Borderline Personality Traits and Adult Attention-Deficit Hyperactivity Disorder Symptoms: A Genetic Analysis of Comorbidity

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Previous research has established the comorbidity of adult Attention-Deficit Hyperactivity Disorder (ADHD) with different personality disorders including Borderline Personality Disorder (BPD). The association between adult ADHD and BPD has primarily been investigated at the phenotypic level and not yet at the genetic level. The present study investigates the genetic and environmental contributions to the association between borderline personality traits (BPT) and ADHD symptoms in a sample of 7,233 twins and siblings (aged 18–90 years) registered with the Netherlands Twin Register and the East Flanders Prospective Twin Survey (EFPTS) . Participants completed the Conners' Adult ADHD Rating Scales (CAARS-S:SV) and the Personality Assessment Inventory-Borderline Features Scale (PAI-BOR). A bivariate genetic analysis was performed to determine the extent to which genetic and environmental factors influence variation in BPT and ADHD symptoms and the covariance between them. The heritability of BPT and ADHD symptoms was estimated at 45 and 36%, respectively. The remaining variance in BPT and ADHD symptoms was explained by unique environmental influences. The phenotypic correlation between BPT and ADHD symptoms was estimated at $r = 0.59$, and could be explained for 49% by genetic factors and 51% by environmental factors. The genetic and environmental correlations between BPT and ADHD symptoms were 0.72 and 0.51, respectively. The shared etiology between BPT and ADHD symptoms is thus a likely cause for the comorbidity of the two disorders. © 2011 Wiley-Liss, Inc.

Key words: attention-deficit hyperactivity disorder; borderline personality disorder; comorbidity; twin study; etiology; genetics

INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is characterized by inattentive, impulsive, and hyperactive behavior [American

Psychiatric Association, 2000]. ADHD has a high prevalence in children with 5% of the individuals under the age of 18 affected worldwide [Polanczyk et al., 2007]. Although ADHD is most commonly first diagnosed during childhood, a large percentage of the patients still meet full or sub threshold DSM-IV criteria for

ADHD in adulthood [Rasmussen and Gillberg, 2000; Barkley et al., 2002; Mannuzza et al., 2003; Faraone et al., 2006; Biederman et al., 2010]. Based on epidemiological data, the prevalence of ADHD in adulthood is estimated at 2–5% [Faraone et al., 2003; Faraone and Biederman, 2005; Kooij et al., 2005; Kessler et al., 2006; Fayyad et al., 2007; Simon et al., 2009; De Graaf et al., 2011].

Adult ADHD is highly comorbid with other axis-I DSM-IV disorders. Most commonly associated with adult ADHD are mood disorders, anxiety disorders, and substance use disorders [Murphy and Barkley, 1996; McGough et al., 2005; Biederman et al., 2006; Kessler et al., 2006; Fayyad et al., 2007; Cumyn et al., 2009]. Personality disorders also often co-occur with adult ADHD. In a clinical sample of 447 adults with ADHD, Cumyn et al. [2009] reported that around 50% had a comorbid personality disorder. Particularly the risk of developing cluster B personality disorders in late adolescence is increased in children with ADHD [Miller et al., 2008]. The relationship between ADHD and border-line personality disorder (BPD) has received most attention because of the similar clinical features of the two disorders. BPD is characterized by identity disturbances, interpersonal difficulties, impulsivity, and emotional lability [American Psychiatric Association, 2000]. Deficits in affect regulation and impulse control are characteristic to both disorders. Two studies retrospectively investigated childhood ADHD as a potential precursor of BPD in adulthood [Fossati et al., 2002; Philipsen et al., 2008]. In both studies ADHD was assessed using the Wender UTAH Rating Scale [WURS; Ward, 1993], a 25-item questionnaire. Based on a sample of 42 patients diagnosed with BPD, Fossati et al. [2002] found that 59.5% of the BPD subjects had a WURS-score indicating a probable childhood ADHD diagnosis. Philipsen et al. [2008] found a somewhat lower prevalence rate of childhood ADHD (41.5%) in a sample of 118 women diagnosed with BPD. Miller et al. [2008] conducted a prospective follow up study of 96 adolescents diagnosed with ADHD in childhood and also found that ADHD portends risk for adult (borderline) personality disorders. A total of 13.5% of the individuals with ADHD had co-occurring BPD in contrast to 1.2% of the control group. The co-occurrence of BPD and ADHD is associated with frequent substance abuse and a higher rate of suicidal behavior [Miller et al., 2008; Ferrer et al., 2010].

The heritability of ADHD and BPD has been established by twin and twin family studies. Heritability estimates around 40% have been reported for BPD and borderline personality traits (BPT) in several studies [Kendler et al., 2008; Torgersen et al., 2008; Distel et al., 2008a; Bornovalova et al., 2009; Distel et al., 2009]. Distel et al. [2009] found that heritability of BPT was explained by both additive genetic (21%) and dominant genetic (24%) factors. Several review articles summarize the results concerning the genetic and environmental factors contributing to ADHD [e.g., Faraone and Biederman, 1998; Faraone and Doyle, 2001; Albayrak et al., 2008; Derks et al., 2009; Sharp et al., 2009] showing that in childhood about 60–80% of the phenotypic variance in ADHD is explained by genetic factors. The remaining 20–40% of the variance is explained by non-shared environmental influences. Shared environmental factors have no or a weak influence. The heritability of ADHD in *adults* has been studied less frequently. Familial clustering of adult

