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GENETIC AND ENVIRONMENTAL FACTORS IN THE DEVELOPMENT OF EXTERNALIZING SYMPTOMS FROM CHILDHOOD TO ADOLESCENCE

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Stockholm 2005

ABSTRACT

Externalizing problems, such as hyperactivity, impulsivity, aggression, violation of legal or social norms, and delinquent behavior, tend to persist from childhood to adolescence. There are also high levels of comorbidity among supposedly different domains of externalizing problems. Previous research also suggests that persistence over time and comorbidity may be two of the strongest predictors of adult outcome, especially risk for antisocial behavior, delinquency and substance abuse. This thesis has therefore applied multivariate twin methods to longitudinal data to clarify the action of genetic and environmental factors in ADHD, antisocial behavior, and psychopathic personality during the development from childhood to adolescence.

The data used in this thesis comes from the Twin study of CHild and Adolescent Development (TCHAD), an ongoing prospective longitudinal study with data collected from parents when the twins were 8-9 years old and from both parents and twins at age 13-14 and 16-17.

Paper I in this thesis shows that the relative high stability in ADHD-symptoms over a 5-year period was to a large extent explained by genetic factors, whereas both genetic and non-shared environmental factors contributed to changes in ADHD symptoms during the period from childhood to early adolescence. Paper II shows that the associations between and within symptoms of hyperactivity-impulsivity and inattention from childhood to adolescence was influenced by persistent cross-subtype, persistent subtype-specific, age-limited cross-subtype, and age-limited subtype-specific genetic influences. Paper III demonstrates that the three psychopathic personality dimensions were significantly linked to a highly heritable "psychopathic personality" factor, even though non-shared environmental factors also contributed significantly. The callous/unemotional and impulsive/irresponsible dimensions were also influenced by unique genetic factors. The results from Paper IV suggest that the association between psychopathic personality and persistent adolescent antisocial behavior was primarily explained by a common genetic factor. Genetic and environmental influences that were unique to persistent adolescent antisocial behavior were mainly explained by shared environmental influences.

The data in this thesis shows that a common genetic factor (i.e., persistent cross-subtype genetic influences) influences the development of ADHD from childhood to adolescence. Comorbidity between supposedly different domains of externalizing problems (i.e., psychopathic personality and persistent adolescent antisocial behavior) is also primarily explained by a common genetic factor. Nevertheless, this thesis also shows etiologic specificity in externalizing problems during the development from childhood to adolescence. The callous/unemotional and impulsive/irresponsible dimensions of the psychopathic personality are influenced by unique genetic variance and the developments of ADHD subtypes have independent genetic etiologies (i.e., persistent subtype-specific genetic influences).

Future research needs to consider the existence of general predisposing factors that influence a broad range of externalizing problems, but also specific predisposing factors that differentiate between different domains of externalizing problems. Identification of early emerging general and specific predisposing factors (e.g., endophenotypic markers) should be of high priority. Knowledge from such studies may not only facilitate identification of susceptibility genes, but also provide tools needed to identify effective intervention targets.

Keywords: Externalizing symptoms, ADHD, antisocial behavior, psychopathic personality, twin study, development, childhood, adolescence, genetic and environmental factors

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-IV):

I. Larsson J.-O., Larsson H, Lichtenstein P.
    Genetic and Environmental Contributions to Stability and Change of ADHD
    Symptoms Between 8 and 13 Years of Age: A Longitudinal Twin Study.
    J Am Acad Child Adolesc Psychiatry, 2004;43(10):1267-1275

II. Larsson H, Lichtenstein P, Larsson J.-O.
    Genetic contributions to the development of ADHD-subtypes from childhood
    to adolescence. Submitted

III. Larsson H, Andershed H, Lichtenstein P.
     A genetic factor explains most of the variation in the psychopathic personality.
     Journal of Abnormal Psychology, in press

IV. Larsson H, Tuvblad C, Andershed H, Grann M, Lichtenstein P.
    Genetic effects in psychopathic personality explain why persistent antisocial
    behavior is heritable. Submitted

CONTENTS

LIST OF ABBREVIATIONS

MZ	Monozygotic
DZ	Dizygotic
ADHD	Attention-Deficit/Hyperactivity Disorder
CD	Conduct Disorder
ODD	Oppositional Defiant Disorder
DSM	Diagnostic and Statistical Manual of Mental Disorder
CBCL	Child Behavior Check List
PCL-R	Psychopathy Checklist – Revised
TCHAD	Twin study of CHild and Adolescent Development
YPI	Youth Psychopathic traits Inventory

INTRODUCTION

Externalizing problems, such as hyperactivity, impulsivity, aggression, violation of legal or social norms, and delinquent behavior affect at least 5-10% of children and adolescents, and account for more than 50% of referrals to mental health clinics (Frick, 1998; Frick & Kimonis, 2005; McMahon, 1994). Numerous studies have demonstrated that externalizing problems tend to persist from childhood to adolescence (e.g., Moffitt, 2003; Willoughby, 2003). There are also high levels of comorbidity among supposedly different domains of externalizing problems (e.g., Waschbusch, 2002). Previous research also suggests that persistence over time and comorbidity may be two of the strongest predictors of adult outcome, especially risk for antisocial behavior, delinquency and substance abuse (e.g., Lilienfeld & Waldman, 1990; Moffitt, 2003; Willoughby, 2003). Thus, an understanding of the etiologic factors that underlie not only persistence in externalizing problems, but also comorbidity among different domains of externalizing problems is needed for the identification of effective intervention targets.

One general approach to assess child and adolescent externalizing problems is represented by the *Diagnostic and Statistical Manual of Mental Disorder* (DSM-IV; American Psychiatric Association, 1994). This approach uses diagnostic criteria to divide symptoms into groups that are hypothesized to be distinct from other groups of symptoms. Externalizing problems in children and adolescents are represented in DSM-IV by Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). These disorders are defined categorically (American Psychiatric Association, 1994). However, many of the DSM-IV defined symptom clusters, including ADHD, ODD and CD, show continuous distributions with no distinct cut-off point that separate normality from abnormality (Rutter, Silberg, O'Connor & Simonoff, 1999; Rutter, 2003).

The present thesis will use a dimensional approach to assess externalizing problems on a continuum in the general population. Externalizing problems will be defined broadly to include not only hyperactivity, impulsivity, inattention, and antisocial behavior, but also psychopathic personality traits. Thus, this thesis will focus on three domains of externalizing problems: (1) ADHD, (2) antisocial behavior, and (3) psychopathic personality.

ADHD

According to a recent review, the prevalence for ADHD in children is between 3% and 9% (Spencer, Biederman, Wilens & Faraone, 2002). The DSM has recognized ADHD as a disorder since the 1960s. Since then, several revisions in the criteria for the diagnosis of ADHD have been made and the disorder has been viewed at times as a multidimensional construct (e.g., DSM-IV), and at other times as a unidimensional construct (e.g., DSM-III-R). The DSM-III-R described a single list of fourteen items, incorporating symptoms of inattention, impulsivity, and hyperactivity with an eight-item cut-off for a diagnosis (American Psychiatric Association, 1987). The DSM-IV (American Psychiatric Association, 1994), on the other hand, conceptualizes ADHD as a disorder with two separate underlying symptom dimensions; a hyperactive-impulsive dimension including excessive activity and impulsive responding and an inattentive dimension including difficulties in sustaining attention, distractibility, lack of task persistence, and disorganization. An important aspect of the DSM-IV definition of ADHD is the specification of three subtypes. The combined subtype requires the presence of six or more hyperactive-impulsive symptoms and six or more inattentive symptoms, whereas the primarily hyperactive-impulsive and the primarily inattentive subtypes only require the six symptoms from each of those separate symptom dimensions.

ANTISOCIAL BEHAVIOR

Antisocial behavior in childhood and adolescence is represented in the DSM-IV by ODD and CD (American Psychiatric Association, 1994). The DSM-IV describes the essential features of ODD as "a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior towards authority figures that persist for at least 6 months" (American Psychiatric Association, 1994, pp. 91), whereas the essential features of CD are described as "a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated" (American Psychiatric Association, 1994, pp. 85). Antisocial behavior has also been defined through empirically derived rating scales, such as Child Behavior Check List (CBCL; Achenbach, 1991), in terms of aggressive (e.g., argues, fights) and delinquent (e.g., uses alcohol or drugs, vandalizes, steals) behavior. Antisocial behavior has also been conceptualized in terms of the violation of legal or social norms, that is, as criminality and delinquency (Rhee & Waldman, 2002).

PSYCHOPATHIC PERSONALITY

Psychopathic personality is, in its adult and full manifestation, considered a serious personality disorder that has been linked to a particularly severe pattern of antisocial behavior (Hare, 2002, 2003). The most common measure used to assess adults, the Psychopathy Checklist - Revised (PCL-R; Hare, 1991, 2003), employs data from a semi-structured interview and from institutional files to assign a rating of psychopathy. The PCL-R conceptualizes psychopathy as a disorder with at least three main symptom dimensions; an arrogant, grandiose, and deceitful interpersonal style, a deficient affective experience, and an impulsive, irresponsible behavioral style (Cleckley, 1976; Cooke & Michie, 2001; Hare, 2003). It should be noted that psychopathy is distinct, but related to the more behavioral-based diagnosis of antisocial personality disorder (American Psychiatric Association, 1994). The overlap between antisocial personality disorder and psychopathy is asymmetric; that is, individuals identified as psychopathic most often receive a diagnosis of antisocial personality disorder, but the reverse is not true (Hare, 1985).

In recent years researchers have attempted to extend the construct of psychopathy downward to children and adolescents (e.g., Andershed, Kerr, Stattin & Levander, 2002; Forth, Kosson & Hare, 2003), which seems necessary to understand the developmental origins of adult psychopathy, and also to understand the mechanisms behind the development and maintenance of severe antisocial behavior in adolescence. Several studies have shown that psychopathic personality traits are present and can be meaningfully assessed in adolescence (e.g., Andershed et al., 2002; Forth et al., 2003; Lynam & Gudonis, 2005; Vitacco, Rogers & Neumann, 2003). Nevertheless, this area of research is quite new and much remains to be done. In particular, it should be noted that the purpose of assessment of psychopathic personality in youth is not to assign a formal diagnosis of psychopathy, but rather to identify adolescents at increased risk for severe and/or persistent antisocial behavior.

