory- Borderline kenmerken schaal (PAI-BOR): normgegevens, factorstructuur en betrouwbaarheid. *Psychologie en Gezondheid*, 37, 38-46.



### **ABSTRACT**

Borderline features scale (PAI-BOR): norms, factor structure and reliability.

Borderline personality disorder (BPD) is a severe personality disorder whose main features include affective instability, identity problems, negative relationships and self-harm. The Personality Assessment Borderline- features (PAI-BOR) scale developed by Morey (1991) assesses these features on a continuous scale. In 2004, the PAI-BOR was translated into Dutch and completed by 8,511 men and women aged 18 to 90 years. The internal consistency (Crohnbach's α) of the Dutch PAI-BOR is good (α = 0.81). Six-month test-retest correlation is 0.78. Thus, BPD features in the general population can reliably be assessed by the Dutch version of the PAI-BOR. The four domains as proposed by Morey (1991) are also found in the Dutch data. The effects of sex, age and educational level on BPD features are discussed and means and standard deviations for twelve sex (3,287 men, 5,224 women) by age (18 - 35, 36 - 90 years) by

level of education (low, middle, high) groups are presented.

### SAMENVATTING

ORDERLINE PERSOONLIJKHEIDSSTOORNIS (BPS) is een ernstige persoonlijkheidsstoornis met als belangrijke kenmerken affectieve instabiliteit, identiteitsproblemen, negatieve relaties en zelfbeschadiging. Een vragenlijst die deze kenmerken op een continue schaal in kaart brengt is de Engelstalige Personality Assessment Borderline- kenmerken schaal. In 2004 is deze vragenlijst vertaald naar het Nederlands en afgenomen bij 8527 mannen en vrouwen in de leeftijd van 18 tot 90 jaar. Dit onderzoek toont aan dat BPS kenmerken in de algemene populatie betrouwbaar vastgesteld kunnen worden met de Nederlandstalige versie van de PAI-BOR. De vier domeinen zoals voorgesteld door de testuitgever dr Morey worden ook gevonden in de Nederlandse data. Het effect van sekse, leeftijd en opleidingsniveau op de aanwezigheid van borderline kenmerken wordt besproken en de normgegevens voor twaalf groepen naar sekse (3287 mannen en 3551 vrouwen), leeftijd (18 - 35 jaar en 36 - 90 jaar) en opleidingsniveau (lager/middelbaar onderwijs, hoger middelbaar onderwijs en hoger onderwijs) worden gepresenteerd.

### **INLEIDING**

OLGENS DE "DIAGNOSTIC and Statistical Manual of Mental Disorders" (DSM-IV) wordt iemand met een borderline persoonlijkheidsstoornis (BPS) gekenmerkt door instabiliteit in het zelfbeeld, stemmingen en relaties. Ook is er sprake van duidelijke impulsiviteit (American Psychiatric Association, 2000). BPS-symptomen komen meestal tot uiting tussen het 17e en 25e levensjaar en nemen geleidelijk af met het ouder worden (Johnson et al., 2000; Samuels et al., 2002; Coid et al., 2006; Lenzenweger et al., 2007).

De meeste kennis over de symptomen van BPS is verkregen door middel van studies in klinische populaties (bijv. Giesen-Bloo et al., 2006; Kernberg, 2003); over het voorkomen van BPS-kenmerken in de algemene bevolking is minder bekend. Een Noorse studie (N = 2053) (Torgersen et al., 2001) en een recent Amerikaans onderzoek (N = 5692) (Lenzenweger et al., 2007) rapporteren op basis van gestructureerde DSM-III-R en DSM-IV interviews dat ongeveer 1% van de algemene bevolking voldoet aan de diagnostische criteria voor BPS. Andere internationale onderzoeken in niet- klinische steekproeven rapporteren prevalenties die variëren van 0,4% tot 1,8 % (Widiger & Weissman, 1991).

Hoewel de diagnose BPS vaker wordt gesteld bij vrouwen dan bij mannen, zijn onderzoeksresultaten met betrekking tot sekseverschillen in de prevalentie van BPS tegenstrijdig. Gebaseerd op een meta-analyse van 75 studies concluderen Widiger & Trull (1993) dat 75% van de mensen met een BPS-diagnose vrouw is. Echter, dit percentage zou het resultaat kunnen zijn van bias in de diagnose in plaats van een echt sekseverschil in de prevalentie van BPS (Widiger, 1998). De twee bovengenoemde grote studies met een op de populatie gebaseerde steekproef vinden geen verschil in de prevalentie van BPS tussen mannen en vrouwen (Lenzenweger et al., 2007; Torgersen et al., 2001).

De Engelstalige *Personality Assessment Inventory-Borderline features* (Pai-Bor) schaal (Morey, 1991, 2003) is een zelfbeoordelingvragenlijst waarmee borderline symptomatologie op een continue schaal in kaart gebracht kan worden. De Pai-Bor bestaat uit 24 items die zijn ingedeeld in vier domeinen (zes items per domein). Elk domein weerspiegelt één van de hoofdkenmerken van borderline persoonlijkheid: Affectieve Instabiliteit, Identiteitsproblemen, Negatieve Relaties en Zelfbeschadiging. De Engelstalige Pai-Bor is betrouwbaar gebleken in verschillende Amerikaanse steekproeven (Morey, 1991; Trull, 1995). Trull (1995) rapporteert een betrouwbaarheid (Cronbach's α) van 0.84 in een populatiebrede steekproef (N = 1697). Morey (1991) onderzocht de betrouwbaarheid van de Pai-Bor in een populatiebrede steekproef (N = 1000), een klinische steekproef (N = 1246) en een steekproef van studenten (N = 1051). Cronbach's α was 0,87, 0,91 en 0,86. Er waren geen sekseverschillen in de populatiebrede steekproef voor de gemiddelde totaal- en domeinscores op de Pai-Bor. De scores namen af met toenemende leeftijd.





Dit artikel geeft de betrouwbaarheid van de Nederlandse vertaling van de PAI-BOR. De effecten van sekse, leeftijd en opleidingsniveau op de PAI-BOR score worden getoetst en gemiddelde PAI-BOR scores voor een grote Nederlandse steekproef worden gerapporteerd als functie van deze variabelen. Ten slotte wordt onderzocht of het vierfactor model van Morey terug te vinden is in de Nederlandse data.

### **METHODE**

### Deelnemers

In 1991 is het Nederlands Tweelingen Register (Boomsma et al., 2006a) begonnen met longitudinaal vragenlijstonderzoek naar gezondheid, leefgewoonten en persoonlijkheid bij adolescenten en volwassenen. In 2004/2005 is voor de zevende keer een vragenlijst verstuurd, waarin voor het eerst de Nederlandse vertaling van de PAI-BOR was opgenomen. De vragenlijst is ingevuld door 8511 personen uit 3262 families: 3287 mannen (39%) en 5224 vrouwen (61%) met een gemiddelde leeftijd van 44,0 (SD = 15,1) en 41,1 jaar (SD = 14,0). De steekproef is ingedeeld in twee leeftijdsgroepen: 18-35 jaar (N =3915) en 36-90 jaar (N = 4596). Na zes maanden heeft een random groep (N = 199) de vragenlijst een tweede keer ingevuld om de test-hertest stabiliteit te kunnen bepalen.