ADHD was reported by Antshel et al. [2009] who found in a sample of high IQ adults that ADHD was more prevalent in first degree relatives of adults with ADHD relative to controls (28% in family members of adults with ADHD versus 5% in family members of IQ matched controls). Only two *twin* family studies till date looked at the genetic influences on adult ADHD [Boomsma et al., 2010; Saviouk et al., 2011]. Both studies used the screening version of the Conners' Adult Rating Scales [CAARS-S:SV; Conners et al., 1999] to assess inattentive and hyperactive symptoms and likely ADHD diagnosis (ADHD-Index) in a large sample of Dutch twins and their family members. Based on data from more than 10,000 individuals, Saviouk et al. [2011] report heritability estimates of 35, 23, and 31% for inattention, hyperactivity, and the ADHD-index, respectively. Including data from the parents of these twins and siblings (N > 12.000) Boomsma et al. [2010] report no cultural transmission from parents to offspring. No evidence for genetic dominance was found. The lower heritability in adults than in children can possibly be explained by age-by-genotype interaction, genotype-environment correlation, or by the fact that ratings of ADHD in adults are based on self-report whereas ratings of ADHD in children are based on parental or teacher reports [Boomsma et al., 2010].

Twin family data can also be used to study the shared etiology between traits. Instead of decomposing the variance of a univariate trait, the *covariance* (comorbidity) between two traits can be decomposed into parts that are due to genetic and environmental factors. 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. Previous studies investigated the association between BPD and ADHD at the phenotypic level. In this manuscript we present a bivariate genetic study of BPT and ADHD symptoms in a large scale population based sample to determine whether shared (genetic and environmental) etiology can explain (part of) the comorbidity between the two disorders.

METHODS
Sample

The data for this study were collected by the Netherlands Twin Register [NTR; Boomsma et al., 2006a]. The NTR was established in 1987 and includes twins, their siblings, spouses, and parents. Every two to three years the twins and their family members are invited to complete questionnaires on physical and mental health, personality, and lifestyle. The data for this study are from the seventh survey carried out 2004–2005. The data collection procedure is explained in more detail in Distel et al. [2007]. Dutch-speaking twins in Belgium were also asked to participate in the survey. They 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 [Derom et al., 2006].

Twins with unknown zygosity and individuals with unknown age were excluded. We included a maximum of two brothers and two sisters per family. The final sample consisted of 7,233 subjects. Detailed information on the sample configuration is given in Table I.

TABLE I. Number of Participants and Complete Twin Pairs by Zygosity and the Mean Age (Range)

	Number of subjects	Complete twin pairs	Mean age (range)
Monozygotic males	840	302	34.66(18.44–76.71)
Dizygotic males	435	120	34.51(18.14–78.21)
Monozygotic females	2,180	875	35.49(18.32–86.42)
Dizygotic females	1,039	347	34.85(18.37–75.89)
Dizygotic opposite sex	1,173	340	32.65(18.04–75.19)
Brothers	569	—	42.09(17.65–90.29)
Sisters	997	—	41.60(17.56–83.99)
Total	7,233	—	35.77(17.56–90.29)

Measures

ADHD behaviors were measured using the Conners' Adult ADHD Rating Scales [CAARS-S:SV; Conners et al., 1999]. The CAARS-S:SV is designed for adults from 18 to 50 years and older, and consists of 30 items reflecting the DSM-IV ADHD symptom measures. The ADHD index is a subset of 12 core items designed to identify the adults that are likely to be diagnosed with ADHD. We used the ADHD Index subscale, because it "represents a measure of overall level of ADHD-related symptoms" [Conners et al., 1999]. All items have a four-answer scale (0–3; *never, once in a while, often, very frequently*), and were scored according to Conners' test manual.

BPT were assessed with the Personality Assessment Inventory-Borderline Features Scale [PAI-BOR; Morey, 1991]. The PAI-BOR consists of four subscales with a total of 24 items. The subscales correspond to the different aspects of BPD (i.e., Affective Instability, Identity Problems, Negative Relationships, and Self-Harm). We used the full scale score for our study. The items have a four-answer scale (0–3; false, slightly true, mainly true, and very true), and were scored according to Morey's test manual.

Validity and reliability of the CAARS and PAI-BOR have been evidenced by multiple studies. The studies support that the CAARS and PAI-BOR are reliable in indicating to what degree ADHD symptoms or borderline personality traits are present in an individual [Trull, 1995; Conners et al., 1999; Trull, 2001; Kooij et al., 2008]. The six-month test–retest correlation assessed on 200 unrelated individuals was 0.78 for the PAI-BOR and 0.67 for the CAARS ADHD index.

Zygosity

Zygosity of same sex twins was determined either from DNA typing (N = 2,757) or from eight self-report survey questions that were included in the questionnaire (N = 4,476). These eight are questions on twin resemblance and confusion of the twins by family members and strangers. The opposite sex twins were classified as dizygotic (DZ). Agreement between zygosity determined by DNA typing and by survey question is about 93–97% [Rietveld et al., 2000; Willemsen et al., 2005].

Statistical Analyses

Variation in human behavior may be caused by genetic and/or non-genetic (environmental) differences between individuals. The relative contributions of genotype and environment to phenotypic variation can be estimated with the classical twin design. The twin design makes use of the fact that monozygotic (MZ) twins are (nearly) genetically identical, and that DZ twins (and non-twin siblings) share on average 50% of their segregating genes [Boomsma et al., 2002]. The classic twin model incorporates this fact, and, depending on which family members are included in a study, permits the estimation of the relative contributions of additive genetic effects (A), non-additive genetic effects (Dominance; D), shared environmental effects (C), and non-shared environmental effects (E). Based on data from only MZ and DZ twins and their siblings either an ADE or an ACE model can be fitted to the data. The choice between these latter two models may be based on prior knowledge or 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) and when the DZ correlation is less than half the MZ correlation, there is evidence for non-additive genetic effects (D). Based on results from previous analyses, and the correlation structure found in the present study (see results section) we fitted an ADE-model to the data [Distel et al., 2009; Boomsma et al., 2010].