TWIN STUDIES

Twin studies have consistently demonstrated the importance of both genetic and environmental influences in psychiatric disorders and symptom dimensions (Plomin, DeFries, McClean & McGuffin, 2001). The twin method is a kind of natural experiment in which the phenotypic resemblance for pairs of genetically identical individuals (Monozygotic (MZ) twins) is compared to the resemblance for pairs of individuals whose coefficient of genetic relationship is only 0.50 (Dizygotic (DZ)

twins). Twin studies have been used for decades to estimate heritability - the proportion of individual differences in a population at a given time that are due to genetic differences among individuals - for disorders and symptom dimensions.

Most twin studies of ADHD have reported heritabilities in the range from 60% to 90% (Rutter et al., 1999). There are only a few twin studies that have estimated the heritability for psychopathic personality traits (Blonigen, Carlson, Krueger & Patrick, 2003; Blonigen, Hicks, Krueger, Patrick & Iacono, 2005; Taylor, Loney, Bobadilla, Iacono & McGue, 2003; Viding, Blair, Moffitt & Plomin, 2005). These studies have reported heritabilities in the 40% to 70% range, which is fairly consistent with most twin studies of normal personality (Bouchard & Loehlin 2001) and antisocial behavior (Rhee & Waldman, 2002).

Recent twin research has moved beyond simple estimations of heritability. Longitudinal twin data (e.g.,Trouton, Spinath & Plomin, 2002; Boomsma et al., 2002) and advances in model fitting techniques and multivariate analysis (Boomsma, Busjahn & Peltonen, 2002; Neale, Boker, Xie & Maes, 2003) allow researchers to address more complex questions about genetic and environmental influences in behaviors. This thesis will concentrate on some of these issues to clarify the action of genetic and environmental factors in ADHD, antisocial behavior, and psychopathic personality during the development from childhood to adolescence. These issues can be organized into, (1) definition of phenotypes, (2) developmental continuity, and (3) comorbidity.

First, definition of phenotypes refers herein to refinements of a particular phenotype at the level of genetic and environmental factors rather than at the level of symptoms. This issue is addressed in Paper III in this thesis (i.e., to what extent can the associations among the three psychopathic personality dimensions be explained by a common genetic factor?).

Second, the processes underlying developmental continuity will in this thesis be covered by genetic and environmental contribution to the development of symptom dimensions over time. This issue is addressed in Papers I and II (e.g., how do genetic factors contribute to stability and change in ADHD symptoms from childhood to early adolescence?)

Finally, this thesis will investigate comorbidity in terms of genetic and environmental contribution to covariance between different phenotypes. Comorbidity is usually used to define coexistence of two or more categorically defined and distinct disorders (Keiley, Lofthouse, Bates, Dodge & Pettit, 2003), such as in DSM-IV. Covariation is more typically used in the context of a dimensional approach and refers

to the statistical degree to which one symptom dimension correlates with another symptom dimension (Keiley et al., 2003). This issue is addressed in Paper IV (i.e., is the association between psychopathic personality and persistent adolescent antisocial behavior explained by a common genetic factor?)

DEFINITION OF PHENOTYPES

Factor analytic work of psychopathic traits has provided empirical support for two, three and four factors underlying these traits (Andershed et al., 2002; Benning, Patrick, Hicks, Blonigen & Krueger, 2003; Cooke & Michie, 2001; Cooke, Michie, Hart & Clark, 2004; Forth et al., 2003; Frick et al., 2000; Hare, 1991; Hare, 2003; Lilienfeld & Andrews, 1996). However, most researchers agree upon a hierarchical model of psychopathic personality, in which a higher order factor is underpinned by at least two highly correlated trait dimensions (Cooke & Michie, 2001; Forth et al., 2003; Hare, 2003). Twin studies have shown that genetic factors are important for psychopathic traits (Blonigen et al., 2003, 2005; Taylor et al., 2003; Viding et al., 2005). However, none of these studies have used a measure that covers the three-factor structure that has been shown to describe the psychopathic personality well in adults (e.g., Cooke & Michie, 2001; Johansson, Andershed, Kerr & Levander, 2002). Thus, there is to date no information available on how genetic and environmental factors contribute to the associations among the three psychopathic personality dimensions. Furthermore, none of the previous twin studies have used a hierarchical model of psychopathy, in which a common latent factor explains the observed covariation among the three dimensions of psychopathic personality.

DEVELOPMENTAL CONTINUITY

Until recently, there was a general view that ADHD was limited to childhood, but follow-up studies have shown that the disorder persists in a sizable number of adults who had been diagnosed with ADHD in childhood (Barkley, Fischer, Edelbrock, Smallish & Barkley, 1990; Klein & Mannuzza, 1991). It has also been shown that symptoms of inattention tend to persist into adolescence to a greater extent than symptoms of hyperactivity-impulsivity (Biederman, Mick & Faraone, 2000; Hart, Lahey, Loeber, Applegate & Frick, 1995). However, the underlying factors contributing to the developmental trajectories of ADHD are not well understood (Willoughby, 2003).

Family studies suggest that persistent ADHD is highly familial (Biederman et al., 1996; Biederman et al., 1998). Two recent longitudinal studies have shown that stability in symptoms of ADHD from early and late childhood is primarily explained by heritable influences. Shared environmental and non-shared environmental influences were overall small (Kuntsi, Rijsdijk, Ronald, Asherson & Plomin, 2005; Rietveld, Hudziak, Bartels, van Bejsterveldt & Boomsma, 2004). However, none of these studies covered the transition from childhood to adolescence. Thus, how genetic and environmental factors contribute to stability and change in ADHD symptoms from childhood to adolescence is currently unknown.

The DSM-IV subtype conceptualization of ADHD has not been free of controversy. It has been suggested that the combined and the primarily inattentive type should be considered distinct and unrelated disorders rather than subtypes of the same disorder (Milich, Balentine & Lynam, 2001). Both family and twin research has been conducted on these subtypes, unfortunately with conflicting findings. Several studies have presented results that are most consistent with a general familial risk for ADHD (e.g., Faraone, Biederman & Friedman, 2000; Nadder, Silberg, Rutter, Maes & Eaves, 2001; Sherman, Iacono & McGue, 1997), whereas others have provided support for subtype-specific familiality (e.g., Rasmussen et al., 2004). Thus, the different subtypes seem to share a genetic component, whereas it is more unclear to what extent there is an independent genetic basis for the development of DSM-IV ADHD subtypes.

There is only one previous longitudinal twin study that has provided data on the hyperactive-impulsive and inattentive symptom dimensions of ADHD. This study found that the covariation over time between hyperactivity, impulsivity, and inattention to a considerable extent is influenced by a common genetic factor, but also that inattention to some extent is influenced by other genes (Nadder, Rutter, Silberg, Maes & Eaves, 2002). However, the short follow-up (19 months) as well as the large age-span of the children (8-16 years) limits the possibility to detect persistent and age-limited genetic influences. Thus, although it is clear that genetic factors play an important role in the etiology of ADHD, little is known about how genetic factors influence the development of the DSM-IV ADHD subtypes from childhood to adolescence.

COMORBIDITY

Comorbidity of supposedly separate psychiatric disorders is the norm in child and adolescent samples (Angold, Costello & Erkanli, 1999; Caron & Rutter, 1991),

especially among externalizing disorders (e.g., ADHD, ODD, CD; Hinshaw, 1987; Lilienfeld & Waldman, 1990; Waschbusch, 2002). Comorbidity between psychopathic personality and ADHD, ODD, and CD has also been noticed (Lynam, 1996; Salekin, Neumann, Leistico, DiCicco & Duros, 2004) and a more general link between psychopathic personality and antisocial behavior is well established (Walters, 2003).

Multivariate twin studies can be used to investigate the nature of comorbidity (Rutter et al., 1999), in which the covariance between different symptom dimensions is explained by common genetic and environmental factors (Waldman & Slutske, 2000). Results from twin studies have fairly consistently demonstrated that the associations among different domains of externalizing problems (i.e., symptoms of ADHD, ODD and CD) largely is explained by a common genetic factor (Krueger et al., 2002; Nadder et al., 2002; Silberg et al., 1996; Young, Stallings, Corley, Krauter & Hewitt, 2000). However, the etiology of the association between psychopathic personality and persistent adolescent antisocial behavior has never been investigated in a longitudinal, genetically sensitive design.

AIMS

The general aim of the work presented in this thesis has been to investigate how genetic and environmental factors contribute to externalizing problems during the development from childhood to adolescence. Multivariate twin methods and a longitudinal study design have been used to address the following research questions;

DEFINITION OF PHENOTYPES

1) How do genetic and environmental factors contribute to the associations among the three psychopathic personality dimensions?

DEVELOPMENTAL CONTINUITY

2) How do genetic and environmental factors contribute to stability and change in symptoms of ADHD from childhood to adolescence?
3) How do genetic factors contribute to the associations between and within hyperactivity-impulsivity and inattention from childhood to adolescence?

COMORBIDITY

4) How do genetic and environmental factors contribute to the associations between psychopathic personality and persistent adolescent antisocial behavior?

METHODS
PARTICIPANTS

The data used in all four papers come from the Twin study of CHild and Adolescent Development (TCHAD). The twins were identified through the population-based Swedish Twin Registry (Lichtenstein et al., 2002). All twins born in Sweden between May 1985 and December 1986, where both twins were alive, and lived in Sweden at the time of the study, comprised the target population. The twins and/or their parents have been contacted in three different waves with a mailed questionnaire: Wave 1 was in 1994 (twins were 8-9 years old), wave 2 was in 1999 (twins were 13-14 years old), and wave 3 was in 2002 (twins were 16-17 years old). Non-responders to the questionnaire were approached with up to three reminders. In Wave 1 the parent-questionnaire had a response rate of 75% (N=1,103). In Wave 2, 73% of the parents (N=1,063), and 78% of the twins (N=2,263) responded. In Wave 3, 74% of the parents (N=1,067), and 82% of the twins (N=2,368) responded to the questionnaire. The continued participation rate for the parent questionnaire was 84% from age 8-9 to 13-14, and 89% from age 13-14 to 16-17. The corresponding number for the twin questionnaire was 92% from age 13-14 to 16-17. Eighty-eight percent of the parents responded at least once and 58% at all three time points. An overwhelming majority of the parent-reported information was supplied by mothers rather than fathers (in the 75% to 90% range).