Instrument: Nederlandse borderline persoonlijkheidsvragenlijst

De Engelstalige Personality Assessment Inventory-Borderline features (PAI-BOR) schaal (Morey, 1991, 2003) bestaat uit 24 items. De Engelse vragenlijst is vertaald naar het Nederlands en daarna terugvertaald naar het Engels door een vertaler met Engels als moedertaal. Deze terugvertaling is goedgekeurd door dr. Morey, de ontwikkelaar van de Engelse vragenlijst en de test uitgeverij (Psychological Assessment Resources). De PAI-BOR bestaat uit vier domeinen: Affectieve Instabiliteit (AI), Identiteitsproblemen (IP), Negatieve Relaties (NR) en Zelfbeschadiging (ZB). Mensen die hoog scoren op het domein AI reageren sterk emotioneel, hebben sterke en elkaar snel opvolgende stemmingswisselingen en hebben moeite om hun woede onder controle te houden. Mensen die hoog scoren op het domein IP zijn onzeker over belangrijke zaken in het leven, voelen zich leeg en vervelen zich snel. Hoogscoorders op NR hebben vaak een geschiedenis van instabiele maar intense relaties en voelen zich bedrogen door naasten. Mensen die hoog scoren op het domein ZB zijn impulsief in situaties die vaak resulteren in negatieve consequenties zoals excessief geld uitgeven, wisselende seksuele contacten en/of middelengebruik. In Tabel 1 staat een korte beschrijving van elk item en het bijbehorende domein. De vier antwoordcategorieën op de items zijn: o helemaal niet waar, I een beetje waar, 2 grotendeels waar en 3 helemaal waar. De items 7, 12, 14, 19, 20 en 24

# Tabel I. Overzicht van de items van de Nederlandse PAI-BOR persoonlijkheidsvragenlijst met het bijbehorende domein, gemiddelde itemscores en standaarddeviaties

Item		Domein	Gemiddelde (SD)
1	Stemmingswisselingen	Al	0.75 (0.75)
4	Hevige stemmingen	Al	0.56 (0.77)
7*	Stabiele stemmingen	Al	1.49 (0.99)
10	Weinig beheersing over woede	Al	0.17 (0.44)
14*	Gelukkig persoon	Al	0.96 (0.85)
18	Kan mijn woede niet uiten	Al	0.53 (0.85)
2	Wisselend zelfbeeld	IP	0.48 (0.68)
5	Gevoel van leegte	IP	0.47 (0.71)
8	Angst om verlaten te worden	IP	0.41 (0.70)
11	Zin van het leven	IP	0.40 (0.68)
15	Niet alleen kunnen zijn	IP	1.39 (0.93)
19*	Niet snel last van verveling	IP	0.77 (0.90)
3	Stormachtige relaties	NR	0.26 (0.60)
6	Gekwetst door naasten	NR	0.60 (0.77)
9	Teleurgesteld in naasten	NR	0.72 (0.85)
12*	Zelden eenzaam	NR	1.18 (1.10)
16	Foute keuze van vrienden	NR	0.78 (0.88)
20*	Duurzame vriendschappen	NR	1.01 (0.75)
13	Impulsief gedrag	ZB	0.30 (0.59)
17	Zelfbeschadiging	ZB	0.05 (0.30)
21	Te impulsief	ZB	0.59 (0.77)
22	Makkelijk geld uitgeven	ZB	0.61 (0.80)
23	Roekeloosheid	ZB	0.13 (0.40)
24*	Welbewust geld uitgeven	ZB	1.02 (0.84)

 $\mbox{Al} = \mbox{Affectieve Instabiliteit; IP} = \mbox{Identiteits problemen; NR} = \mbox{Negatieve Relaties; ZB} = \mbox{Zelfbeschadiging; SD} = \mbox{standaard deviatie.}$ 

\*Deze items zijn omgecodeerd zodat een hoge score een BPS-kenmerk weergeeft.

zijn omgecodeerd. Voor het berekenen van de totaalscores en de scores per domein is de handleiding van Morey gevolgd, die aangeeft dat er geen totaal- of domeinscore berekend mag worden als 20% of meer items ontbrekende waarden bevatten. De overige ontbrekende waarden kregen een score van nul.







Statistische analyses

Om te bepalen of de steekproef representatief is voor de Nederlandse bevolking is nagegaan wat het geboorteland en het hoogst gevolgde opleidingsniveau is van de deelnemers. Het opleidingsniveau van de deelnemers is onderverdeeld in vier niveaus: lager onderwijs, middelbaar onderwijs (mavo, lbo, vmbo, lager secundair), hoger middelbaar onderwijs (havo, vwo, mbo, hoger secundair) en hoger onderwijs (universiteit, hoger niet-universitair, hbo). Verder hebben de deelnemers aangegeven of de hoogst gevolgde opleiding wel of niet met een diploma is afgerond. Het geboorteland en het opleidingsniveau van de steekproef is vergeleken met het geboorteland en het opleidingsniveau van de Nederlandse bevolking.

De interne consistentie (Cronbach's a) van de PAI-BOR is berekend in SPSS voor de vier domeinscores en de totaalscore. De zes maanden test-hertest stabiliteit (Pearson correlatie coëfficiënt) is berekend met behulp van de hertest gegevens van 199 personen (één persoon per familie) die de vragenlijst voor de tweede keer hebben ingevuld.

De gemiddelde totaalscore en domeinscores op de PAI-BOR zijn berekend voor de twee leeftijdsgroepen en voor mannen en vrouwen waarbij onderscheid is gemaakt in opleidingsniveaus, maar niet in of de opleiding wel of niet met een diploma is afgerond. Omdat er weinig mensen uit de steekproef lager onderwijs als hoogst gevolgde opleiding hebben, zijn de categorieën lager onderwijs en middelbaar onderwijs in de tabel met normgegevens samengevoegd.

Het effect van sekse, leeftijd en opleidingsniveau op de PAI-BOR score is getoetst met *mixed modeling* in spss. Hierbij is gecorrigeerd voor de afhankelijkheid van personen die uit dezelfde familie komen (ouders, kinderen, broers/zussen). De hoofdeffecten van sekse, leeftijd en opleidingsniveau en de twee- en driewegs interactie effecten tussen deze variabelen op de totale PAI-BOR en de domein scores zijn getoetst. Een p-waarde van 0,05 of minder werd als een significant effect geïnterpreteerd.

Met Multi Groep Confirmatieve Factoranalyse (MGCFA) voor ordinale data in Mplus (versie 4.21) (Muthén & Muthén, 2005) is onderzocht of de vier domeinen van de PAI-BOR zoals voorgesteld door Morey (1991) de Nederlandse data goed weergeven. Bij MGCFA voor ordinale data wordt voorondersteld dat de geobserveerde discrete variabelen indicatoren zijn voor niet geobserveerde (latente) continue respons variabelen en dat deze latente respons variabelen voorspeld worden door de latente factoren (Flora & Curran, 2004; Millsap & Yun-Tein, 2004). Omdat de frequentie van de vierde categorie voor bijna alle items laag was, zijn de derde en vierde categorie (score 2 en 3) samengevoegd voor de MGCFA. De 'complex' optie in Mplus is gebruikt om te corrigeren voor de afhankelijkheid tussen de observaties omdat er vaak meer dan één persoon per familie in de steekproef voorkomt. Dit is een goede manier om voor afhankelijkheid te corrigeren bij analyse van familiedata (Rebollo et al., 2006a). Om te bepalen of het vierfactor model goed past op de Nederlandse data zijn de voor afhankelijkheid gecorrigeerde χ²

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Tabel 2. Onderzoekspopulatie naar opleidingsniveau										
			8		Middelbaar		Hoger Middelbaar onderwijs		Hoger onderwijs	
	N	Niveau onbek- end	Wel di- ploma	(nog) geen diploma	Wel diplo- ma	(nog) geen di- ploma	Wel di- ploma	(nog) geen di- ploma	Wel di- ploma	(nog) geen di- ploma
Mannen 18-35 jaar	1409	54	3	3	160	15	329	32	679	134
Mannen 36-90 jaar	1878	123	34	59	434	60	400	39	689	40
Vrouwen 18-35 jaar	2506	69	12	8	283	28	681	64	1173	188
Vrouwen 36-90 jaar	2718	223	46	88	842	147	635	62	633	42
Totale steekproef	8511	469 6%						197 2%		

-waarde en de Root Mean Error of Approximation (RMSEA; Steiger, 1990) gebruikt. Yu (2002) heeft het gebruik van deze indices bij confirmatieve factor analyse met ordinale data beoordeeld en heeft grenswaarden voorgesteld om aan te geven of een model goed past. Een RMSEA kleiner dan 0,05 geeft aan dat een model goed past en een RMSEA tussen de 0,05 en 0,08 geeft aan het model adequaat past. Zowel de  $\chi^2$  toets als de RMSEA zijn niet onafhankelijk van steekproefgrootte en modelcomplexiteit dus er zijn geen absolute standaarden om te bepalen of een model bij de data past (Schermelleh-Engel & Moosbrugger, 2003a; Yu, 2002). Over het algemeen geldt dat hoe groter de steekproef en hoe complexer het model, hoe sneller de nulhypothese van goede fit wordt verworpen.