In a bivariate ADE model the association between BPT and ADHD symptoms was modeled as a function of genetic or environmental factors that influence both disorders. The MZ and DZ cross-trait cross-twin correlations provide the information needed to estimate the overlap of additive genetic and unique environmental factors. If the DZ cross-trait cross-twin correlation is half the MZ cross-trait cross-twin correlation the influence of A on the covariance of BPT and ADHD symptoms is indicated. If the DZ cross-trait cross-twin correlation is smaller than half the MZ cross-trait cross-twin correlation, this suggest that non-additive genetic factors also are of importance.

Statistical analyses were carried out using structural equation modeling in Mx by full-information maximum likelihood [Neale et al., 2006]. Data from complete and incomplete twin pairs were included in the analysis which corrects for ascertainment bias and improves estimates of means and variances. The fit of different

models was compared with likelihood-ratio tests (LRT). An LRT provides a χ^2-test with the degrees of freedom (df) being equal to the difference in the number of parameters in the two models. Significance indicates a worse fit of the constrained model compared to the full model. Because of the large sample size we used a more conservative P-value of 0.01.

In a saturated model we tested for heterogeneity of correlations among males and females. Tests for heterogeneity included constraining the correlations between males and females within zygosity to be equal (quantitative sex differences; MZ males = MZ females and DZ males = DZ females) and constraining the correlations between same sex DZ twins and dizygotic opposite sex (DOS) twins to be equal (qualitative sex differences; DZ males = DZ females = DOS). Based on prior analyses sex was included as regression coefficient in the means model for BPT and age was included as regression coefficient in the means model for BPT and ADHD symptoms. For the same reason, correlations were constrained to be equal for DZ twin pairs and sibling pairs and the variances were constrained to be equal for males and females [Distel et al., 2008a; Boomsma et al., 2010].

As stated above, the observed variances of BPT and ADHD symptoms, and the observed covariance between the two disorders, are decomposed in the bivariate ADE model into genetic variance (A and D), and environmental variance (E). For DZ twins and non-twin siblings the correlation of the A and D factors are fixed to 0.5 and 0.25, respectively whereas for MZ twins the correlation is 1.0 for both A and D. The full ADE bivariate Cholesky model can be tested against several more constrained models. Constraining the contribution of additive genetic effects and dominant genetic effects to zero permits testing whether A and D contribute significantly to the total variance of BPT and ADHD symptoms. Similarly, effects of A, D, and E on the covariance between BPT and ADHD symptoms (represented by the path coefficients a_{21}, d_{21}, and e_{21} in Fig. 1) can each be fixed to zero to evaluate the significance of shared genetic and environmental influences. Non-significance of the LRT test comparing the constrained to the full model can be considered as evidence that the constrained covariance factor does not play a role in explaining the correlation between BPT and ADHD symptoms.

RESULTS

Preliminary data exploration showed a slightly right-skewed distribution of the BPT data, which was addressed by a square-root transformation to approximate normality.

Testing the Correlations for Sex Differences

Table II shows the results of the tests performed in the saturated model. The phenotypic correlation between BPT and ADHD symptoms was the same for males and females (model 1). There were no quantitative or qualitative sex differences in the correlations for BPT (models 2–4) and ADHD symptoms (models 5–7) or in the covariance between them (models 8–10). This means that the heritability of BPT and ADHD symptoms is equal for males and females (no quantitative sex differences) and that the same genes influence variance in BPT and ADHD symptoms in males and females (no qualitative sex differences). Similarly, the covariance decomposition into a part due to genetic and a part due to environmental influences is equal for males and females. The (cross) correlations from the full and the most constrained saturated model (printed in bold) are shown in Table III. The MZ twin correlation was more than twice the DZ/sibling correlation for both
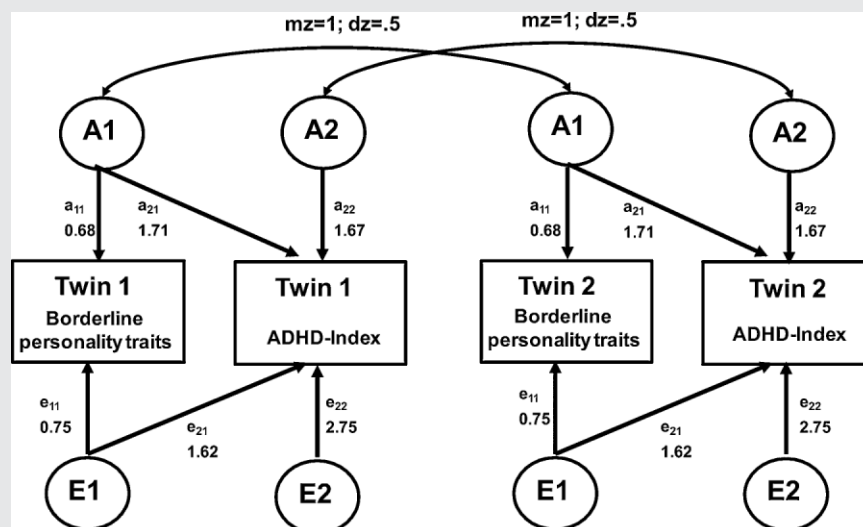

FIG. 1. Graphical representation of the best fitting bivariate genetic model. Squares represent the measured variables borderline personality traits (BPT) and attention-deficit hyperactivity disorder (ADHD) symptoms. A1 represents the genetic variance that is common to BPT and ADHD symptoms. E1 represents the unique environmental factors that are common to BPT and ADHD symptoms. Path coefficients a and e represent the influence of latent additive genetic and unique environmental factors on the phenotype. All latent A and E factors have unit variances. For clarity reasons only the twins are drawn in this figure although non-twin siblings were also included in the analyses.