REPRESENTATIVENESS OF THE SAMPLE
Attrition rate

We have shown that there are no significant differences in sex ratio, externalizing symptoms, or ADHD symptoms between responders and subjects lost to follow-up at wave 2 (See Paper I; Tuvblad, Eley, Lichtenstein, 2005). We have also tested whether subjects lost to follow up at wave 3 differed from responders on measures at wave 2. Multivariate logistic regression analyses showed non-significant odds-ratios (OR) for sex (OR= .69, 95% CI: .48-1.00) and twin reported antisocial behavior (OR=1.22, 95% CI: 0.77-1.93) (Paper IV). A similar analyses using the parent-report data showed a significant odds-ratio (OR) for hyperactivity-impulsivity (OR= 1.15, 95% confidence interval 1.01-1.30), and non-significant OR for sex (OR= 1.01, 95% confidence interval 0.76-1.35), family socioeconomic status (OR= .92, 95% confidence interval 0.85-1.00),

and inattention (OR= .99, 95% confidence interval 0.85-1.16) measured at wave 2 (Paper III).

Telephone interview

We conducted a telephone follow-up for the twins who did not respond to the self-report questionnaire in wave 3. To avoid making the telephone interview too long we used a reduced battery of items from selected parts of the self-report questionnaire (e.g., psychopathic personality and antisocial behavior). The telephone interview sample consisted of 165 twins and they were not included in later analyses. The results show that telephone-responders scored higher than questionnaire-responders in the measure of psychopathic personality (Responders: mean= 34,15; Non-responders: mean=37,76; mean-difference=3.61, $t = -5.92$, $df = 2310$, $p < .001$), but not in antisocial behavior (Tuvblad et al., in press). There were significant differences between telephone-responders and questionnaire-responders in socioeconomic status ($\chi^2 =27.63$, $p < .001$). That is, twins who responded to the questionnaire more often came from higher socioeconomic status families than the twins who responded to the telephone interview.

Neighborhood characteristics

We also conducted some analyses in order to detect any biases between participants and non-participants with regard to neighborhood characteristics. No significant differences were found for unemployment level (t=-1.13, df=2,925, p=.26), basic educational level (t=-1.65, df=2,925, p=.10), buying power (t=-1.27, df=2,925, p=.21) or neighborhood crime-rate (t=.97, df=2,937, p=.33). However, for ethnic diversity (t=-3.63, df=2,925, p=.00) there was a significant difference, indicating that non-participating families lived in neighborhoods characterized by ethnic heterogeneity (Tuvblad et al., in press).

ZYGOSITY DETERMINATION

The current zygosity determination of the same-sexed twin pairs is based on algorithms derived from discriminant analyses on 106 twin pairs participating in the clinical study with known zygosity (based on 16 polymorphic DNA-markers). This algorithm only classifies pairs that have a 95 % probability of being correctly classified as monozygotic (MZ) or dizygotic (DZ). Zygosity was classified by using separate algorithms to parent's response (wave 1, wave 2, and wave 3) and to children's response (wave 2 and wave 3) using 4 questions dealing with the twins' physical similarity and the frequency with which people confuse them. Zygosity was scored as unknown in cases of contradictions between any of the five zygosity assignments. It

should be noted that in earlier reports from the TCHAD-study we have used other algorithms for zygosity classification. However, we have used the best available zygosity diagnose at each time point, and the variations between the different methods are small and of limited importance.

MEASURES

ADHD symptoms (Paper I and Paper II)

A binary scaled checklist with 21-24 items based on DSM (American Psychiatric Association, 1980; 1987; 1994) was completed by the parents at waves 1, 2, and 3. The parents were asked to check symptoms persisting for at least six months. The checklist items that were used in Paper I and Paper II are presented in Table 1.

Table 1. Parent-reported symptoms of ADHD, hyperactivity-impulsivity and inattention included in Paper I and Paper II.

ADHD-symptom	Included in		
	Paper I	Paper II	Wave
Has great difficulty sitting still – is very restless (ants up their pants)	III-R	IV-H-I	1,2,3
Can never sit still	III-R	IV-H-I	1,2,3
Is, regardless of activity, extremely easy disturbed by sounds, light or other people	III-R	IV-Inatt	1,2,3
Can never wait for his/her turn	III-R	IV-H-I	1,2,3
Blurts out answers to questions before they have been completed	III-R	IV-H-I	1,2,3
Seldom manages to complete tasks he/she has already started	III-R	IV-Inatt	1,2,3
Lacks endurance	III-R	IV-Inatt	1,2,3
Runs from one thing to another	III-R	IV-H-I	1,2,3
Can not play calmly and quietly	III-R	IV-H-I	1,2,3
Talks all the time	III-R	IV-H-I	1,2,3
Interrupts and intrudes on others or interferes into other children's games	III-R	IV-H-I	1,2,3
Appears as if he/she is not listening	III-R	IV-Inatt	1,2,3
Loses, forgets or misplaces things which are important to him/her at school or at home (e.g. toys, school books)	III-R	IV-Inatt	1,2,3
Never seems to understand that something might be dangerous	III-R		1,2,3
Gets up and walks away from the desk during class, or stands up in other situations in which remaining seated is expected		IV-H-I	2,3
Runs around and/or climbs on everything		IV-H-I	1,2,3
Is always "on the go", as if he/she is driven by a motor		IV-H-I	1,2,3
Needs constant supervision, can never be left alone		IV-H-I	1,2
Often fails to notice details or is sloppy with schoolwork or other activities		IV-Inatt	2,3
Is easily distracted by other events during play		IV-Inatt	1,2,3
Plays completely unorganized		IV-Inatt	1,2,3
Avoids tasks which require mental effort and endurance (e.g. work at school, homework)		IV-Inatt	2,3

Note. III-R = ADHD scale that covers the DSM-III-R conceptualization of ADHD; IV-H-I = hyperactivity-impulsivity scale based on DSM-IV conceptualization of ADHD; IV-Inatt = inattention scale based on DSM-IV conceptualization of ADHD.

Fourteen of these checklist items (the items labeled III-R in the Paper I column in Table 1) from the parent-response at wave 1 (twins were 8-9 years old) and wave 2 (twins were 13-14 years old) were used in Paper I to create a dimensional scale that covers the DSM-III-R conceptualization of ADHD (American Psychiatric Association, 1987). Children with missing values for two or more ADHD symptoms were excluded from the analyses and missing values for only one of the 14 ADHD symptoms was coded as "no symptom". The symptoms were scored as 0 if the item was not true for the child and 1 if the item was true, and then summed up in a total score (Steffenson et al., 1999). Internal consistencies for the DSM-III-R based scale that were calculated separately for age and sex ranged from .78 to .85 (at age 8-9: boys = .83; girls = .78, and at age 13-14: boys = .85; girls = .84).

Most of the checklist items (see Table 1) from the parent-response at waves 1, 2 and 3 were used in Paper II to create two dimensional scales based on the DSM-IV conceptualization of ADHD (American Psychiatric Association, 1994). Due to the changes in DSM during the follow-up period and because the twins in the sample were growing older, the questionnaire that was used at the three measurement occasions differs slightly in item content (Table 1). For example, the item "needs constant supervision, can never be left alone" was excluded in wave 3 (twins were 16-17 years old). Internal consistencies for the DSM-IV based symptom dimensions were calculated separately for age and ranged from .68 to .83 (hyperactivity-impulsivity: at age 8-9 = .80, at age 13-14 = .83, and at age 16-17 = .81; inattention: age 8-9 = .68, at age 13-14 = .79, and at age 16-17 = .82).

Psychopathic personality traits (Paper III and Paper IV)

The 50 items long Youth Psychopathic traits Inventory (YPI; Andershed, et al., 2002) was filled out by each twin at wave 3 (twins were 16-17 years old). The YPI measures each psychopathic trait with five items making up ten internally consistent subscales (Andershed, et al., 2002) using a four-point Likert-type response scale ranging from "Does not apply at all" to "Applies very well". Two sample items of each of the ten subscales and Cronbach alphas are presented in Table 2. As can be seen, the internal consistencies for YPI's ten subscales (comprised of five items each) ranged from .58 to .79 (Table 2).

Table2. Cronbach's alpha coefficiens and sample item for the ten sub-scales of the YPI.

Subscale	Alpha	Sample items
Dishonest charm	.79	I have the ability to con people by using my charm and smile.
		When I need to, I use my smile and charm to use others.
Grandiosity	.70	I am better than everyone on almost everything.
		I am more important and valuable than other people.
Lying	.74	Sometimes I lie for no reason, other than because it is fun.
		I have often gotten into trouble because I have lied too much.
Manipulation	.77	I can get almost anyone to believe anything.
		To get people to do what I want, I often find it efficient to con them.
Callousness	.58	When other people have problems it is often their own fault, therefore one should not help them.
		I often become sad or moved by watching sad things on tv or film (R).
Unemotionality	.63	I usually feel calm when other people are scared.
		I don't let my feelings affect me as much as other people do.
Remorselessness	.70	I have the ability not to feel guilt and regret about things that I think other people would feel guilty about.
		To feel guilty and remorseful about things you have done that have hurt other people is a sign of weakness.
Impulsiveness	.68	It often happens that I do things without thinking ahead.
		I prefer to spend my money right away rather than save it.
Thrill-seeking	.73	I like to do thing just for the thrill of it.
		I get bored quickly by doing the same thing.
Irresponsibility	.68	It happened several times that I have borrowed something and then lost it.
		I have cut class more than most people.

Importantly, the ten subscales have been shown to form a theoretically meaningful three-factor structure consisting of (1) a grandiose/manipulative dimension (including the subscales dishonest charm, grandiosity, lying and manipulation), (2) a callous/unemotional dimension (including the subscales callousness, unemotionality and remorselessness), and (3) an impulsive/irresponsible dimension (including the subscales impulsiveness, thrill-seeking and irresponsibility) (Andershed et al., 2002). This three-factor structure was also supported in our sample (Paper III). Internal consistencies for the three psychopathic personality dimensions ranged from .66 to .82, and the correlations among the three dimensions ranged from .40 to .60, which is in line with previous findings (Andershed et al., 2002). Moreover, in recent study using a sample of serious adolescent offenders, the YPI was shown to predict a range of short-term institutional misbehaviors, to manifest good test-retest reliability, to be negatively

related to anxiety, and to be associated with the Psychopathy Checklist-Revised: Youth Version (PCL:YV; Forth, et al., 2003; Skeem & Cauffman, 2003).

Antisocial behavior (Paper IV)

At age 13-14 and 16-17 each twin completed a 32-34 item long questionnaire indicating the frequency with which they had participated in illegal acts in the past twelve months. The questionnaire covered three different areas; (1) property offences including 20 items such as vandalism, breaking, entering and shop lifting, (2) drug-related offences including 4 items about using and selling various types of illicit drugs, (3) violent offences including 8 items about simple assault, fighting, robbery, and arson. Five items of property offences, two items of drug-related offences and three items of violent offences are presented in Table 3 together with prevalences at age 16-17. For example, at age 16-17 the prevalence of shop-lifting during the past twelve month was 17%.