### RESULTATEN

In Tabel 2 is het opleidingsniveau van de populatie samengevat voor mannen en vrouwen in de verschillende leeftijdsgroepen. In de onderzochte populatie heeft 37% van de proefpersonen een opleiding aan het hoger onderwijs afgerond met een diploma. Van de totale Nederlandse bevolking (15-65 jaar) heeft 25% een onderwijsniveau van hbo of hoger (Blom et al., 2007). Het opleidingsniveau van de personen in onze steekproef is dus hoger dan in de algemene bevolking. Bijna alle deelnemers (97%) zijn in

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Tabel 3. Gemiddelden en standaarddeviaties van de domeinscores en de totaalscore van de PAI-BOR voor de vier normgroepen per opleidingsniveau en de totale steekproef

		N	Affectieve instabiliteit	Identit- eits- proble- men	Nega- tieve relaties	Zelf be- schadiging	Totaal score
Mannen							
18-35 jaar	Lager en middel- baar onderwijs	181	4.9 (3.0)	4.4 (3.1)	5.0 (3.0)	4.0 (2.5)	18.1 (8.8)
	Hoger middelbaar onderwijs	361	4.0 (2.5)	3.4 (2.2)	4.3 (2.6)	3.2 (2.4)	15.0 (7.1)
	Hoger onderwijs	813	3.7 (2.8)	3.6 (2.4)	3.9 (2.6)	2.5 (2.2)	13.5 (7.2)
36-90 jaar	Lager en middel- baar onderwijs	587	4.5 (2.8)	3.7 (2.5)	4.8 (2.8)	2.6 (2.2)	15.5 (7.9)
	Hoger middelbaar onderwijs	439	3.7 (2.5)	3.1 (2.1)	4.0 (2.3)	2.4 (2.0)	13.1 (6.5)
	Hoger onderwijs	729	3.8 (2.8)	2.9 (2.1)	3.8 (2.4)	2.1 (1.9)	12.6 (6.9)
Vrouwen							
18-35 jaar	Lager en middel- baar onderwijs	331	5.5 (3.2)	5.0 (3.2)	5.4 (3.1)	3.4 (2.6)	19.2 (9.6)
	Hoger middelbaar onderwijs	745	5.0 (3.3)	4.9 (3.0)	5.0 (3.0)	3.0 (2.4)	17.9 (8.8)
	Hoger onderwijs	1361	4.9 (3.2)	4.6 (2.8)	4.5 (2.7)	2.6 (2.3)	16.5 (8.3)
36-90 jaar	Lager en middel- baar onderwijs	1123	4.4 (2.7)	3.9 (2.6)	4.7 (2.7)	2.7 (2.2)	15.5 (7.4)
	Hoger middelbaar onderwijs	697	4.3 (3.0)	3.4 (2.4)	4.4 (2.6)	2.7 (2.2)	14.8 (7.3)
	Hoger onderwijs	675	4.5 (3.0)	3.2 (2.3)	4.3 (2.6)	2.3 (2.0)	14.4 (7.2)
Totale steek- proef		8511	4.4 (3.0)	3.9 (2.7)	4.5 (2.7)	2.7 (2.3)	15.4 (8.0)

NB. Informatie over opleidingsniveau is afwezig voor 469 personen.

Nederland geboren, de generaliseerbaarheid van de resultaten uit deze studie beperken zich dan ook tot deze groep.

De 24 items van de Nederlandstalige PAI-BOR met de gemiddelde itemscores en standaarddeviaties staan weergegeven in Tabel 1. Achter ieder item staat aangegeven tot welke factor het item behoort volgens de indeling van Morey. De gemiddelde score van







de items lopen uiteen van 0,05 voor het item over zelfbeschadiging (item 17) en 1,49 voor het item over de stabiliteit van stemmingen (item 7).

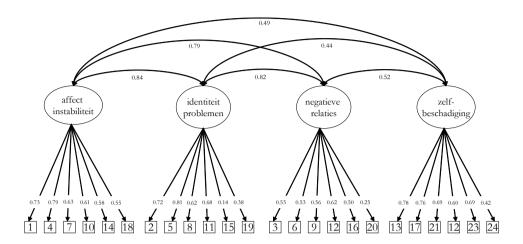
De interne consistentie van de totaalscore van de Nederlandse PAI-BOR is goed ( $\alpha$  = 0.81). De interne consistenties van de vier domeinschalen AI ( $\alpha$  = 0.69), IP ( $\alpha$  = 0.59), NR ( $\alpha$  = 0.52) en ZB ( $\alpha$  = 0.62) blijken enigszins lager dan de interne consistentie van de totaalscore. De zes maanden test-hertest stabiliteit Pearson correlatie coëfficiënt is voor de totale score 0.78 en voor de domeinschalen AI, IP, NR en ZB respectievelijk 0.75, 0.65, 0.60 en 0.64.

Gemiddelde scores en standaarddeviaties van mannen en vrouwen in de twee leeftijdsgroepen op de PAI-BOR en de vier domeinen zijn in Tabel 3 weergegeven per opleidingsniveau. Er is in deze tabel geen onderscheid gemaakt tussen de mensen die een opleiding met een diploma hebben afgerond en mensen die de opleiding (nog) niet met een diploma hebben afgerond.

Het effect van sekse, leeftijd en opleidingsniveau op de PAI-BOR totaalscore en de vier subscores is onderzocht met mixed modeling. Er waren geen driewegs interacties tussen sekse, leeftijd en opleidingsniveau. Een tweewegs interactie tussen sekse en leeftijd bleek aanwezig voor de totaal score ( $F_{(1,7293.117)}$  = 29.104, p < 0.01), en de domeinen at  $(F_{(1,7466,569)} = 23.836, p < 0.01), \text{ ip } (F_{(1,7387.687)} = 76.389, p < 0.01) \text{ en Nr } (F_{(1,7277.034)} = 15.665, p < 0.01)$ < 0.01). Het effect van leeftijd op de totale PAI-BOR score en de domeinen AI, IP en NR is voor mannen sterker dan voor vrouwen. Er was een tweewegs interactie tussen sekse en opleidingsniveau voor de totale PAI-BOR score ( $F_{(2,7640.733)}$  = 5.038, p < 0.01) en de domeinen ai  $(F_{(2,7779.485)} = 6.145, p < 0.01)$ , ip  $(F_{(2,7739.678)} = 49.987, p < 0.01)$ , nr  $(F_{(2,7617.998)} = 49.987, p < 0.01)$ 5.439, p < 0.01) en ZB ( $F_{(2,7973.876)}$  = 3.615, p = 0.027). Hoofdeffecten van sekse, leeftijd en opleidingsniveau waren ook aanwezig. Vrouwen scoren significant hoger dan mannen op de totale score ( $F_{(1,7514.692)} = 58.368$ , p < 0.01) en op de domeinschalen AI ( $F_{(1,7663.740)} = 58.368$ 50.261, p < 0.01), IP  $(F_{(1.7622.791)} = 135.299, p < 0.01)$  en NR  $(F_{(1.7498.435)} = 28.892, p < 0.01)$ . Oudere deelnemers hebben significant lagere scores dan jongere op de totale vragenlijst  $(F_{(1.8010.112)} = 153.209, p < 0.01)$  en de vier domeinschalen at  $(F_{(1.7951.576)} = 41.463, p < 0.01)$ , IP  $(F_{(1,7975,366)} = 213.048, p < 0.01), NR <math>(F_{(1,8003.784)} = 22.468, p < 0.01)$  en ZB  $(F_{(1,7875.781)} = 21.468, p < 0.01)$ 132.783, p < 0.01). Mensen met een lager opleidingsniveau hebben significant hogere scores dan mensen met een hoger opleidingsniveau op de totale vragenlijst  $(F_{(2,7697,794)})$ 72.283, p < 0.01) en de domeinschalen at  $(F_{(2,7593.273)} = 20.619, p < 0.01)$ , NR  $(F_{(2,7702.193)} = 20.619, p < 0.01)$ 54.790, p < 0.01) en ZB ( $F_{(2.7957.189)}$  = 19.499, p < 0.01).