TABLE II. Saturated Model-Fitting Results for Borderline Personality Traits (BPT) and Attention-Deficit Hyperactivity Disorder (ADHD) Symptoms

		Test	−2LL	χ^2	Δdf	P
0.	Saturated model		56629.347			
1.	r_{phen} males = r_{phen} females	1 vs. 0	56631.427	2.080	1	0.556
Tests for sex differences in BPT correlations						
2.	MZM = MZF	2 vs. 1	56631.440	0.013	1	0.909
3.	DZM = DZF	3 vs. 2	56631.621	0.181	1	0.671
4.	DZM = DZF = DOS	4 vs. 3	56633.350	1.729	1	0.189
Tests for sex differences in ADHD symptoms correlations						
5.	MZM = MZF	5 vs. 4	56633.368	0.018	1	0.893
6.	DZM = DZF	6 vs. 5	56638.016	4.648	1	0.031
7.	DZM = DZF = DOS	7 vs. 6	56638.987	0.971	1	0.324
Tests for sex differences in cross correlations						
8.	MZM = MZF	8 vs. 7	56639.022	0.035	1	0.852
9.	DZM = DZF	9 vs. 8	56640.222	1.200	1	0.273
10.	DZM = DZF = DOS	10 vs. 9	56641.162	0.940	1	0.332

−2LL, −2 log likelihood; χ^2, chi-square; df, degrees of freedom; P, P-value; r_{phen}, phenotypic correlation; MZ, monozygotic; DZ, dizygotic; M, males; F, females; DOS, dizygotic opposite sex.

TABLE III. Estimates of the Phenotypic Correlation and (Cross) Twin Correlations for Borderline Personality Traits and Attention-Deficit Hyperactivity Disorder Symptoms

Phenotypic correlation males	0.57
Phenotypic correlation females	0.59
Phenotypic correlation	**0.59**
Borderline personality traits	
Monozygotic male twin pairs	0.46
Monozygotic female twin pairs	0.47
Monozygotic twin pairs	**0.47**
Male sibling pairs	0.18
Female sibling pairs	0.22
Sibling pairs with opposite sex	0.16
Sibling pairs	**0.19**
Attention-deficit hyperactivity disorder symptoms	
Monozygotic male twin pairs	0.35
Monozygotic female twin pairs	0.37
Monozygotic twin pairs	**0.36**
Male sibling pairs	0.05
Female sibling pairs	0.21
Sibling pairs with opposite sex	0.12
Sibling pairs	**0.16**
Cross trait correlations	
Monozygotic male twin pairs	0.28
Monozygotic female twin pairs	0.30
Monozygotic twin pairs	**0.29**
Male sibling pairs	0.09
Female sibling pairs	0.16
Sibling pairs with opposite sex	0.08
Sibling pairs	**0.12**

BPT and ADHD symptoms which indicates the possible influence of non-additive genetic effects.

Bivariate Genetic Analysis

Genetic model fitting results are shown in Table IV. The contribution of D could be constrained at zero without worsening of the model fit (model 1–3). The constrained models with the effects of A (model 4 and 5) fixed at zero resulted in a significant deterioration of the model fit. Figure 1 shows a graphical representation of the bivariate model and gives the path coefficients from the best fitting model. The total variance in BPT can be written as $(a^2_{11}) + (e^2_{11})$. The heritability of BPT [calculated as $(a^2_{11})/(a^2_{11}) + (e^2_{11})$] was estimated at 45%. The influence of E on individual differences in BPT [calculated as $(e^2_{11})/(a^2_{11}) + (e^2_{11})$] was estimated at 55%. Total variance in ADHD symptoms can be written as $(a^2_{21}) + (a^2_{22}) + (e^2_{21}) + (e^2_{22})$. The heritability of ADHD symptoms [calculated as $(a^2_{21}) + (a^2_{22})/(a^2_{21}) + (a^2_{22}) + (e^2_{21}) + (e^2_{22})$] was estimated at 36%. The influence of E on ADHD symptoms [calculated as $(e^2_{21}) + (e^2_{22})/(a^2_{21}) + (a^2_{22}) + (e^2_{21}) + (e^2_{22})$] was estimated at 64%. The genetic and environmental covariance may be written as $(a_{11} \times a_{21})$ and $(e_{11} \times e_{21})$, respectively. The genetic correlation (rGa) [calculated as $a_{11} \times a_{21}/(\sqrt{(a^2_{11})} \times \sqrt{(a^2_{21} + a^2_{22})})$] was estimated at 0.72 and the environmental correlation [calculated as $e_{11} \times e_{21}/(\sqrt{(e^2_{11})} \times \sqrt{(e^2_{21} + e^2_{22})})$] at 0.51. The percentage of the phenotypic correlation explained by A may be calculated as $\sqrt{(h^2_{bpd})} \times rG \times \sqrt{(h^2_{adhd})}$ divided by the phenotypic correlation. Likewise, the percentage of the phenotypic correlation explained by E may be calculated as $\sqrt{(e^2_{bpd})} \times rE \times \sqrt{(e^2_{adhd})}$ divided by the phenotypic correlation. Based on these calculations the phenotypic correlation can be explained for 49% by A and 51% by E (see Table V).