The questionnaire is part of an extensive battery of questions that has been developed by the Department of Criminology at Stockholm University (Ring, 1999). The items included in the questionnaire were initially derived from *Delinquent Behavior among Young People in the Western World* comparing self-reported studies from 13 countries. Factor analyses of the self-reported delinquency items in the currant sample resulted in a single factor with a high internal consistency at both time points (wave 2: Cronbach's alpha: $\alpha=.87$; wave 3: $\alpha=.92$). Consequently, the scale was analyzed as a single composite scale at each wave.

Table 3. Prevalences and sample items for property offences, drug-related offences and violent offences.

	Prevalence (%) at age 16-17
Property offences	
Shop-lifting	17.0
Vandalism	15.0
Bike theft	9.0
Burglary	4.0
Theft from car	2.5
Drug related offences	
Use drugs	5.0
Sell soft drugs	0.1
Violent offences	
Arson	3.0
Beat someone	2.5
Threaten for money	1.0

TWIN METHODOLOGY

The twin method is a natural experiment that relies on the different levels of genetic relatedness between MZ and DZ twin pairs to estimate the contribution of genetic and environmental factors to individual differences in a phenotype of interest. MZ twins are genetically identical, whereas dizygotic twins share on average 50 % of their segregating genes. A measure of the similarity between twins is given by calculating the intraclass correlation. Comparisons between the intraclass correlations for MZ and DZ twins provide information about the genetic and environmental effects that are present. For example, a genetic effect is indicted if twin similarity is greater among MZ than DZ twin pairs.

In the basic twin model, the total variance of a measured phenotype (Y) can be divided into additive genetic factors (A), shared environmental factors (C), and non-shared environmental factors (E). Shared environmental factors refer to non-genetic influences that contribute to similarity within pairs of twins. Non-shared environmental factors are those experiences that make siblings dissimilar.

$$\text{Variance } (Y) = A + C + E$$

The correlation for MZ twin pairs is assumed to be due to both additive genetic and shared environmental influences (A+C). The DZ pairs share on average only half of their segregated genes, and thus, the correlation is assumed to be due to the sum of half the additive genetic factor, plus the shared environmental factor (½A+C). Heritability is defined as the proportion of total phenotypic variation explained by genetic factors (Plomin et al., 2001).

The partitioning of phenotypic variance into genetic and environmental factors is usually illustrated in a path diagram (see Figure 1). Latent variables are depicted in circles, whereas observed phenotypes are depicted in rectangles. Genetic (A), shared (C), and non-shared environmental (E) effects on the measured phenotype are shown for both members of a twin pair. The genetic correlation (r_a) between MZ twin pairs is set at 1. The corresponding genetic correlation (r_a) for like-sexed DZ twins is 0.5. The shared environmental correlation (r_c) is set to 1 for both groups, based on the equal environment assumption. By definition there is no within-pair correlation between the non-shared environmental factors. Figure 1 illustrates a path diagram for a twin pair.
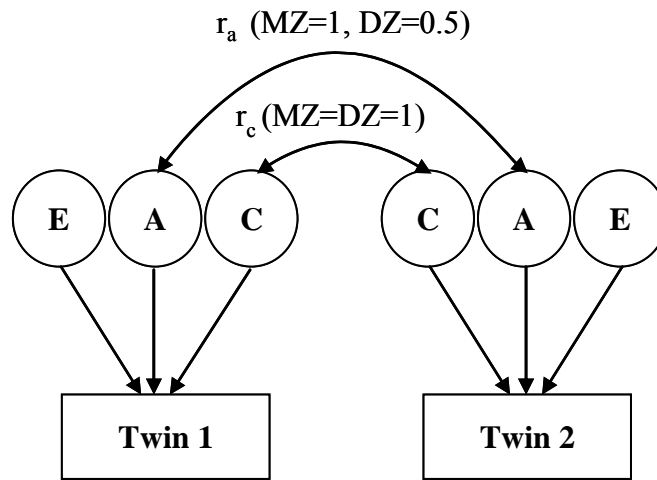
Figure 1. Basic path diagram for univariate twin data.

Sex-differences (Paper I and Paper III)

A series of four models can be fitted in order to test for sex differences (Neale & Martin, 1989); (1) A constrained model which assumes equal genetic and environmental variance components for boys and girls; (2) A scalar sex limitation model tests whether the relative influence of genetic and environmental factors is the same but there are variance sex differences; (3) A heterogeneity model assumes that although the same sets of genes and shared environment are important for boys and girls, the relative magnitude of their importance may differ; (4) A model that not only allows different values of a, c, and e for males and females, but also allows the genetic or shared environmental correlation between the members of the opposite-sex pairs to vary.

Cholesky decomposition (Paper I and Paper III)

A bivariate Cholesky model (Neale & Cardon, 1992) was used to investigate the importance of genetic and environmental influences on stability and change in ADHD symptoms (Paper I). Figure 2 illustrates a path diagram of the model containing only one of the twins in the pair, where A is genetic factors, C is shared environmental factors, and E is non-shared environmental factors. The assumptions in the basic univariate twin model also apply to the bivariate Cholesky model. The model decomposes the variance in ADHD at time 2 into variance in common with ADHD at time 1 (A_1, C_1, E_1), and variance unique to ADHD at time 2 (A_2, C_2, E_2). The estimates in Figure 2 (e.g., a_{11}, a_{21}, a_{22}) can be used for calculating how much of the stability and change are accounted for by genetic and environmental effects.
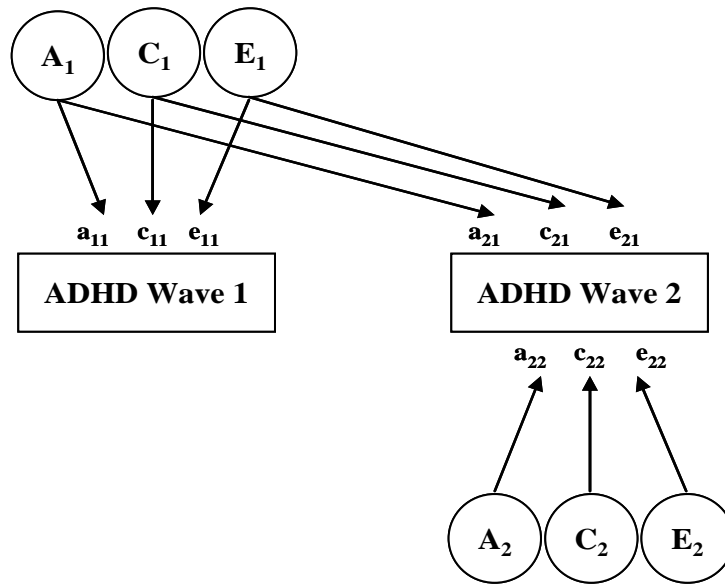
Figure 2. Bivariate Cholesky model for the longitudinal genetic analyses of ADHD.

A series of bivariate Cholesky models was fitted to estimate the genetic correlations between the three psychopathic personality dimensions (Paper III). A genetic correlation varies from +1.0 and -1.0 and indicates the extent to which genetic influences in one measure overlap with those on the second measure.

Extended independent pathway model (Paper II)

An extended independent pathway model (Nadder et al., 2001; Nadder et al., 2002) was used to examine how genetic influences contribute to the associations between and within the hyperactive-impulsive scale and the inattentive scale across the three time points. Figure 3 illustrates a path diagram of the model containing only one of the twins in the pair. The model includes several genetic and environmental factors to explain the covariation between the measures, but for simplicity we only present the genetic factors. As can be seen in Figure 3, the model defines the genetic factors as: persistent cross-subtype genetic effects (A1), persistent subtype-specific genetic effects (A2), age-limited cross-subtype genetic effects (A3), and age-limited subtype-specific genetic effects (A4). Persistent genetic effects refer to genetic factors that operate over successive time-points, whereas age-limited genetic effects refer to genetic factors that operate at a given time point.
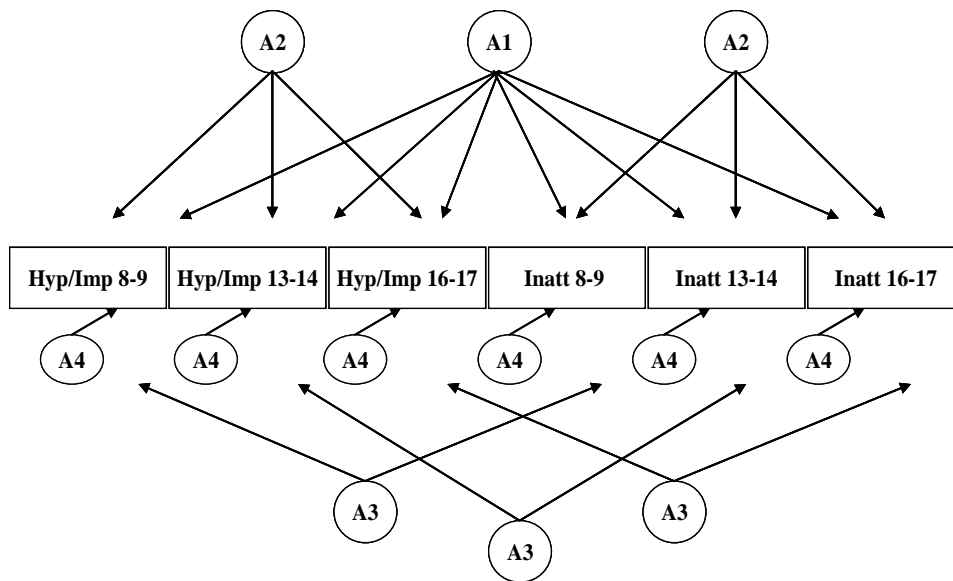
Figure 3. Extended independent pathway model for the two scales of ADHD, measured at three time points (at age 8-9, 13-14, and 16-17). Latent variables are depicted in circles, whereas observed variables are depicted in rectangles. Hyp/Imp = hyperactivity-impulsivity; Inatt = inattention.

Common pathway model (Paper III)

A common pathway model (Kendler, Heath, Martin & Eaves, 1987) was used to study the variance shared among the three psychopathic personality dimensions. The common pathway model assumes that both genetic and environmental effects contribute to an intermediate latent variable, which in turn is responsible for the observed pattern of covariation between the measures in the model. Residual variance unique to each measure is also decomposed into unique genetic and environmental factors. The common pathway model is a similar but more restricted model than the independent pathway model. Thus, to evaluate how well the common pathway model describes the data, we compared the fit of the two models (Paper III).