Om na te gaan of het vierfactor model van Morey ook op de Nederlandstalige PAI-BOR van toepassing is, is een Multi Groep Confirmatieve Factoranalyse uitgevoerd. De geschatte factorladingen van de items en correlaties tussen de dimensies van Morey's vierfactor model zijn weergegeven in Figuur I. Alle factorladingen zijn hoger dan 0.40, met uitzondering van de items 15, 19 en 20. De domeinen AI, IP en NR zijn sterk gecorreleerd, terwijl het zB domein minder sterk samenhangt met de andere drie domeinen.





Figuur I. Geschatte factorladingen van de items op de 4 factoren van de PAI-BOR en de correlaties tussen de 4 factoren in een Nederlandse steekproef

Het vierfactor model geeft de Nederlandse data adequaat weer (RMSEA = 0.08,  $\chi^2_{(157)}$  = 9881.31, p = 0.000).

### DISCUSSIE

In deze studie is de betrouwbaarheid en de factorstructuur van de Nederlandse vertaling van de PAI-BOR beoordeeld. De PAI-BOR data van 8511 mannen en vrouwen van verschillende leeftijden en opleidingsniveaus zijn hiervoor gebruikt. De steekproef is representatief voor de Nederlandse bevolking, hoewel het opleidingsniveau hoger ligt (37% hoger onderwijs) dan dat van de algemene bevolking (25% hoger onderwijs) en het grootste gedeelte van de steekproef in Nederland is geboren (97%). Uit eerdere onderzoeken is gebleken dat sociaal economische status, rookgedrag, sportgedrag en religieuze achtergrond van de steekproef redelijk tot goed vergelijkbaar zijn met die van de Nederlandse bevolking (Boomsma et al. , 1999; 2002b; De Moor et al., 2006; Koopmans et al., 1999).

De Nederlandse versie van de PAI-BOR blijkt op basis van deze studie voldoende betrouwbaar ( $\alpha$  = 0.81) en is vergelijkbaar met de betrouwbaarheid van de Engelse vragenlijst gemeten in een Amerikaanse populatiebrede steekproef ( $\alpha$  = 0.87) (Morey, 1991). De betrouwbaarheid van de domeinschalen is lager ( $\alpha$  = 0.52 tot  $\alpha$  = 0.68) dan de betrouwbaarheid van de totale schaal zoals ook gerapporteerd door Morey ( $\alpha$  = 0.62 tot  $\alpha$  = 0.71). De lagere betrouwbaarheid van de domeinschalen is deels te verklaren door het





geringere aantal items per domein. De hertest meting zes maanden na de eerste meting liet een goede stabiliteit van de vragenlijst zien. De test-hertest stabiliteit coëfficiënt was 0.78 voor de totale score en voor de domeinschalen AI, IP, NR en ZB respectievelijk 0.75, 0.65, 0.60 en 0.64. De test-hertest betrouwbaarheid correlaties gerapporteerd door Morey zijn enigszins hoger (0.90 voor de totale score en 0.81 tot 0.85 voor de domeinscores), wat mogelijk te verklaren is door de kortere tijd tussen de twee metingen (28 dagen versus 6 maanden). Waarschijnlijk zegt de zes maanden test-hertest correlatie meer over de stabiliteit van BPS kenmerken dan over de betrouwbaarheid van de vragenlijst.

Vrouwen hebben significant hogere totaal-, AI-, IP- en NR scores dan mannen. Dit is in tegenstelling tot wat is gerapporteerd door Morey (1991) die in zijn steekproef geen sekse verschillen vond. De verschillen tussen mannen en vrouwen in de Nederlandse steekproef zijn echter klein (2,0 punten op de totaalscore, Cohen's d = 0.3) (Cohen, 1969). Over het algemeen ontstaan BPS-symptomen in de vroege volwassenheid (American Psychiatric Association, 2000) en nemen ze daarna geleidelijk af (Stone, 1990; Coid et al., 2006). In onze studie vertonen jongere mensen meer BPS-symptomen dan ouderen, zoals ook gerapporteerd door Morey (1991). Longitudinaal onderzoek naar het verloop van borderline kenmerken in twee klinische populaties liet zien dat sommige symptomen blijvend zijn, terwijl andere verbetering laten zien (Zanarini et al., 2007; Skodol et al., 2005). Een laag opleidingsniveau is in onze studie geassocieerd met meer BPS kenmerken. Dit is in overeenstemming met wat werd gerapporteerd door Torgersen et al. (2001) die in een grote populatie brede steekproef vonden dat de diagnose BPS geassocieerd is met minder gevolgde onderwijsjaren.

Bij een studie over persoonlijkheidseigenschappen in de normale populatie moet men rekening houden met een mogelijke invloed van non-respons op de resultaten. Wanneer personen met veel borderline kenmerken bijvoorbeeld minder geneigd zijn om een vragenlijst in te vullen, kan dit de validiteit van de studie ondermijnen. We hebben een non-respons onderzoek uitgevoerd waarbij de PAI-BOR score van mensen afkomstig uit families waarin veel mensen de vragenlijst invulden werd vergeleken met de PAI-BOR score van mensen afkomstig uit families waarin weinig mensen de vragenlijst invulden. De PAI-BOR scores van mensen uit weinig coöperatieve families waren hoger dan de PAI-BOR score van mensen uit hoog coöperatieve families. Het verschil was echter klein (minder dan één punt op een schaal van 0 tot 72) en zal waarschijnlijk een geringe invloed op de resultaten hebben gehad (Distel et al., 2007).

Vragenlijstonderzoek is een veelgebuikte en efficiënte methode om gegevens te verzamelen van grote groepen mensen, zoals nodig is voor grootschalige epidemiologisch en genetisch onderzoek. Dit onderzoek laat zien dat BPS-kenmerken in de algemene populatie betrouwbaar vastgesteld kunnen worden met de Nederlandstalige versie van de PAI-BOR. De totale score is betrouwbaarder dan de domeinscores gezien het geringe aantal items per domein. De vier domeinen zoals voorgesteld door de testuitgever dr.



Morey zijn ook terug te vinden in de Nederlandse data en de gemiddelde pai-bor scores voor twaalf groepen kunnen met enige voorzichtigheid geïnterpreteerd worden als normgegevens.







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DE PERSONALITY ASSESSMENT

INVENTORY- BORDERLINE

KENMERKEN SCHAAL IN RELATIE

TOT DE REVISED NEO

PERSONALITY INVENTORY EN

DE NEO FIVE FACTOR

**INVENTORY** 

229

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### **ABSTRACT**

The Personality Assessment Inventory-Borderline features scale in relation to the Neo Personality Assessment Inventory and the Neo Five Factor Inventory.

The Personality Assessment Inventory-Borderline features scale (Pai-Bor) was developed by Morey to assess borderline symptomatology by means of self-report. This appendix describes a study in which we investigated whether the Revised Neo Personality Inventory (Neo-Pi-R) and the Neo Five Factor Inventory (Neo-FFI) explain an equal amount of variance in Pai-Bor scores. Multiple regression analysis showed that the five dimensions of the Neo-Pi-R and the Neo-FFI explain 50% and 41% of the variance in Pai-Bor scores, respectively. The 30 facets of the Neo-Pi-R explain about 10% more variance in Pai-Bor score than the five main personality dimensions. The Pai-Bor is positively associated with neuroticism and openness to experience and negatively associated with agreeableness and conscientiousness. Variance in borderline symptomatology could thus be almost equally well explained by the 60 item Neo-FFI and the 240 item Neo-PI-R.

### SAMENVATTING

E Personality Assessment Inventory-Borderline features scale (Paibor) is door dr. Morey ontwikkeld om borderline symptomatologie in kaart te brengen door middel van een zelf beoordelingsvragenlijst. Dit appendix beschrijft een studie waarin we hebben onderzocht of de Revised Neo Personality Inventory (Neo-PI-R) en de Neo Five Factor Inventory (Neo-FFI) evenveel variatie in Pai-Bor scores verklaren. Multipele regressie analyse liet zien dat de vijf dimensies van de Neo-PI-R en de Neo-FFI respectievelijk 50% en 41% van de variantie in Pai-Bor scores verklaren. De 30 subschalen van de Neo-PI-R verklaren over het algemeen weer ruim 10% meer variantie dan de vijf hoofddimensies van de Neo-PI-R. Er bestaat een positieve relatie tussen de Pai-Bor score en neuroticisme en openheid voor ervaringen en een negatieve relatie tussen de Pai-Bor score en altruïsme en consciëntieusheid. Borderline symptomatologie wordt nagenoeg even goed verklaard uit de verkorte Neo-FFI als uit de uitgebreide Neo-PI-R.