TABLE IV. Bivariate Genetic Model Fitting Results of Borderline Personality Traits (BPT) and Attention-Deficit Hyperactivity Disorder (ADHD) Symptoms

	Test	−2LL	χ^2	Δdf	P
0: Full model		53170.957			
1: $d_{21} = 0$	1 vs. 0	53172.328	1.371	1	0.242
2: D BPT $= 0$	2 vs. 1	53174.349	2.021	1	0.155
3: D ADHD symptoms $= 0$	3 vs. 2	53174.349	0	1	1.000
4: $a_{21} = 0$	4 vs. 3	53392.697	218.348	1	<0.001
5: A $= 0$	5 vs. 3	53661.853	487.504	3	<0.001
6: $e_{21} = 0$	6 vs. 3	53712.868	538.519	1	<0.001

A, genetic factors; D, non-additive genetic factors; a_{21}, cross trait covariance additive genetic factor; d_{21}, cross trait covariance non-additive genetic factor; e_{21}, cross trait covariance non-shared environmental factors; −2LL, −2 log likelihood; df, degrees of freedom; P, P-value.

DISCUSSION

This study presents a genetic analysis of the comorbidity of adult ADHD symptoms and BPT. While previous studies focused on clinical and phenotypic resemblance of the two disorders, our aim was to decompose the phenotypic correlation between BPT and ADHD symptoms in terms of shared genetic and environmental influences. A high correlation between BPT and ADHD symptoms ($r = 0.59$) was found in this large population based sample. The genetic analyses showed that this correlation can be explained for 49% by additive genetic factors, and for 51% by unique environmental factors. Genetic factors explained 36% of the variance in ADHD symptoms and 45% in BPT. The heritability estimates for BPT symptoms is likely to include some dominant genetic effects [see Distel et al., 2009], but for ADHD in adults genetic dominance does not seem to play a role [Boomsma et al., 2010]. It is therefore unlikely that non-additive genetic factors contribute in any major way to the covariance of the two traits.

Further research is needed to investigate the underlying sources of the genetic and non-shared environmental factors that influence both BPT and ADHD symptoms. Biological factors influencing both BPT and ADHD may contribute to dysregulation of systems that influence impulsive aggression such as the serotonergic system or the hypothalamic–pituitary–adrenal axis system [Gollan et al., 2005]. Genetic linkage studies of BPD and ADHD may provide information on the sources of shared genetic influences. Distel et al. [2008b] found that chromosomal region 9p24.1 was linked to BPT

in Dutch adults (LOD = 3.55). Three other regions (1q31.1, 4p16.1, and 18q23) were suggestively linked to BPT (LOD = 1.60, 1.49, and 1.44, respectively). Around the location of the most pronounced linkage peak (9p24.1) the protein tyrosine phosphatase receptor type delta (PTPRD) gene is located. A genome wide association study conducted by Anney et al. [2008] reported an association between ADHD and the PTPRD gene. Elia et al. [2010] found four independent deletions within the PTPRD gene which frequently presented with ADHD. In addition, a genome wide linkage scan reported the region of the PTPRD gene to be associated with nicotine dependence [Li et al., 2007], a phenotype highly associated with ADHD and BPD [Wilens et al., 2008; Pulay et al., 2010]. The PTPRD gene is thus a good candidate to include in a biological pathway increasing the risk for both disorders.

Environmental exposures that influence BPD include traumatic life events, such as sexual or physical abuse and parental divorce, loss or illness. These risk factors are common in patients with BPD and thought to be etiologically linked to BPD [Zanarini et al., 1997; Helgeland and Torgersen, 2004; Bandelow et al., 2005; Horesh et al., 2008]. Rucklidge et al. [2006] found that retrospectively assessed childhood emotional abuse and neglect was more common in adults with ADHD than in a control group. However, the authors conclude that it is not clear whether children who show typical ADHD behavior are more likely to be exposed to trauma or whether experiencing a trauma in childhood increases the likelihood of developing ADHD. Lehn et al. [2007] used the discordant MZ twin design as a tool to identify environmental risk factors that may explain the discordance within identical twin pairs. Compared with unaffected co-twins, affected twins had lower birth weight and delayed physical growth and motor development. Differences between discordant and concordant groups included maternal smoking during pregnancy and living with only one parent. Although trauma has not been linked etiologically to ADHD with certainty one may speculate that for children with ADHD, adverse childhood experiences are a risk factor for developing BPD in adulthood. In other words, the interaction between a "sensitive" genotype (i.e., the genetic predisposition to ADHD) and adverse environmental influences in childhood may lead to the development of BPD in adulthood.

Some limitations of the present study should be noted. First, some selection bias may have been present in the sample.

TABLE V. Genetic Correlation, Environmental Correlation, and Amount of Phenotypic Correlation Between Attention-Deficit Hyperactivity Disorder Symptoms and Borderline Personality Traits Explained by Genes and Environment

Phenotypic correlation (r_p)	0.59
Genetic correlation	0.72
Environmental correlation	0.51
r_p explained by genes	49%
r_p explained by environmental factors	51%

A non-response study showed that individuals from families in which only some individuals participate in the study show slightly more BPT than individuals from families in which most individuals participate in the study [Distel et al., 2007]. For the ADHD index scale of the CAARS this information is not presented in the Distel et al. [2007] publication, but applying the analyses to the ADHD index showed that, after bonferroni correction [Distel et al., 2007] there was no significant effect of non-response [$F(1, 3,277) = 5.34$, $P = 0.021$]. Second, BPT and ADHD symptoms were assessed using questionnaires. Features clinically associated with BPD and ADHD were assessed in a large population based sample with the PAI-BOR and the CAARS which both have shown to discriminate well between patients and non-patients. However, replication of the results using other measures, such as clinical interviews, is necessary. Third, although there are shared genetic and environmental risk factors that explain the association between BPT and ADHD symptoms there are alternative explanations [see e.g., Neale and Kendler, 1995; Middeldorp et al., 2006] for comorbidity some of which are nested under the general bivariate model of shared genetic etiology, such as (reciprocal) causation. Other genetically informative longitudinal and cross-sectional designs, as described by De Moor et al. [2008], should be applied to test for a causal relationship between ADHD symptoms and BPT.