Extended common pathway model (Paper IV)

The common pathway model can be extended to include multiple intermediate latent variables, such as a two-factor common pathway model (McArdle & Goldsmith, 1990). A two-factor common pathway model was used to examine the genetic and environmental contribution to the association between the latent psychopathic personality factor and the latent persistent adolescent antisocial behavior factor. In our study, the model defines the latent psychopathic personality factor as the covariation among the three psychopathic personality dimensions, while the latent persistent adolescent antisocial behavior factor is defined as the covariation among antisocial behavior measured at age 13-14 and 16-17 (see Figure 5 on page 25). By using this

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model it was possible to investigate the nature of the relationship between these two latent variables (i.e., psychopathic personality and persistent adolescent antisocial behavior) by decomposing the variance and covariance into common and unique genetic and environmental influences.

Model fitting

All scales in the thesis were independently transformed ($\log_{10}(x+1)$) prior to analyses to increase normality of their distributions. All univariate and multivariate models in this thesis were fitted to raw data, allowing the inclusion of cases in which information is available from only one twin in a pair, and cases in which information is available about a pair from just one measure, which increases power in the analyses. Modeling was performed with the structural equation modeling package Mx (Neale, Boker, Xie & Maes, 2003), which provides maximum-likelihood estimates of the different parameters. Goodness of fit of models was assessed by a likelihood-ratio χ^2 – test, which is the difference between -2 log likelihood (-2 ll) of the full model from that of the restricted model. This difference is distributed as a χ^2. The degrees of freedom (df) for this test are equal to the difference between the number of estimated parameters in the full model and that in a restricted model.

RESULTS

DEFINITION OF PHENOTYPES

One of the main aims in Paper III was to investigate how genetic and environmental factors contribute to the associations among the three psychopathic personality dimensions. To address this issue we first fitted a series of bivariate Cholesky models to estimate the genetic correlations between each of the three psychopathic personality dimensions. The genetic correlations between the grandiose/manipulative, callous/unemotional and impulsive/irresponsible dimensions ranged from .59 to .78, with the greatest genetic association between the grandiose/manipulative and impulsive/irresponsible dimensions. These results suggest a substantial genetic overlap among the three dimensions. Next, we fitted a common pathway model (Kendler et al., 1987) to explore the covariance among all three psychopathic personality dimensions simultaneously. This model is in line with the empirically supported hierarchical model of psychopathy (Cooke & Michie, 2001). That is, we used a model in which a latent construct of what we chose to label "psychopathic personality" is underpinned by the three psychopathic personality dimensions. The model fitting analyses showed that the common pathway model gave a more parsimonious representation of the data compared to the independent pathway model (Δ-2 LL(4)=7.66, p <.11).

Figure 4 presents the squared standardized path estimates and confidence intervals for the full common pathway model. In this model, additive genetic factors explained 63% of the variance in the latent "psychopathic personality" factor, while non-shared environmental factors explained the remaining 37% of the variance. Shared environmental influences did not contribute to the explanation of "psychopathic personality". The decomposition of the unique genetic effects revealed that additive genetic factors explained 22% of the variance in both the callous/unemotional dimension and the impulsive/irresponsible dimension, whereas the unique genetic effect in the grandiose/manipulative dimension was negligible.
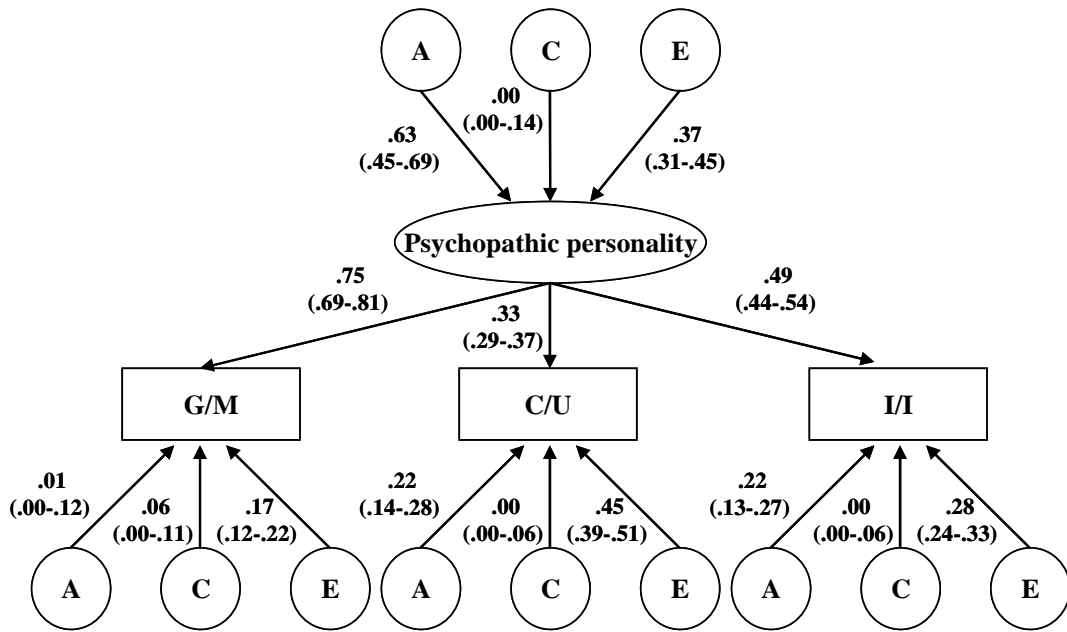
Figure 4. Squared path estimates for the full common pathway model, with 95% Confidence Intervals. G/M = grandiose/manipulative dimension; C/U = callous/unemotional dimension; I/I = impulsive/irresponsible dimension.

DEVELOPMENTAL CONTINUITY

The results from Paper 1 show that there were relatively strong correlations between DSM-III-R ADHD symptoms measured at age 8-9 and at age 13-14 (boys: r=0.51; p<.001; girls: r=0.51; p<.001). Bivariate Cholesky models were fitted to investigate the genetic and environmental contribution to the stability. The parameter estimates from this model were used to calculate how much of the stability and change that were explained by genetic and environmental factors (Table 4).

Table 4. Proportion of stability and change due to genetic and environmental effects from longitudinal model-fitting for ADHD symptoms in 8-9 and 13-14-year-old children.

Model	Proportion of variation					
	Boys			Girls		
	A	C	E	A	C	E
Stability	74%	16%	10%	79%	6%	15%
Change	62%	0%	38%	55%	0%	45%

Note: A=genetic effects, C=shared environmental effects, E=non-shared environmental effects.

As can be seen, the stability in ADHD-symptoms over a 5-year period was to a large extent explained by genetic factors (boys: 74%; girls: 79%; See Table 4). Both genetic (boys: 62%; girls: 55%) and non-shared environmental (boys: 38%; girls: 45%) factors contributed to changes in ADHD symptoms during the period from childhood to early adolescence.

In Paper II, the longitudinal analysis was extended to mid-adolescence. Further, a DSM-IV conceptualization allowed us to investigate the development of hyperactive-impulsive and inattentive symptom dimensions of ADHD. That is, the longitudinal analysis included measures of hyperactivity-impulsivity and inattention at age 8-9, 13-14, and 16-17. The phenotypic correlations suggested a relatively high stability over successive time points in the hyperactive-impulsive scale (girls: r=0.38-0.52, boys: r=0.34-0.54) and the inattentive scale (girls: r=0.37-0.60, boys: r=0.35-0.58).

Table 5. Model fitting results for the hyperactive-impulsive and the inattentive scales

| Model | -2ll | df | Model comparison | | | |
			Compared to model	Δ-2ll	Δdf	P
Girls						
1. ACE Independent pathway	5153.13	4074	-	-	-	-
2. AE Independent pathway	**5154.19**	**4095**	**1**	**1.06**	**21**	**.99**
Testing persistent genetic effects						
3. Drop A1	5290.68	4101	2	136.49	6	.00
4. Drop A2	5169.53	4101	2	15.34	6	.02
Testing age-limited genetic effects						
5. Drop A3	5186.42	4098	2	32.23	3	.00
6. Drop A4	5210.72	4101	2	56.53	6	.00
Boys						
1. ACE Independent pathway	5805.21	4090	-	-	-	-
2. AE Independent pathway	**5813.52**	**4111**	**1**	**8.31**	**21**	**.99**
Testing persistent genetic effects						
3. Drop A1	5938.26	4117	2	124.74	6	.00
4. Drop A2	5848.75	4117	2	35.23	6	.00
Testing age-limited genetic effects						
5. Drop A3	5881.07	4114	2	67.56	3	.00
6. Drop A4	5846.38	4117	2	32.86	6	.00

Note: A1, Persistent cross-subtype genetic effects; A2, Persistent subtype-specific genetic effects; A3, age-limited cross-subtype genetic effects; A4, age-limited subtype-specific genetic effects. The best fitting model is highlighted in bold. A P-value below 0.05 represents a significant loss of fit.

An important aim in Paper II was to examine how genetic factors contribute to the observed associations between and within the hyperactive-impulsive scale and the

inattentive scale across the three time points. An extended independent pathway model was used to specify four broad genetic components: persistent cross-subtype genetic effects (A1), persistent subtype-specific genetic effects (A2), age-limited cross-subtype genetic effects (A3), and age-limited subtype-specific genetic effects (A4). A series of reduced models was fitted to test whether all four broad factors were necessary for an adequate fit of the model. The model fitting results are presented in Table 5.

For both girls and boys, a model that included all four genetic components provided the best fit to the data (in bold in Table 5). The parameter estimates from the best fitting models were used to calculate how much of the total genetic variance in each measure that was due to persistent cross-subtype, persistent subtype-specific, age-limited cross-subtype, and age-limited subtype-specific genetic influences. The proportion of genetic variance explained by persistent genetic factors (i.e., by A1 and A2) and age-limited factors (i.e., by A3 and A4) are presented in Table 6. As can be seen, 45-90% of the total genetic variance in each measure was explained by persistent genetic influences. For example, in hyperactivity-impulsivity at age 8-9 for girls, 51% of the genetic variance was due to persistent genetic influences (Table 6).