### **INTRODUCTIE**

EN ZELFBEOORDELINGVRAGENLIJST WAARMEE borderline persoonlijkheid symptomatologie op een continue schaal in kaart gebracht kan worden is de Engelstalige Personality Assessment Inventory-Borderline features schaal (PAI-BOR; Morey, 1991). De PAI-BOR bestaat uit 24 items met vier onderliggende factoren (zes items per factor) die elk één van de hoofdkenmerken van borderline persoonlijkheid weerspiegelen: affectieve instabiliteit (AI), identiteitsproblemen (IP), negatieve relaties (NR) en zelfbeschadiging (ZB). De Engelstalige PAI-BOR is betrouwbaar en valide gebleken in verschillende Amerikaanse steekproeven (Morey, 1991). In dit appendix wordt de criteriumvaliditeit van de Nederlandse vertaling van de PAI-BOR gerapporteerd in een groep eerstejaars psychologie en pedagogiek studenten door na te gaan in hoeverre borderline persoonlijkheid verklaard kan worden door de 'Big Five' persoonlijkheidsdimensies gemeten met de Revised Neo-Personality Inventory (Neo-PI-R) en de Neo Five Factor Inventory (Neo-FFI; Costa & McCrae, 1992).

### **MFTHODE**

#### **Deelnemers**

In 2004 is de PAI-BOR afgenomen bij een steekproef van 306 (16% mannen) eerstejaars psychologie en pedagogiek studenten. De gemiddelde leeftijd was 20,9 jaar (SD = 4.5). De minimum leeftijd was 17 en de maximum leeftijd 59 jaar. Door 283 personen is ook de NEO-PI-R ingevuld.

### Vragenlijsten

Nederlandse PAI-BOR persoonlijkheidsvragenlijst

De Engelstalige PAI-BOR is vertaald naar het Nederlands. De Nederlandse versie is daarna terugvertaald naar het Engels door een vertaler met Engels als moedertaal. Deze terugvertaling is goedgekeurd door dr. Morey, de ontwikkelaar van de Engelse vragenlijst. De vier antwoordcategorieën van de items zijn: o Helemaal niet waar, I Een beetje waar, 2 Grotendeels waar en 3 Helemaal waar. Voor de totaalscores en de scores per dimensie kunnen somscores berekend worden. In deze steekproef bevatte geen van de items ontbrekende waarden. Gemiddeldes, standaard deviaties en de geobserveerde range van de scores op de PAI-BOR zijn in Tabel I weergegeven. Er bleken in deze steekproef geen verschillen te bestaan tussen mannen en vrouwen wat betreft de gemiddelde



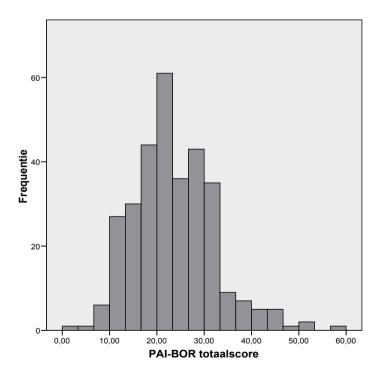
Tabel I. Gemiddeldes (M), standaard deviaties (SD) en de geobserveerde range van de PAI-BOR							
	Totaal score	Affectieve instabiliteit	Identiteits- problemen	Negatieve relaties	Zelf-bescha- diging		
M (SD)	23.4 (8.5)	7.1 (3.1)	5.8 (2.8)	6.0 (2.7)	4.5 (3.3)		
range	3-58	0-17	0-16	1-15	0-15		

scores en standaard deviaties op de PAI-BOR. In Figuur 1 is de frequentieverdeling van de totaalscores op de PAI-BOR weergegeven.

### NEO-PI-R persoonlijkheidsvragenlijst

232

De NEO-PI-R is een gestandaardiseerde vragenlijst die de vijf hoofddimensies van persoonlijkheid meet (Costa & McCrae, 1992; Hoekstra et al., 1996). De NEO-PI-R bestaat uit 240 items met vijf antwoordmogelijkheden. De vijf hoofdschalen zijn Neuroticisme (N), Extraversie (E), Openheid voor ervaringen (O), Altruïsme (A) en Consciëntieusheid (C). Iedere hoofdschaal bestaat uit 48 items en kan weer onderver-



Figuur I. Frequentieverdeling van de totaalscores op de PAI-BOR.



Tabel 2. Pearson correlaties tussen de PAI-BOR en de vijf schalen van de
NEO-PI-R en de NEO-FFI

	NEO-PI-R	NEO-FFI
Neuroticisme	0.574**	0.462**
Extraversie	0.021	-0.085
Openheid voor ervaringen	0.201**	0.145*
Altruisme	-0.335**	-0.384**
Consciëntieusheid	-0.4 2**	-0.321**
*p < 0.05, ** p < 0.01		

deeld worden in zes subschalen met elk acht items. De verkorte versie van de Neo-PI-R, de Neo-FFI, bestaat uit een selectie van 60 items uit de Neo-PI-R. Voor deze studie zijn de scores op de vijf hoofdschalen (elk bestaande uit 12 items) van de Neo-FFI berekend met de items uit de Neo-PI-R. De scores op alle hoofd- en subschalen zijn somscores. Ontbrekende waarden op items (0,05% van alle antwoorden) zijn opgevuld met de itemgemiddeldes.

### Statistische analyses

De criteriumvaliditeit is onderzocht met behulp van multipele regressieanalyses in SPSS. Er is gekeken in hoeverre de scores op de PAI-BOR (totaalscores en scores van de subschalen) verklaard kunnen worden uit de schalen van de NEO-PI-R (de vijf hoofdschalen van de NEO-PI-R, de vijf hoofdschalen van de NEO-PI-R).

### **RESULTATEN**

Tabel 2 laat zien dat de correlaties tussen de PAI-BOR en de vijf persoonlijkheidsschalen op basis van de NEO-PI-R en de NEO-FFI zeer veel gelijkenis vertonen. Tabel 3 geeft de correlaties tussen de PAI-BOR en de 30 facetten van de NEO-PI-R. De sterkste associatie bestaat tussen de PAI-BOR en de facetten van de schaal neuroticisme.

Regressieanalyse laat zien dat de vijf hoofddimensies van de NEO-PI-R ongeveer 10% meer variantie verklaren dan de vijf dimensies gebaseerd op de NEO-FFI voor zowel de totaalscore (50,1% versus 40,7%) als de subschalen AI en ZB van de PAI-BOR (42,1% versus 32,4% voor AI en 47,3% versus 34,6% voor ZB). De subschalen IP en NR van de PAI-BOR worden in even hoge mate door de dimensies van de NEO-PI-R als de NEO-FFI verklaard (32,8% versus 33,8% voor IP en 24,9% versus 24,7% voor NR). De 30 subschalen van de NEO-PI-R verklaren over het algemeen weer ruim 10% meer variantie dan de vijf hoofd-