Our findings are interesting in light of the proposal to include "Disruptive Mood Dysregulation Disorder" (DMDD) in the DSM-5 [American Psychiatric Association: DSM-5 Development: Proposed Revisions, 2011]. A study on severe mood dysregulation characterized by abnormal mood (anger or sadness), hyperarousal, and increased reactivity to negative emotional stimuli showed that 86.3% of these children are diagnosed with ADHD [Leibenluft, 2011]. Longitudinal studies focused on DMDD as a developmental manifestation of axis-I disorders and showed that these youths are at increased risk for depression [Brotman et al., 2006; Stringaris et al., 2009; Leibenluft, 2011]. Studies on the Child Behavior Checklist Dysregulation profile (previously known as juvenile bipolar disorder profile) show a high stability in symptoms between age 7 and age 12 and an increased risk for problems with regulating affect, behavior, and cognition [Boomsma et al., 2006b; Althoff et al., 2010]. There are no studies that investigated the risk of youths with DMDD for personality disorders. The overlapping criteria of DMDD and BPD (temper outbursts and negative mood in DMDD described as affective instability with intense episodic dysphoria in BPD) and the high comorbidity of both disorders with depression and ADHD, raises the hypothesis that the children fulfilling criteria for ADHD and DMDD may have the highest chance to develop BPD at adulthood. If ADHD and DMDD are precursors for BPD in adulthood this may have important implications for treatment. Prospective longitudinal studies spanning childhood and the adult age range are needed to further elucidate the relationship between childhood ADHD and DMDD and BPD at adulthood.

ACKNOWLEDGMENTS

REFERENCES

Albayrak O, Friedel S, Schimmelmann BG, Hinney A, Hebebrand J. 2008. Genetic aspects in attention-deficit/hyperactivity disorder. J Neural Transm 115:305–315.

Althoff RR, Verhulst FC, Rettew DC, Hudziak JJ, van der Ende J. 2010. Adult outcomes of childhood dysregulation: A 14-year follow-up study. J Am Acad Child Adolesc Psychiatr 49:1105–1116.

American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders. (text revision) 4th edition. Washington, DC: American Psychiatric Press.

American Psychiatric Association. DSM-5 development: Proposed revisions. (6-24-2011). D 00 disruptive mood dysregulation disorder. http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=397.

Anney RJL, Lasky-Su J, O'Dushlaine C, Kenny E, Neale BM, Mulligan A, Franke B, Zhou KX, Chen W, Christiansen H, rias-Vasquez A, Banaschewski T, Buitelaar J, Ebstein R, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen H, Asherson P, Faraone SV, Gill M. 2008. Conduct disorder and ADHD: Evaluation of conduct problems as a categorical and quantitative trait in the international multicentre ADHD genetics study. Am J Med Genet Part B 147B:1369–1378.

Antshel KM, Faraone SV, Maglione K, Doyle A, Fried R, Seidman L, Biederman J. 2009. Is adult attention deficit hyperactivity disorder a valid diagnosis in the presence of high IQ? Psychol Med 39:1325–1335.

Bandelow B, Krause J, Wedekind D, Broocks A, Hajak G, Ruther E. 2005. Early traumatic life events, parental attitudes, family history, and birth risk factors in patients with borderline personality disorder and healthy controls. Psychiatr Res 134:169–179.

Barkley RA, Fischer M, Smallish L, Fletcher K. 2002. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. J Abnorm Psychol 111:279–289.

Biederman J, Monuteaux MC, Mick E, Spencer T, Wilens TE, Klein KL, Price JE, Faraone SV. 2006. Psychonathology in female with attention-deficit/hyperactivity disorder: A controlled, five-year prospective study. Biol Psychiatr 60:1098–1105.

Biederman J, Petty CR, Evans M, Small J, Faraone SV. 2010. How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. Psychiatr Res 177:299–304.

Boomsma D, Busjahn A, Peltonen L. 2002. Classical twin studies and beyond. Nat Rev Genet 3:872–882.

Boomsma DI, de Geus EJ, Vink JM, Stubbe JH, Distel MA, Hottenga JJ, Posthuma D, van Beijsterveldt TC, Hudziak JJ, Bartels M, Willemsen G. 2006a. Netherlands twin register: From twins to twin families. Twin Res Hum Genet 9:849–857.

Boomsma DI, Rebollo I, Derks EM, Van Beijsterveldt TCEM, Althoff RR, Rettew DC, Hudziak JJ. 2006b. Longitudinal stability of the CBCL-juvenile bipolar disorder phenotype: A study in Dutch twins. Biol Psychiatr 60:912–920.

Boomsma DI, Saviouk V, Hottenga JJ, Distel MA, De Moor MHM, Vink JM, Geels LM, van Beek JHDA, Bartels M, de Geus EJC, Willemsen G.

2010. Genetic epidemiology of attention deficit hyperactivity disorder (ADHD Index) in adults. PLoS ONE 5:e10621.DOI: 10.1371/journal.pone.0010621.