Table 6. Proportion of genetic variance (%) from the best fitting model

	Hyp/imp-8-9	Hyp/imp-13-14	Hyp/imp-16-17	Inatt-8-9	Inatt-13-14	Inatt-16-17
Girls						
Persistent genetic effects						
A1	31	72	44	37	72	60
A2	20	2	7	8	18	6
Age-limited genetic effects						
A3	16	2	18	45	1	12
A4	33	24	31	10	9	22
Boys						
Persistent genetic effects						
A1	44	54	28	40	60	48
A2	6	21	39	5	14	14
Age-limited genetic effects						
A3	18	20	27	39	17	11
A4	32	5	6	16	9	27

Note: Hyp/imp = hyperactive-impulsive; Inatt = Inattentive. Persistent genetic effects refer to genetic factors that operate over successive time-points, whereas age-limited genetic effects refer to genetic factors that operate at a given time point.
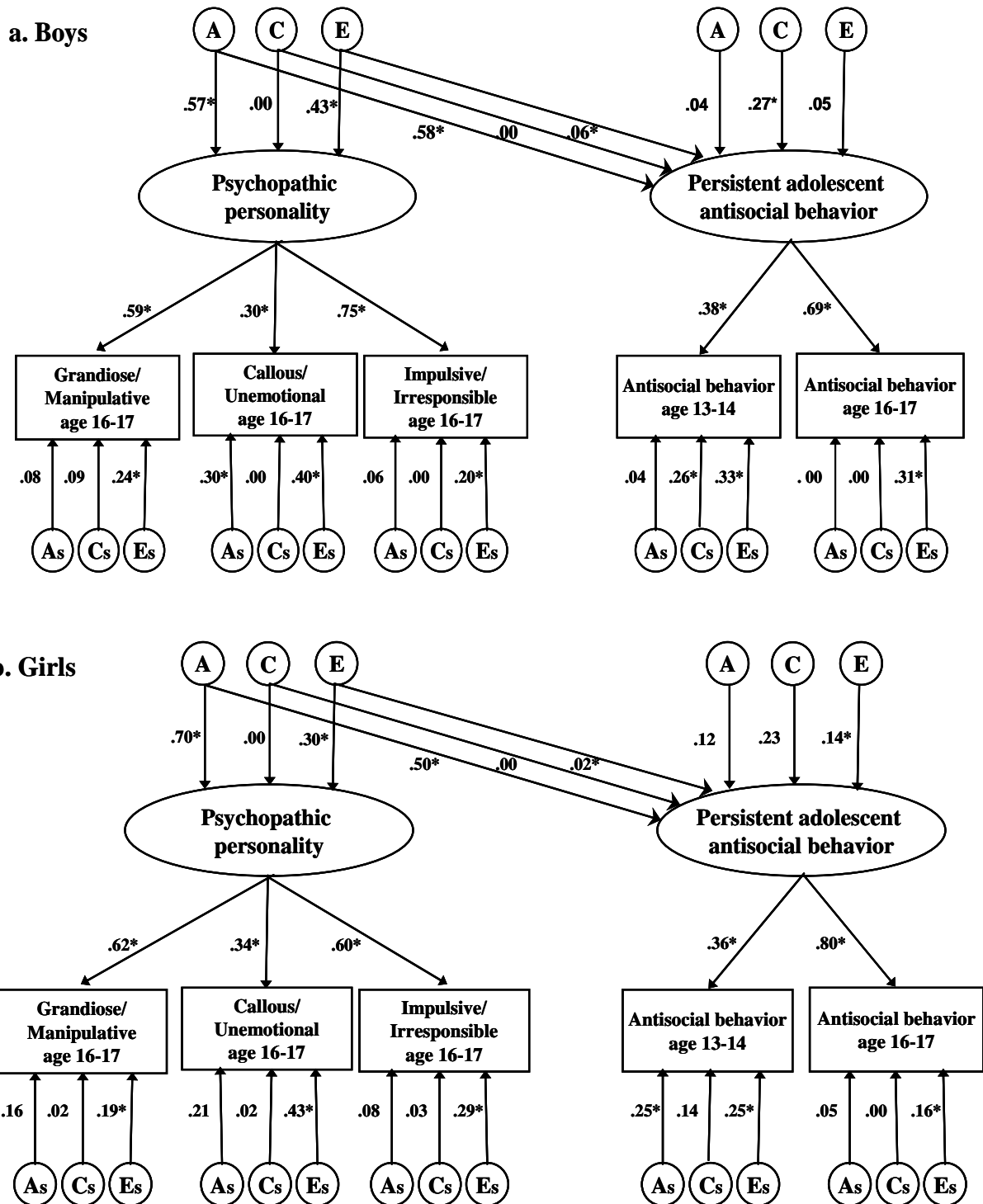
COMORBIDITY

The main aim of Paper IV was to investigate how genetic and environmental factors contribute to the associations between psychopathic personality and persistent adolescent antisocial behavior. Psychopathic personality was defined as the covariation among the three psychopathic personality dimensions, whereas persistent adolescent antisocial behavior was defined as the covariation among antisocial behavior measured at age 13-14 and 16-17. A two-factor common pathway model was fitted to examine the nature of the association between the latent psychopathic personality factor and the latent persistent adolescent antisocial behavior factor. Figure 5 displays the standardized squared path estimates from the two-factor common pathway model for psychopathic personality traits and persistent adolescent antisocial behavior in boys (a) and girls (b) at ages 13-14 and 16-17.

The heritability estimate for persistent adolescent antisocial behavior is given by summing the two genetic paths that loads on the latent persistent adolescent antisocial behavior factor. The heritability was relatively large (boys: .58+.04; girls: .50+.12), explaining 62% of the variance in persistent adolescent antisocial behavior for both boys and girls.

Genetic effects for psychopathic personality were of substantial importance for the variance in persistent adolescent antisocial behavior (boys: 58%; girls: 50%). Non-shared environmental effects (boys: 6%; girls: 2%) were, however, only modestly mediated via psychopathic personality.

Genetic and environmental influences that were unique to persistent adolescent antisocial behavior and not in common with psychopathic personality were mainly explained by shared environmental influences (boys: 27%; girls; 23%), whereas the unique genetic influences seemed to be of negligible importance.

a. Boys

Psychopathic personality

.57* .00 .43*

.58* .00 .06*

Persistent adolescent antisocial behavior

.04 .27* .05

.59* .30* .75*

Grandiose/ Manipulative age 16-17

Callous/ Unemotional age 16-17

Impulsive/ Irresponsible age 16-17

.38* .69*

Antisocial behavior age 13-14

Antisocial behavior age 16-17

.08 .09 .24*

.30* .00 .40*

.06 .00 .20*

.04 .26* .33*

.00 .00 .31*

As Cs Es   As Cs Es   As Cs Es   As Cs Es   As Cs Es

b. Girls

Psychopathic personality

.70* .00 .30*

.50* .00 .02*

Persistent adolescent antisocial behavior

.12 .23 .14*

.62* .34* .60*

Grandiose/ Manipulative age 16-17

Callous/ Unemotional age 16-17

Impulsive/ Irresponsible age 16-17

.36* .80*

Antisocial behavior age 13-14

Antisocial behavior age 16-17

.16 .02 .19*

.21 .02 .43*

.08 .03 .29*

.25* .14 .25*

.05 .00 .16*

As Cs Es   As Cs Es   As Cs Es   As Cs Es   As Cs Es

Figures 5a and 5b. The latent variables A (additive genetic factor), C (shared environmental factor), and E (non-shared environmental factor) are depicted in circles. Ovals denote the two latent factors (i.e., *psychopathic personality traits* and *persistent adolescent antisocial behavior*). Measured variables are depicted in rectangles (i.e., grandiose/manipulative age 16-17- - antisocial behavior age 16-17). As (additive genetic): is residual variance specific to each measure, likewise for Cs (shared environment), and Es (non-shared environment). Note that the latent variable C: shared environment on *psychopathic personality traits* was set to zero. Significant estimates are marked with *.

DISCUSSION

An increased understanding of the etiologic factors that underlie persistence in externalizing problems from childhood to adolescence, and the comorbidity among supposedly different domains of externalizing problems, may generate knowledge that is critical for the identification of effective intervention targets.

Multivariate twin methods and a longitudinal study design provide means to address complex questions about genetic and environmental factors in behaviors. This thesis has focused on some issues that may clarify the action of genetic and environmental factors in ADHD, antisocial behavior, and psychopathic personality during the development from childhood to adolescence. That is, three broad issues have been addressed (i.e., definition of phenotypes, developmental continuity, and comorbidity) by examining four more specific research questions:

First, how do genetic and environmental factors contribute to the associations among the three psychopathic personality dimensions? Second, how do genetic and environmental factors contribute to stability and change in symptoms of ADHD from childhood to adolescence? Third, how do genetic factors contribute to the associations between and within hyperactivity-impulsivity and inattention from childhood to adolescence? Finally, how do genetic and environmental factors contribute to the associations between psychopathic personality and persistent adolescent antisocial behavior? Answers to these research questions, its relation to previous research, and direction for future research are outlined below.

DEFINITION OF PHENOTYPES

Paper III in this thesis is the first study that has used a hierarchical twin model to examine the genetic and environmental contribution to the covariation among the three psychopathic personality dimensions (i.e., grandiose/manipulative, callous/unemotional, and impulsive/irresponsible dimensions). Results show that the three psychopathic personality dimensions are significantly linked to a highly heritable "psychopathic personality" factor. The callous/unemotional and impulsive/irresponsible dimensions were also influenced by significant unique genetic factors.

The finding of a common latent "psychopathic personality" factor is consistent with the notion of a hierarchical model of the psychopathic personality construct (Cooke & Michie, 2001; Forth et al., 2003). This thesis extends previous knowledge (Blonigen et al., 2003, 2005; Taylor et al., 2003; Viding et al., 2005) in showing that genetic

influences are of particular importance for the latent "psychopathic personality" factor. The results are, however, largely in line with one previous twin study demonstrating the importance of a common genetic factor for the different dimensions of psychopathic personality (Taylor et al., 2003).

A main research goal is therefore to find out which etiologic processes that are shared between the three psychopathic personality dimensions. This thesis has conceptualized these processes as latent genetic and environmental factors, but it may also be useful to conceptualize these processes at different levels of abstraction (e.g., measured genes, brain functioning, neuropsychological measures, and personality). Theories that have linked psychopathic personality to cognitive (e.g., Newman, 1998), emotional (e.g., Patrick, 1994), neurological (e.g. Blair, 1999) and personality (e.g., Lynam, 2002; Widiger, 1998) processes may provide useful information concerning the observed common genetic components.

The finding of unique genetic variance in the callous/unemotional and impulsive/irresponsible dimensions suggests some etiologic independence. This is consistent with one previous twin study, which also found residual genetic effects in the callous/unemotional dimension of psychopathy (Taylor et al., 2003). Another essential research goal is therefore to find out which etiologic processes that may distinguish between the three dimensions. One line of research has linked psychopathic personality to a combination of personality traits found within the five factor model of personality (e.g., Lynam, 2002; Widiger, 1998). These studies suggest that the callous/unemotional dimension may assess traits that are conceptually close to low neuroticism, whereas the impulsive/irresponsible dimension assesses traits in similarity to low conscientiousness (Lynam, 2002). This may explain the observed etiologic independence within each psychopathic personality dimensions at the level of normal personality.