Tabel 3. Pearson Correla	ties tussen de F	PAI-BOR en	de 30 face	ten van de l	NEO-PI-R
	Totaal score	Al	IP	NR	ZB
Neuroticisme					
Angst	0.398**	0.417**	0.472**	0.355**	-0.067
Ergernis	0.552**	0.595**	0.353**	0.373**	0.255**
Depressie	0.488**	0.465**	0.552**	0.408**	0.009
Schaamte	0.168**	0.173**	0.304**	0.104	-0.079
Impulsiviteit	0.442**	0.290**	0.170**	0.218**	0.549**
Kwetsbaarheid	0.356**	0.370**	0.410**	0.239**	0.019
Extraversie					
Hartelijkheid	-0.069	-0.121*	-0.154**	-0.091	0.145*
Sociabiliteit	-0.060	-0.174**	-0.122*	-0.112	0.212**
Dominantie	0.026	-0.071	-0.162**	0.075	0.216**
Energie	0.141*	0.013	-0.081	0.109	0.336**
Avonturisme	0.149*	0.035	0.006	0.003	0.348**
Vrolijkheid	-0.102	-0.170**	-0.239**	-0.121*	0.204**
Openheid voor ervaringen					
Fantasie	0.272**	0.262**	0.177**	0.072	0.246**
Esthetiek	0.146*	0.142*	0.089	0.112	0.075
Gevoelens	0.304**	0.379**	0.213**	0.175**	0.098
Verandering	-0.128*	-0.094	-0.202**	-0.179**	0.081
ldeeën	0.055	0.150*	0.017	0.094	-0.094
Waarden	0.059	0.114	-0.031	-0.032	0.098
Altruïsme					
Vertrouwen	-0.337**	-0.315**	-0.222**	-0.370**	-0.077
Oprechtheid	-0.259**	-0.161**	-0.087	-0.162**	-0.312**
Zorgzaamheid	-0.071	-0.101	-0.059	-0.109	0.054
Inschikkelijkheid	-0.383**	-0.365**	-0.159**	-0.266**	-0.289**
Bescheidenheid	-0.176**	-0.115	0.005	-0.166**	-0.214**
Medeleven	-0.031	-0.028	0.072	-0.088	-0.042
Consciëntieusheid					
Doelmatigheid	-0.425**	-0.284**	-0.349**	-0.205**	-0.364**
Ordelijkheid	-0.196**	-0.064	-0.141*	0.050	-0.371**
Betrouwbaarheid	-0.268**	-0.151*	-0.148*	-0.074	-0.366**
Ambitie	-0.137*	-0.066	-0.177**	0.112	-0.237**
Zelfdiscipline	-0.384**	-0.249**	-0.315**	122*	-0.390**
	-0.398**	-0.140*	-0.152*	114	-0.680**





Tabel 4. Gestandaardiseerde regressiecoëfficienten van regressie van	1
PAI-BOR op NEO-PI-R en NEO-FFI	

	NEO-PI-R					NEO-FFI				
	Ν	Е	0	Α	С	Ν	Е	0	Α	С
TOT	0.753**	0.021	0.202**	-0.336**	-0.427**	0.459**	-0.081	0.141*	-0.344**	-0.333**
Al	0.538**	-0.111	0.260**	-0.295**	-0.221**	0.461**	-0.225**	0.194**	-0.259	-0.204**
IP	0.539**	-0.177**	0.083	-0.125**	-0.293**	0.531**	-0.222**	0.081	-0.186**	-0.258**
NR	0.414**	-0.034	0.077	-0.298**	-0.078	0.388**	-0.105	0.074	-0.289**	-0.023
ZB	0.175**	0.346**	0.141*	-0.242**	-0.588**	-0.028	0.286**	0.049	-0.248**	-0.433**

 $^*p < 0.01$ . TOT = PAI-BOR totaalscore; AI = Affectieve Instabiliteit; IP = Identiteitsproblemen; NR = Negatieve Relaties; ZB = Zelfbeschadiging; N = Neuroticisme; E = Extraversie; O = Openheid voor ervaringen; A = Altruïsme; C = Consciëntieusheid.

dimensies van de NEO-PI-R (respectievelijk 63,1 versus 50,1%, 53,9 versus 42,1%, 44,9 versus 32,8%, 38,8 versus 24,9% en 64,4% versus 42,1% voor de totaalscore van PAI-BOR, AI, IP, NR en ZB).

Tabel 4 bevat een overzicht van de gestandaardiseerde regressiecoëfficiënten uit de regressieanalyses van de PAI-BOR op de NEO-PI-R en de NEO-FFI. De gestandaardiseerde regressiecoëfficiënten van de analyses met de NEO-PI-R en de NEO-FFI vertonen opvallend veel gelijkenis. De PAI-BOR totaalscore wordt in grote mate verklaard door een hoge score op N en in kleinere mate door lage scores op altruïsme en consciëntieusheid en hoge scores op openheid voor ervaringen. Opmerkelijk is dat de subschalen AI, IP en NR net als de totaalscore in grote mate door neuroticisme bepaald worden, terwijl dit voor zb niet geldt. De score op zb wordt grotendeels verklaard door hoge scores op extraversie en lage scores op altruïsme en consciëntieusheid.

### DISCUSSIE

Bovenstaande resultaten wijzen erop dat de criteriumvaliditeit van de Nederlandstalige PAI-BOR goed is. Borderline symptomatologie kan voor een groot deel verklaard worden uit neuroticisme (positief verband) en voor een kleiner deel uit altruïsme en consciëntieusheid (negatief verband) en uit openheid voor ervaringen (positief verband). Opvallend hierbij is dat borderline symptomatologie nagenoeg even goed verklaard wordt uit de verkorte NEO-FFI als uit de uitgebreide NEO-PI-R (4I versus 50%). De 30 facetten van de NEO-PI-R verklaren 10% meer variantie in PAI-BOR scores dan de vijf hoofddimensies van de NEO-PI-R. De samenhang tussen borderline symptomatologie en de vijf hoofddimensies van persoonlijkheid komt sterk overeen met de bevindingen van Morey (1991).









#### Nederlands Tweelingen Register (NTR)

#### Oost-Vlaams Meerlingenregister

Datum

Uw brief van

Telefax 020-5988832 Bijlagen Vragenlijst en informatiefolder

November 2004

Ons kenmerk Liist 7 Telefoon Nederland

Telefoon België 09-2402914

020-5988817 b.g.g. 020-5988787

Postadres: Van der Boechorststraat 1, 1081 BT Amsterdam



### vrije Universiteit amsterdam

Geachte heer, mevrouw,

Wij nodigen u uit om deel te nemen aan een vragenlijstonderzoek bij twee- en meerlingen en hun familieleden in Nederland en België. Dit onderzoek richt zich op gezondheid en leefgewoonten. In de bijgevoegde informatiefolder kunt u meer lezen over de achtergronden van dit onderzoek. U doet mee door de vragenlijst in te vullen en deze naar ons op te sturen in de antwoordenvelop (postzegel is niet nodig). Uw deelname wordt zeer op prijs gesteld.

De vragenlijst wordt toegestuurd aan meerlingen en hun broers, zussen, ouders en partners. Als er familieleden zijn die geen vragenlijst hebben ontvangen maar wel mee willen doen, neemt u dan a.u.b. contact met ons op. Wij sturen dan één of meerdere vragenlijsten na. In Nederland kunt u contact opnemen met Marijn Distel (<a href="vragenlijstNTR@psy.vu.nl">vragenlijstNTR@psy.vu.nl</a>). Zij is telefonisch te bereiken op het nummer 020-5988817 (b.g.g. 020-5988792). In België kunt u contact opnemen met Catherine Derom (<a href="catherine.derom@uz.kuleuven.ac.be">catherine.derom@uz.kuleuven.ac.be</a>) of Lut De Zeure (<a href="twinlokaal@hotmail.com">twinlokaal@hotmail.com</a>). Beiden zijn telefonisch te bereiken op het nummer 09-2402914. Ook als u na het lezen van deze brief en de informatiefolder nog vragen heeft kunt u natuurlijk contact met ons opnemen.

Wij hopen dat u bereid bent om aan dit onderzoek mee te werken. Met het invullen van deze vragenlijst levert u een belangrijke bijdrage aan het wetenschappelijk onderzoek naar de achtergronden van gezondheidsverschillen tussen mensen.

Uw deelname is geheel vrijwillig. Als u vragen te indringend of te vervelend vindt hoeft u deze, als u daar tegenop ziet, niet in te vullen.

Wij willen u bij voorbaat zeer hartelijk danken voor uw medewerking. Met vriendelijke groet,

Mw prof. dr. D.I. Boomsma, Mw dr. J.M. Vink Mw dr. C.A. Derom

Afdeling Biologische Psychologie Van der Boechorststraat 1, Amsterdam

Twins UZ Gent De Pintelaan 185 PB 91 B-9000 Gent

237

ps marijn distel.indd 237 05/08/09 11:14:30





#### familieonderzoek naar gezondheid en leefgewoonten

In Nederland en België wordt grootschalig onderzoek gedaan naar gezondheid en leefgewoon ten. Tweelingen en hun familiele den doen mee door het invullen van vragenlijsten.