Bornovalova MA, Hicks BM, Iacono WG, Mcgue M. 2009. Stability, change, and heritability of borderline personality disorder traits from adolescence to adulthood: A longitudinal twin study. Dev Psychopathol 21:1335–1353.

Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E. 2006. Prevalence, clinical correlates, and clinical course of severe mood dysregulation in children. Biol Psychiatr 60:991–997.

Conners CK, Erhardt D, Sparrow EP. 1999. Conners' adult ADHD rating scales (CAARS). New York: Multi-Health Systems.

Cumyn L, French L, Hechtman L. 2009. Comorbidity in adults with attention-deficit hyperactivity disorder. Can J Psychiatr Rev Canad Psychiatr 54:673–683.

De Graaf R, ten Have M, van Gool C, van Dorsselaer S. 2011. Prevalence of mental disorders and trends from 1996 to 2009. Results from the Netherlands Mental Health Survey and Incidence Study-2. Soc Psychiatr Psychiatr Epidemiol [Epub ahead of print].

De Moor MHM, Boomsma DI, Stubbe JH, Willemsen G, de Geus EJC. 2008. Causality in genetic epidemiology: An application to exercise and depression. Behav Genet 65:897–905.

Derks EM, Hudziak JJ, Boomsma DI. 2009. Genetics of ADHD, hyperactivity, and attention problems. In: Kim Yong-Kyu, editor. Handbook of behavior genetics. New York: Springer. pp 1361-1378 .

Derom CA, Vlietinck RF, Thiery EW, Leroy FO, Fryns JP, Derom RM. 2006. The east flanders prospective twin survey (EFPTS). Twin Res Hum Genet 9:733–738.

Distel MA, Hottenga JJ, Trull TJ, Boomsma DI. 2008b. Chromosome 9: Linkage for borderline personality disorder features. Psychiatr Genet 18:302–307.

Distel MA, Ligthart L, Willemsen G, Nyholt DR, Trull TJ, Boomsma DI. 2007. Personality, health and lifestyle in a questionnaire family study: A comparison between highly cooperative and less cooperative families. Twin Res Hum Genet 10:348–353.

Distel MA, Rebollo-Mesa I, Willemsen G, Derom CA, Trull TJ, Martin NG, Boomsma DI. 2009. Familial resemblance of borderline personality disorder features: Genetic or cultural transmission? PLoS ONE 4:e5334.DOI: 10.1371/journal.pone.0005334.

Distel MA, Trull TJ, Derom CA, Thiery EW, Grimmer MA, Martin NG, Willemsen G, Boomsma DI. 2008a. Heritability of borderline personality disorder features is similar across three countries. Psychol Med 38:1219–1229.

Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, D'arcy M, Deberardinis R, Frackelton E, Kim C, Lantieri F, Muganga BM, Wang L, Takeda T, Rappaport EF, Grant SFA, Berrettini W, Devoto M, Shaikh TH, Hakonarson H, White PS. 2010. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatr 15:637–646.

Faraone SV, Biederman J. 1998. Neurobiology of attention-deficit hyperactivity disorder. Biol Psychiatr 44:951–958.

Faraone SV, Biederman J, Mick E. 2006. The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. Psychol Med 36:159–165.

Faraone SV, Doyle AE. 2001. The nature and heritability of attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 10:299–316.

Faraone SV, Biederman J. 2005. What is the prevalence of adult ADHD? Results of a population screen of 966 adults. J Atten Disord 9:384–391.

Faraone SV, Sergeant J, Gillberg C, Biederman J. 2003. The worldwide prevalence of ADHD: Is it an American condition? World Psychiatr 2:104–113.

Fayyad J, De Graaf R, Kessler R, Alonso J, Angermeyer M, Demyttenaere K, de Girolamo G, Haro JM, Karam EG, Lara C, Lepine JP, Ormel J, Posada-Villa J, Zaslavsky AM, Jin R. 2007. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatr 190:402–409.

Ferrer M, Andion O, Matali J, Valero S, Navarro JA, Ramos-Quiroga JA, Torrubia R, Casas M. 2010. Comorbid attention-deficit/hyperactivity disorder in borderline patients defines an impulsive subtype of borderline personality disorder. J Pers Disord 24:812–822.

Fossati A, Novella L, Donati D, Donini M, Maffei C. 2002. History of childhood attention deficit/hyperactivity disorder symptoms and borderline personality disorder: A controlled study. Compr Psychiatr 43:369–377.

Gollan JK, Lee R, Coccaro EF. 2005. Developmental psychopathology and neurobiology of aggression. Dev Psychopathol 17:1151–1171.

Helgeland MI, Torgersen S. 2004. Developmental antecedents of borderline personality disorder. Compr Psychiatr 45:138–147.

Horesh N, Ratner S, Laor N, Toren P. 2008. A comparison of life events in adolescents with major depression, borderline personality disorder and matched controls: A pilot study. Psychopathology 41:300–306.

Kendler KS, Aggen SH, Czajkowski N, Roysamb E, Tambs K, Torgersen S, Neale MC, Reichborn-Kjennerud T. 2008. The structure of genetic and environmental risk factors for DSM-IV personality disorders a multivariate twin study. Arch Gen Psychiatr 65:1438–1446.

Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM. 2006. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. Am J Psychiatr 163:716–723.

Kooij JJS, Buitelaar JK, Van den Oord EJ, Furer JW, Rijnders CAT, Hodiamont PPG. 2005. Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. Psychol Med 35:817–827.

Kooij SJJ, Boonstra MA, Swinkels SH, Bekker EM, de Noord I, et al. 2008. Reliability, validity, and utility of instruments for self-report and informant report concerning symptoms of ADHD in adult patients. J Atten Disord 11:445–458.