Similar to recent twin studies of psychopathic traits (Blonigen et al., 2003, 2005; Taylor et al., 2003; Viding et al., 2003), shared environmental factors produced a negligible contribution to the variance in the psychopathic personality. These results are also consistent with evidence reported across many twin studies of psychopathology and personality (Bouchard & Loehlin, 2001; Bouchard & McGue, 2003). Non-shared environmental factors, on the other hand, were shown to contribute significantly to individual differences in psychopathic personality. One possible interpretation of this result is that differences in peer relationships may account for some of the observed non-shared environmental influences (Pike & Plomin, 1997).

DEVELOPMENTAL CONTINUITY

Paper I and Paper II in this thesis investigated the genetic and environmental contribution to stability and changes in symptoms of ADHD from childhood to adolescence. These two studies show that there is a relatively strong continuity in ADHD symptoms from childhood to adolescence, which is consistent with other studies (Barkley, Fischer, Smallish, & Fletcher, 2002). This stability is to a large extent explained by genetic factors, which is in line with results from other longitudinal twin studies that covered symptoms of ADHD from early and late childhood (Kuntsi et al., 2005; Rietveld et al., 2004). Similar to others (Nadder et al., 2002; Rietveld et al., 2004), Paper I in this thesis showed that environmental factors are involved in both stability and change in ADHD symptoms from childhood to early adolescence. Thus, it is important to note that environmental factors also are involved in the development of ADHD. This thesis can not identify the specific environments responsible for these findings, but prenatal environment might be one example (Taylor & Rogers, 2005).

Twin studies have established that genetic factors operate between and within the hyperactive-impulsive and inattentive dimensions of ADHD (Nadder et al., 2002; Sherman et al., 1997), but very little is still known about how genetic factors contribute to the development of these symptom dimensions from childhood to adolescence. The main focus in Paper II was therefore to examine how genetic factors contribute to the associations between and within hyperactivity-impulsivity and inattention from childhood to adolescence.

Results showed that a common genetic component (i.e., persistent cross-subtype influences) influences hyperactivity-impulsivity and inattention over time. This finding is broadly consistent with results from one previous longitudinal twin study (Nadder et al., 2002) and could be interpreted as persistent genetic influences on ADHD of the "combined type". A significant next question to answer is how this common genetic component is associated with developmental outcomes in adulthood (e.g., criminality). Another interesting issue to examine in future research is how the common genetic component is associated with ADHD in adults (Shaffer, 1994), which could further improve the understanding of the developmental course of ADHD. Unfortunately, there is no information available that demonstrate the importance of genetic and environmental factors in adult ADHD symptoms (Thapar, 2003). Nevertheless, one could still hypothesize that the identified persistent cross-subtype genetic factor also influences ADHD symptoms in adulthood. Clearly, further longitudinal twin studies are

needed to clarify the mechanisms that explain not only persistence in ADHD, but also the increased risk for other adjustment problems in adulthood.

The finding of persistent subtype-specific influences reminds us that the developments of ADHD subtypes also have independent genetic etiologies, which would be expected if the inattentive subtype partly is a distinct attentional disorder (Milich et al., 2001). Thus, these results also provide support for persistent genetic influences on the primarily "hyperactive-impulsive type" and primarily "inattentive type" of ADHD. The finding of persistent subtype-specific influences may have implications for the evaluation of other symptom dimensions that commonly co-occur with ADHD. An interesting hypothesis worth testing is whether the persistent subtype-specific genetic factor that influence inattention also operate in the development of learning problems (Willcutt et al., 2000), but not in the development of other externalizing problems (Milich et al., 2001). The opposite may be true for the persistent subtype-specific genetic factor that influences hyperactivity-impulsivity. These hypotheses could in practice be tested by fitting a series of further extended independent pathway models (i.e., the extended independent pathway model; Figure 3).

It is important to appreciate that this thesis not only reveals persistent genetic influences on ADHD symptoms, but also age-limited genetic effects. That is, in line with previous cross-sectional twin studies (e.g., Sherman et al., 1997), this thesis found that both common (i.e., influencing both hyperactivity-impulsivity and inattention) and unique (i.e., influencing only hyperactivity-impulsivity or inattention) genetic factors influence ADHD symptoms at age 8-9, 13-14, and 16-17.

The finding of persistent cross-subtype, persistent subtype-specific, age-limited cross-subtype, and age-limited subtype-specific genetic factors could be considered to increase power in the search for genes behind ADHD. For example, molecular genetic studies could focus on the common genetic component (e.g., persistent cross-subtype influences) by using a factor score that captures the shared genetic variance (Boomsma & Dolan, 1998).

There is a growing interest in using endophenotypes to understand the complex etiology of ADHD (Waldman, 2005). Endophenotypes refers to biologically based phenotypes that are assumed to be more closely linked to gene expression than the manifest symptoms (Almasy & Blangero, 2001; Gottesman & Gould, 2003). It has been argued that neuropsychological measures in the domain of executive functioning may represent promising endophenotypes for ADHD (Doyle et al., 2005). In light of this thesis, it would be interesting to investigate which endophenotypes that operate

over successive time-points and which endophenotypes that operate at a given time point. Similarly, it seems important to identify those endophenotypes that influence both hyperactivity-impulsivity and inattention as well as those that influence each symptom dimension independently. Finally, it may also be worth examining if endophenotypic markers early in life predict stability and changes in ADHD symptoms.

One of the aims of Paper IV was to examine the genetic and environmental contribution to persistent adolescent antisocial behavior. This question is of particular interest, given that the group of individuals exhibiting persistent antisocial behavior accounts for a substantial number of all criminal offences (Loeber & Farrington, 2000). Paper IV is the first study to investigate the heritability of persistent adolescent antisocial behavior. The finding of a heritability of 62% for persistent adolescent antisocial behavior in both boys and girls is largely in line with a heritability estimate of 82% reported in a cross-sectional study on childhood antisocial behavior pervasive across settings (Arseneault et al., 2003). These estimates are somewhat higher than the estimate of 40% for adolescent and adult antisocial behavior reported in a meta-analysis of 51 twin and adoption studies (Rhee & Waldman, 2002), highlighting the importance of longitudinal and multivariate studies for understanding the etiology of serious antisocial behavior. The results can also be interpreted as support for the developmental taxonomy that differentiates the most deviant criminals over the life course from those likely to show temporary difficulties during adolescence, in which it has been proposed that life-course persistent antisocial behavior is related to heritable aspects of temperament, and more strongly influenced by genetic factors, whereas adolescence-limited antisocial behavior is more transient and has its origin in social peer pressure (Moffitt, 2003).

COMORBIDITY

The main aim of Paper IV was to examine how genetic and environmental factors contribute to the associations between psychopathic personality and persistent adolescent antisocial behavior. The finding of a significant link between psychopathic personality and persistent adolescent antisocial behavior confirms previous research (Walters, 2003). Importantly, this thesis also showed that this association primary is explained by a common genetic factor. The mechanisms underlying this common genetic factor are still an open question that we can only speculate about. Several rather different processes are possible.

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Psychopathic personality and persistent adolescent antisocial behavior may represent different manifestations of a common genetically influenced higher-order factor (e.g., a general externalizing or behavior disinhibition factor). For example, several multivariate twin studies suggest a highly heritable shared intermediate latent phenotype as an explanation for the comorbidity among different domains of externalizing problems (e.g., ADHD, CD, novelty seeking) (Krueger et al., 2002; Young, et al., 2000). It has been argued that behavior disinhibition (e.g., inability to inhibit behavior) may be a promising candidate for such an intermediate phenotype (Krueger, 1999; Krueger, Caspi, Moffitt & Silva, 1998; Krueger et al., 2002; Sher & Trull, 1994; Young, et al., 2000). Thus, one possibility is that psychopathic personality and persistent adolescent antisocial behavior represent different manifestations of a more general disinhibition factor. Such an interpretation would predict that a common set of genes influence not only psychopathic personality and antisocial behavior, but also ADHD. It is therefore central to investigate whether the genetic predisposition for psychopathic personality is specifically related to antisocial behavior, or whether the genetic risk also is associated with other symptom dimensions. A predisposing factor that is genetically related to several different symptom dimensions might be better viewed as a general predisposing factor, whereas a predisposing factor that explains genetic effects in only one symptom dimension may be more specifically involved in the etiology of that particular dimension (Goldsmith, Lemery & Essex, 2004).

Another possible explanation for a genetic overlap between the two constructs is that psychopathic personality mediates the genetic risk for persistent adolescent antisocial behavior. This explanatory model assumes that psychopathic personality is more closely tied to the underlying etiological processes than persistent adolescent antisocial behavior, and/or that psychopathic personality is temporally followed by persistent antisocial behavior. These issues could be further examined in a cross-lagged twin design (e.g., Burt, McGue, Krueger & Iacono, 2005) or by including presumed endophenotypes of both psychopathic personality and persistent adolescent antisocial behavior.

However, there are other possible explanations to the observed comorbidity (Rutter, 1997). First of all, it is possible that antisocial behavior precedes the psychopathic personality traits. Secondly, it is possible that the significant association between psychopathic personality and persistent adolescent antisocial behavior may be explained by shared method variance. There are, however, two reasons to believe that this bias is of limited importance. First, we used a model of psychopathic personality

where overt antisocial and criminal behaviors are not a part of the definition. Thus, there was no item overlap between the measure of psychopathic personality and the measure of antisocial behavior. Second, in support of a real etiologic distinction between the two constructs we found shared environmental influences in persistent adolescent antisocial behavior, but not in psychopathic personality. Thus, shared environmental effects are not mediated via psychopathic personality. It is tempting to speculate that these results may be a manifestation of the distinction between basic tendencies and characteristic adaptations, the former being basic core personality traits and the latter being overt manifestations that have developed as a product of the interplay between the basic tendencies and environmental influences (McCrae & Costa, 1995). Thus, the three-factor model of psychopathy might be more of basic tendencies or primary symptoms of psychopathy, whereas antisocial behavior could be viewed as characteristic adaptations or secondary symptoms of psychopathy (see also Cooke & Michie, 2001).