#### waarom tweelingfamilies?

Tweelingfamilies vormen voor de wetenschap een unieke groep, want met hun hulp wordt onder

zocht in welke mate een bepaalde eigenschap erfelijk is. Eeneiige tweelingen zijn genetisch 100% identiek Twee-eiige tweelingen, broers en zussen en ouders en kinderen delen gemiddeld de helft van hun erfelijk materiaal.Stel nu dat erfelijke aanleg van belang is voor het ontstaan van overgewicht. Dan zullen eeneiige tweelingen vaker allebei ongeveer hetzelfde lichaams gewicht hebben dan twee-eiige tweelingen, broers en zussen, die geen tweelingpaar zijn of ouders en kinderen. Eenei jaet weelingen hebben immers dezelfde erfelijke aanleg. Door ook echtgenoten/partners van tweelingen te betrekken bij het onderzoek kan worden nagegaan hoeveel invloed de omgeving heeft op lichaamsgewicht, maar ook op andere eigenschappen  $zo als\, sport gedrag of\, persoon lijkheid of\, op\, gezondheid$ 



#### onderzoek naar gezondheid, leefgewoonten en persoonlijkheid

Sommige mensen ervaren hun lichamelijke en geestelijkegezondheidals erg goed, terwijl anderen dat in mindere mate doen of zich juist ongezond voelen. Sommige mensen vinden het heerlijk om regelmatigte sporten, terwiil andere mensen liever een boek lezen of ty kiiken. Sommige mensen maken zich snel ongerust terwiil anderen altiid onbezoradziin. Door vragen te stellen over gezondheid, leefgewoonten en persoonlijkheid wordt geprobeerdom in kaart te brengenof deze verschillen tussen mensen worden verklaard door verschillen in hun omgeving (zoals sport gedrag van ouders of partner, beroep, hoeveelheid vrije tijd en werk,



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school vrienden) of door verschillen in erfelijke aanlea.

#### al eerder meegedaan

Velen van u hebben al eerder meegedaan aan onderzoek. Het zal u misschien opvallen dat som mige vragen ook in voorgaandelijsten zijn gesteld. Tochis het van groot belang dat u deze vragen weer beantwoordt. Door regelmatig dezelfde vragen te stellen kunnen belangrijke veranderingen in iemands leven in kaart worden gebracht. Op deze manier kunnen we bijvoorbeeld onderzoeken hoe gezondheid en Jeefgewoonten veranderen als mensen ouder worden.

#### internationaal

Dit onderzoekis onderdeelvan een groot internationaal project. Naast tweelingen en hun familieleden uit Nederlanden België doen ook tweelingen en hun familieledenuit Australië mee.

#### vertrouwelijk

We hopen van harte dat u bereid zult zijn aan dit onderzoek deel te nemen. Alle informatie wordt strikt vertrouwelijk behandeld. Persoonlijke gegevens, zoals naam en adres, worden losgekoppeld van uw antwoorden. De gegevensworden uit sluitend voor wetenschappelijke doeleinden gebruikt





Misschien heeft u een partner, of broers, zussen en ouders die graag mee willen doen aan dit onderzoek, maar die geen vragenlijst van ons hebben ontvangen. Wij sturen graag een vragenlijstaan iedereen ouder dan 16 jaar die mee wil doen. U kunt dan telefonischcontact opnemenof reageren via e-mail.

In Nederland kunt u contact opnemen met SuzanneThijs (sm.thijs@psy.vu.nl) of Marijn Distel (md.distel@psy.vu.nl).Zij zijn telefonisch te bereiken op het nummer020-444.88.17( b.g.g. 020-444.87.87)  $In Belgi\"{e}kuntu contactopnemen met Catherine Derom$ (catherine.derom@uz.kuleuven.ac.b) of Lut De Zeure (twinlokaal@hotmail.com). Zii ziin telefonisch te bereiken op het nummer 09-240.29.14

#### tenslotte

238

Door het invullen van de vragenlijst levert u een belan grijke bijdrage aan het wetenschappelijke onderzoek naar gezondheid en leefgewoonten. De medewerking van zoveel mogelijk tweelingen, hun partners en hun  $familiele den is \ van essentie elbelang \ voor \ de \ voortgang$ van het onderzoek. Dit geldt zowel voor mensen die al eerdermeegedaanhebbenals voor mensendie voor het eerst meedoen, zowel voor tweelingen en hun partners als voor broers, zussen en ouders. Met uw medewerking kunnen we meer te weten komen over de factorer die van invloed zijn op gezondheid,leefgewoontenen persoonliikheid







Maart 2005

#### Geachte heer/mevrouw,

Eind november heeft u als het goed is een vragenlijst ontvangen van het Nederlands Tweelingen Register. Volgens onze administratie hebben wij uw vragenlijst nog niet ontvangen. Wij hopen van harte dat u aan dit onderzoek mee wilt werken en dat wij nog een ingevulde vragenlijst van u zullen ontvangen. U levert daarmee een belangrijke bijdrage aan de wetenschap!

Als uzelf of een familielid de vragenlijst niet heeft ontvangen of als u nog vragen heeft, neem dan alstublieft contact met ons op. U kunt ook onze website raadplegen: <a href="www.tweelingenregister.org">www.tweelingenregister.org</a>. Onder het kopje "nieuws" staat informatie over dit onderzoek en kunt u de antwoorden op veelgestelde vragen lezen. Ook kunt u via de website een adreswijziging doorgeven.

Ingevulde lijsten kunnen worden teruggestuurd in de antwoordenveloppe. Heeft u die niet meer in uw bezit, dan kunt u de lijst sturen naar het antwoordnummer van het Nederlands Tweelingen Register wat op de andere zijde staat (een postzegel is niet nodig).

Als u de vragenlijst ondertussen al heeft ingevuld en teruggestuurd kunt u deze herinnering als niet verstuurd beschouwen en willen wij u hartelijk bedanken.

Met vriendelijke groet,

Mw prof.dr. Dorret Boomsma, Mw dr. Jacqueline Vink Mw dr. Catherien Derom

### Familieonderzoek naar Gezondheid en Leefgewoonten



Nederlands Tweelingen Register Afd. Biologische Psychologie, VU Antwoordnummer 2941 1000 SN Amsterdam Tel. 020-598 8817

Email: vragenlijstNTR@psy.vu.nl

EIRTS.

Oost-Vlaams Meerlingenregister Twins UZ Gent De Pintelaan 185 PB 91 B-9000 Gent Tel. 09-2402914 catherine derom@uz kuleuven ac h

catherine.derom@uz.kuleuven.ac.be/twinlokaal@hotmail.com



239

Vrije Universiteit amsterdam











**(** 



Uw brief van

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Bijlagen

Ons kenmerk

Uw kenmerk Telefoon Nederland

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Postadres: Van der Boechorststraat 1, 1081 BT Amsterdam



#### vrije Universiteit amsterdam

Geachte heer, mevrouw,

In november 2004 heeft u van ons een vragenlijst ontvangen (lichtgroene kaft) in het kader van onderzoek bij tienduizenden twee- en meerlingfamilies in Nederland en België. Dit onderzoek richt zich op gezondheid en leefgewoonten. Wij hebben van u een ingevulde vragenlijst ontvangen waarvoor wij u heel hartelijk bedanken. Uw bijdrage levert een belangrijke bijdrage aan het wetenschappelijk onderzoek naar gezondheidsverschillen tussen mensen.

Wij zijn nu bezig met een vervolgonderzoek waarin we een verkorte vragenlijst sturen aan een paar honderd willekeurig gekozen deelnemers, die al eerder meededen. Dat doen we omdat het belangrijk is om inzicht te krijgen in de mate waarin antwoorden op de vragen kunnen veranderen over een korte tijd. Sportgedrag, bijvoorbeeld, kan in een paar maanden tijd veranderen en dat geldt natuurlijk ook voor roken of stemming. Wij willen u daarom vragen of het mogelijk is dat u deze verkorte versie van de vragenlijst invult en aan ons terugstuurt.