Lehn H, Derks EM, Hudziak JJ, Heutink P, Van Beijsterveldt TCEM, Boomsma DI. 2007. Attention problems and attention-deficit/hyperactivity disorder in discordant and concordant monozygotic twins: Evidence of environmental mediators. J Am Acad Child Adolesc Psychiatr 46:83–91.

Leibenluft E. 2011. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatr 168:129–142.

Li MD, Sun D, Lou XY, Beuten J, Payne TJ, Ma JZ. 2007. Linkage and association studies in African- and Caucasian-American populations demonstrate that SHC3 is a novel susceptibility locus for nicotine dependence. Mol Psychiatr 12:462–473.

Mannuzza S, Klein RG, Moulton JL. 2003. Persistence of attention-deficit/hyperactivity disorder into adulthood: What have we learned from the prospective follow-up studies? J Atten Disord 7:93–100.

McGough JJ, Smalley SL, McCracken JT, Yang M, Del'Homme M, Lynn DE, Loo S. 2005. Psychiatric comorbidity in adult attention deficit

hyperactivity disorder: Findings from multiplex families. Am J Psychiatr 162:1621–1627.

Middeldorp CM, Cath DC, Boomsma DI. 2006. A twin-family study of the association between employment,burnout and anxious depression. J Affect Disord 90:163–169.

Miller CJ, Flory JD, Miller SR, Harty SC, Newcorn JH, Halperin JA. 2008. Childhood attention-deficit/hyperactivity disorder and the emergence of personality disorders in adolescence: A prospective follow-up study. J Clin Psychiatr 69:1477–1484.

Morey LC. 1991. The personality assessment inventory: Professional Manual. Odessa, FL: Psychological Assessment Resources.

Murphy K, Barkley RA. 1996. Attention deficit hyperactivity disorder adults: Comorbidities and adaptive impairments. Compr Psychiatr 37: 393–401.

Neale MC, Booker SM, Xie G, Maes HHM. 2006. Mx: Statistical modeling. 7th editionRichmond, VA: Department of Psychiatry.

Neale MC, Kendler KS. 1995. Models of comorbidity for multifactorial disorders. Am J Hum Genet 57:935–953.

Philipsen A, Limberger MF, Lieb K, Feige B, Kleindienst N, Ebner-Priemer U, Barth J, Schmahl C, Bohus M. 2008. Attention-deficit hyperactivity disorder as a potentially aggravating factor in borderline personality disorder. Br J Psychiatr 192:118–123.

Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. 2007. The worldwide prevalence of ADHD: A systematic review and metaregression analysis. Am J Psychiatr 164:942–948.

Pulay AJ, Stinson FS, Ruan WJ, Smith SM, Pickering RP, Dawson DA, Grant BF. 2010. The relationship of DSM-IV personality disorders to nicotine dependence-results from a national survey. Drug Alcohol Depend 108:141–145.

Rasmussen P, Gillberg C. 2000. Natural outcome of ADHD with developmental coordination disorder at age 22 years: A controlled, longitudinal, community-based study. J Am Acad Child Adolesc Psychiatr 39: 1424–1431.

Rietveld MJ, Der Valk JC, Bongers IL, Stroet TM, Slagboom PE, Boomsma DI. 2000. Zygosity diagnosis in young twins by parental report. Twin Res 3:134–141.

Rucklidge JJ, Brown DL, Crawford S, Kaplan BJ. 2006. Retrospective reports of childhood trauma in adults with ADHD. J Atten Disord 9:631–641.

Saviouk V, Hottenga JJ, Slagboom EP, Distel MA, de Geus EJC, Willemsen G, Boomsma DI. 2011. ADHD in dutch adults: Heritability and linkage study. Am J Med Genet B Neuropsychiatr Genet 156B:352–362.

Sharp SI, McQuillin A, Gurling HMD. 2009. Genetics of attention-deficit hyperactivity disorder (ADHD). Neuropharmacology 57:590–600.

Simon V, Czobor P, Balint S, Meszaros A, Bitter I. 2009. Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis. Br J Psychiatr 194:204–211.

Stringaris A, Cohen P, Pine DS, Leibenluft E. 2009. Adult outcomes of youth irritability: A 20-year prospective community-based study. Am J Psychiatr 166:1048–1054.

Torgersen S, Czajkowski N, Jacobson K, Reichborn-Kjennerud T, Roysamb E, Neale MC, Kendler KS. 2008. Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of norwegian twins: A multivariate study. Psychol Med 38:1617–1625.

Trull TJ. 1995. Borderline personality-disorder features in nonclinical young-adults .1. Identification and validation. Psychol Assess 7:33–41.

Trull TJ. 2001. Structural relations between borderline personality disorder features and putative etiological correlates. J Abnorm Psychol 110: 471–481.

Ward MF. 1993. The Wender Utah Rating-Scale - An aid in the retrospective diagnosis of childhood attention-deficit hyperactivity disorder. Am J Psychiatr 150:885–890.

Wilens TE, Vitulano M, Upadhyaya H, Adamson J, Sawtelle R, Utzinger L, Biederman J. 2008. Cigarette smoking associated with attention deficit hyperactivity disorder. J Pediatr 153:414–419.

Willemsen G, Posthuma D, Boomsma DI. 2005. Environmental factors determine where the Dutch live: Results from the Netherlands twin register. Twin Res Hum Genet 8:312–317.

Zanarini MC, Williams AA, Lewis RE, Reich RB, Vera SC, Marino MF, Levin A, Yong L, Frankenburg FR. 1997. Reported pathological childhood experiences associated with the development of borderline personality disorder. Am J Psychiatr 154:1101–1106.