We nodigen dit keer slechts een kleine groep mensen uit. Daarom kunnen we u als dank voor uw herhaalde deelname een kleine attentie sturen. Dit is de stappenteller op de foto hiernaast. Hiermee kunt u zelf uw dagelijkse lichamelijke activiteit of energieverbruik meten. U kunt achterin de vragenlijst aangeven of u er prijs op stelt om de NTRstappenteller te ontvangen.

Wij willen u vriendelijk vragen om uw medewerking, maar hebben er uiteraard alle begrip voor als het u op dit moment niet goed zou uitkomen opnieuw mee te doen. Graag danken we u bij voorbaat voor uw herhaalde deelname!

Met vriendelijke groet,

60mm/nb Mw prof. dr. D.I. Boomsma,

Mw dr. J.M. Vink,

Mw drs. M.A. Distel

Afdeling Biologische Psychologie

Van der Boechorststraat 1, Amsterdam





#### Nederlands Tweelingen Register (NTR)

Datum November 2005 Uw brief van

Telefax 020-598 8832 Bijlagen adresformulier en antwoordenvelop

Ons kenmerk offspring Uw kenmerk b.g.g. 020-598 8792 Telefoon 020-598 8817

Email

vragenlijstntr@psy.vu.nl

Postadres: Van der Boechorststraat 1, 1081 BT Amsterdam



### vrije Universiteit amsterdam

Geachte heer, mevrouw,

U staat ingeschreven bij het Nederlands Tweelingen Register (NTR) en heeft één of meerdere keren meegewerkt aan het onderzoek naar gezondheid en leefgewoonten. Wij laten u hierbij heel graag weten dat wij uw deelname zeer op prijs stellen.

Bij het NTR staan meerlingen en hun ouders, broers, zussen en partners ingeschreven. Op dit moment zijn we bezig met een uitbreiding van het NTR. We zouden daarvoor graag de kinderen van deelnemers uitnodigen om zich in te schrijven bij het NTR. We wenden ons daarom tot u met het verzoek of u aan uw kinderen wilt vragen of ze, nu of in de toekomst, mee willen werken aan onderzoek van het NTR.

Als uw kinderen hun toestemming geven, wilt u dan op het bijgevoegde adresformulier hun naam en (post)adres invullen? U kunt het formulier in de bijgevoegde antwoordenvelop (postzegel niet nodig) aan ons terug sturen. Wij sturen uw volwassen kinderen dan een informatiepakket en een aanmeldingsformulier toe. Uw minderjarige kinderen worden niet zelf benaderd, maar uitsluitend via de ouders.

De deelname van uw kinderen vormt een belangrijke toevoeging aan het wetenschappelijke onderzoek. Wij hopen van harte dat u bereid bent dit verzoek met uw kinderen te bespreken.

Wij willen u en uw kind(eren) bij voorbaat zeer hartelijk danken. Met vriendelijke groet,

Mw. prof. dr. D.I. Boomsma Mw. drs. M.A. Distel

Afdeling Biologische Psychologie

Van der Boechorststraat 1, Amsterdam



### Adresformulier Nederlands Tweelingen Register

Hoeveel kinderen heeft u? Ik heb \_\_\_\_\_ kind(eren).

Wilt u van uw <b>thuiswonende</b> kinderen hieronder de gegevens noteren?				
Achternaam:				
Geslacht: o man o vrouw				
Geboortedatum:				
Achternaam:				
	Initialen:			
Geslacht: o man o vrouw				
Geboortedatum:				
Achternaam:				
	Initialen:			
Geslacht: o man o vrouw				
Geboortedatum:				
A 14				
Achternaam:				
Geslacht: o man o vrouw	_Initialen:			
Geboortedatum.				
Achternaam:				
Roepnaam:	_Initialen:			
Geslacht: o man o vrouw				
Geboortedatum:				

De gegevens van uw uitwonende kinderen kunt u aan de andere zijde noteren.







Nederlands Tweelingen Register (NTR)

Datum augustus 2006 Ons kenmerk I lw hrief van

Telefax 020-598 8832 Bijlagen aanmeldingsformulier, vragenlijst,

Uw kenmerk b.g.g. 020-598 8787

Telefoon 020-598 8817

informatiefolder en twinfo

vragenlijstntr@psv.vu.nl

Postadres: Van der Boechorststraat 1, 1081 BT Amsterdam



#### vrije Universiteit amsterdam

Geachte heer, mevrouw,

Bij het Nederlands Tweelingen Register (NTR) staan meerlingen en hun ouders, broers, zussen en partners ingeschreven. Tenminste één van uw ouders staat ingeschreven bij het NTR. Op dit moment zijn we bezig met een uitbreiding van het register. We zouden u als kind van een deelnemer graag uitnodigen om zich in te schrijven.

Onderzoek van het NTR richt zich op het verklaren van verschillen tussen mensen in bijvoorbeeld gezondheid en leefgewoonten. In de informatiefolder kunt u meer lezen over tweeling en familieonderzoek.

U schrijft zich in bij het NTR door het aanmeldingsformulier in te vullen en te ondertekenen. Na aanmelding kunt u in de toekomst schriftelijk benaderd worden met de vraag of u mee wilt werken aan een onderzoek. Meestal wordt u gevraagd thuis een vragenlijst in te vullen. Ook zult u één keer per jaar ons informatiebulletin ontvangen met de belangrijkste onderzoeksresultaten en leuke wetenswaardigheden over meerlingen.

Wij zijn zo vrij geweest om de vragenlijst behorende bij het familieonderzoek naar gezondheid en leefgewoonten al toe te sturen en hopen dat u bereid bent om deze in te vullen en samen met het aanmeldingsformulier aan ons terug te sturen in de bijgevoegde antwoordenvelop (postzegel niet nodig). Uw adresgegevens worden bij binnenkomst gescheiden van de vragenlijst verwerkt. Als u het aanmeldingsformulier liever apart van de vragenlijst verstuurt kunt u het aanmeldingsformulier in een ongefrankeerde envelop versturen naar: Nederlands Tweelingen Register; M.A. Distel; Antwoordnummer 2941; 1000 SN Amsterdam.

Wij hopen van harte dat u bereid bent deel te nemen aan onderzoek van het NTR. Wij willen u bij voorbaat zeer hartelijk danken.

Met vriendelijke groet,

Mw. prof. dr. D.I. Boomsma Mw. drs. M.A. Distel

Afdeling Biologische Psychologie

Van der Boechorststraat 1, Amsterdam





### Aanmeldingsformulier Nederlands Tweelingen Register

Achternaam:		Meisjesnaam*:
Achternaam waar	onder u wilt worden aangesch	nreven:
Voorna(a)m(en):		
Roepnaam:		
Geslacht:	o man o vrouw	Geboortedatum:
Straat:		Huisnummer:
Postcode en woor	nplaats:	
Land:		Email:
Telefoon 1:		Telefoon 2:
* Indien anders dan	eerder genoemd.	
Wilt u hieronder a	aankruisen wat op u van toepa	ssing is? (meerdere antwoorden mogelijk)
o Ik ben zelf een	o tweeling o drieling o vierling	ng. Ik ben als $\circ$ eerste $\circ$ tweede $\circ$ derde $\circ$ vierde geboren.
Ik ben een broe	r/zus van een meerling.	
<ul> <li>Ik ben partner v</li> </ul>	van/ getrouwd met een meerlin	ng.
O Ik ben vader/me	oeder van een meerling.	
O Ik ben zoon/doo	chter van een meerling.	
o Ik ben zoon/doo	chter van de broer/zus van een	meerling.
O Anders, nameli	jk	
e	•	r gezondheid en leefgewoonten invullen?
,	gevoegde papieren vragenlijst	
Olk meld mij we	l aan bij het NTR maar ik vul	dit keer de vragenlijst niet in.
Wilt u bij een ev	entuele verhuizing uw adres	wijziging aan ons doorgeven met de bijgevoegde verhuiskaart?
Vindt u het goed	dat wij uw adresgegevens opv	ragen bij de gemeentelijke basisadministratie wanneer u bij een
verhuizing vergee	et een adreswijziging aan ons o	door te geven? ○ ja ○ nee
Handtekening:		_Datum:
Opmerkingen:		











## LIST OF PUBLICATIONS





### **ARTICLES**

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