FURTHER INVESTIGATIONS OF THE NATURE OF THE COMORBIDITY

Previous research has shown that that the association between symptoms of ADHD and antisocial behavior is largely explained by a common genetic factor (Nadder et al., 2002; Silberg et al., 1996). This thesis has shown that genetic factors influence the association between psychopathic personality and persistent adolescent antisocial behavior. Even though comorbidity between ADHD, antisocial behavior, and psychopathic personality has been recognized (Salekin et al., 2004), the etiologies of these associations have never been examined. Thus, the etiology underlying the comorbidity between psychopathic personality and ADHD is currently unknown.

In an attempt to further address these issues, we recently conducted a study using the current sample (i.e., TCHAD) and a co-twin control design. The main aim of this study was to examine the nature of the associations among ADHD and antisocial behavior with psychopathic personality (Forsman, Larsson, Andershed & Lichtenstein, submitted). This study shows that the etiology of the association between persistent conduct problems and psychopathic personality is due to shared genetic factors, which is a replication of the results from this thesis. However, the study did not find a significant association between persistent ADHD and psychopathic personality, nor did it support the suggestion that the combination of ADHD symptoms and antisocial behavior confers a special risk for psychopathic personality (Lynam, 1996). This may suggest that genetic factors that influence the association between ADHD and

antisocial behavior (Nadder et al., 2002; Silberg et al., 1996), are partly distinct from the genetic factors that influence the association between psychopathic personality and antisocial behavior (Paper IV). Thus, future research needs to consider the existence of a higher-order factor (e.g., disinhibition) that influences different domains of externalizing problems, but also lower-order processes that distinguish between different dimensions of externalizing problems.

DIMENSIONAL VIEW

This thesis has used a dimensional approach to investigate continuous distributions of externalizing problems in the general population. It has been shown that both genetic and environmental factors explain individual differences in externalizing problems (i.e., ADHD-symptoms, antisocial behavior scores, psychopathic personality). An important question is whether these results are generalisable to individuals with a categorical diagnosis of a particular externalizing disorder (e.g., ADHD diagnosis). The answer to this question would be positive if individuals with externalizing disorders truly represent the extreme manifestation of a continuous underlying distribution of symptoms. On the other hand, if individuals with externalizing disorders are better represented as dichotomous entities with specific etiologies then the answer to this question would be negative.

There are a number of approaches to investigate the dimensional/categorical nature of externalizing symptoms. There is one twin approach called DeFries and Fulker (DF) extreme analysis (DeFries & Fulker, 1985, 1988) that allows for a test of whether the heritability is the same at the extreme end of the continuum as in the normal range of scores. Several twin studies have shown that the heritability of high externalizing scores (e.g., ADHD, psychopathic personality) is no different than the heritability for scores across the normal range (Deater-Deckard, Reiss, Hetherington & Plomin, 1997; Levy et al., 1997; Stevenson, 1992; Viding et al., 2005). Taxometric techniques (e.g., Meehl, 1992) are another approach that can be used to investigate the dimensional or categorical nature of disorders. This approach has been used in several studies of psychopathic personality (Harris, Rice & Quinsey, 1994; Marcus, John & Edens, 2004; Skilling, Harris, Rice & Quinsey, 2002; Skilling, Quinsey & Craig, 2001). Interestingly, none of these studies support a taxon underlying the personality dimensions of psychopathy (e.g., Callous, unemotional dimension), while some support a taxon underlying the behavioral, social deviance dimension of psychopathy (Harris et al 1994; Skilling et al., 2002; Skilling et al., 2001). It has also

been argued that identifying a taxon does not preclude that the behavior pattern, belief, affect, cognition, or attitude included within the taxon would not be better understood as maladaptive variants along an underlying dimension (Widiger, 2001).

Due to power limitations, DF-analyses have not been performed in this thesis. Based on results from previous studies, it appears reasonable to assume a dimensional view also in our data. However, since this assumption has not been finally tested, and maybe more importantly, that our telephone interview of the non-responders indicates that the individuals with the most externalizing problems might be underrepresented, generalizations to the most extreme groups (i.e., children with a clinical ADHD diagnosis) should be done with caution.

SEX-DIFFERENCES

This thesis confirms the well known sex difference with boys displaying more externalizing problems than girls (Cale & Lilienfeld, 2002; Gaub & Carlson, 1997; Rutter, Caspi & Moffitt, 2003). This was observed in relation to ADHD, hyperactivity-impulsivity, inattention, antisocial behavior, and psychopathic personality. Such differences were not, however, evident in hyperactivity-impulsivity at age 16-17, largely due to a more apparent decline in symptoms with age in boys compared to girls (Paper II). This finding may explain the non-significant sex differences in the impulsive/irresponsible dimension at age 16-17 (Paper III).

In contrast to other twin studies (Rhee, Waldman, Hay & Levy, 1999), this thesis has presented significant cross-sectional sex differences in genetic and environmental influences in a symptoms of ADHD at age 8-9 and at age 13-14 (Paper I). Significant sex differences in genetic and environmental influences have also been found in antisocial behavior at age 13-14 and at age 16-17, but not in psychopathic personality (Paper III). The results from the multivariate genetic analyses in both Paper II and Paper IV also showed significant sex-differences in the genetic and environmental parameter estimates. However, the fact that the same model was appropriate for both sexes (Paper II) and the similar pattern in the genetic and environmental influences in boys and girls(Paper II and Paper IV), suggest only small sex-differences in the genetic and environmental contributions.

TWIN METHODOLOGICAL ISSUES

One common misunderstanding of results from twin studies involves the level of analyses. Twin studies focus mostly on individual differences and have little to say

about processes that influence the mean level of a symptom dimension in a particular population. Another common misinterpretation is that the results of twin studies support a strict genetic determinism. The underlying conceptual model in twin studies is multifactorial in which psychiatric disorders and symptom dimensions are influenced by multiple genes and environments in a probabilistic rather than a deterministic manner. Further, a substantial heritability in psychiatric disorders and symptom dimensions does not imply extreme improbability of change. Finally, it is important to emphasize that twin research provides evidence for the importance of both genetic and environmental influences (Plomin et al., 2001).

Generalizability

Twin data may not be generalisable to singletons. That is, one criticism of the twin method is that twins differ from singletons in several important aspects, and therefore results from twin studies do not generalize to the population as a whole. One argument against differences between twins and singletons is that twins exhibit similar means, frequencies and prevalences as singletons for many traits and adult diseases (Evans & Martin, 2000). It should be noted that conflicting results are reported in the literature (e.g., Levy, Hay, McLaughlin, Wood & Waldman, 1996). Nevertheless, two previous reports (Larsson, Lichtenstein, Fried, El-Sayed & Rydelius, 2000; Eley, Lichtenstein & Moffitt, 2003) have shown that mean levels in emotional and behavior problems according to CBCL (Achenbach, 1991) in the current TCHAD sample is similar to what has been found in other Swedish samples. Further, the prevalence of children having eight or more ADHD symptoms in the current sample was 4.7% at age 8-9 and 3.1% at age 13-14 (Paper I), numbers that are in line with other reports from Sweden (Kardesjö & Gillberg, 1998).

Equal environment assumption

One of the most fundamental assumptions in twin studies is the equal environment assumption. It assumes that environmentally caused similarity is roughly the same for both types of twins (i.e., MZ and DZ) reared in the same family. If the assumption is violated because MZ twins experience more similar environments than DZ twins, this violation would inflate estimates of genetic influence. Studies that have tested the equal-environment assumption have found it to be valid for anxiety disorder, ADHD, ODD and CD (Cronk, Slutske, Madden, Bucholz, Reich & Heath, 2002).

Non-additive genetic effects (Dominance)

In the basic twin model we are interested in the additive genetic variance; that is, individual differences caused by the independent effects of alleles or loci that add up.

Individual differences can also be due to non-additive genetic variance; that is, due to the effects of alleles (dominance) or loci (epistasis) that interact with other alleles or loci (Plomin et al., 2001). Offspring receive only one allele from each parent and not a combination of alleles at a locus. Therefore, non-additive genetic influence will not be transmitted from one generation to another. Thus, if non-additive genetic variance is important for a symptom dimension, the correlation for DZ twins will be less then half the correlation for MZ twins. The basic twin models can include additive and non-additive effects independent of each other, but there is not enough information in the models to differentiate non-additive from shared environmental effects. If non-additive genetic effects are present and these effects are not included in the models, then this variance will be estimated as additive genetic variance (often called broad heritability estimates).

The pattern of intraclass correlations in our self-report measures of psychopathic personality and antisocial behavior suggests that non-additive genetic effects are of limited importance, which is consistent with results from other twin studies (Bouchard & Loehlin, 2001; Rhee & Waldman, 2002; Taylor et al., 2003).

The pattern of intraclass correlations for our DSM-III-R based measures of ADHD was best by explained by additive genetic effects, shared environmental, and non-shared environmental effects. This is consistent with other studies using similar measures (Levy & Hay, 2001). Intraclass correlations for the DSM-IV based measure of ADHD (i.e., hyperactivity-impulsivity and inattention) suggest mostly additive genetic effects, but also some non-additive effects.

Contrast effects

A very low DZ twin correlation in combination with larger variance among DZ twins appears to be explained by maternal rating biases whereby mothers tend to contrast their twins (Simonoff et al., 1998). The pattern of intraclass correlations and variances suggests that contrast effects are of limited importance in our data, which is consistent with results from other twin studies of personality, psychopathic personality, and antisocial behavior (Bouchard & Loehlin, 2001; Rhee & Waldman, 2002; Taylor et al., 2003). However, several twin studies have shown very low or even negative DZ twin correlations for ADHD symptoms (Eaves et al., 1997; Thapar, Harrington & Ross, 2000). On the other hand, in other large twin studies there has been no evidence of this type of bias (Gjone, Stevenson & Sundet, 1996; Levy et al., 1997). Contrast effects seem to vary depending both on the type of measure used and the age of the children (Kuntsi et al., 2005; Rietveld et al., 2004; Thapar, 2003). Nevertheless, the use of

multi-informant designs or inclusion of presumed endophenotypic markers should add further power to separate genetic and environmental influences from those generated by the process of measurement error.

Assortative mating

The basic twin model assumes random mating in the parent generation. Assortative mating tends to increase similarity between DZ twins, thereby biasing the heritability estimates downward and the shared environmental estimates upward. Assortative mating for most personality traits has been found to be low in magnitude (Maes et al., 1998), suggesting that the effects of positive assortment do not have to be considered when modeling the variance in psychopathic personality. However, at least one study suggests that this assumption is invalid for antisocial behavior (Krueger, Moffitt, Caspi, Bleske & Silva, 1998). This may suggest that part of the shared environment found in persistent adolescent antisocial behavior (in Paper IV) may be due to positive assortment.

Gene-environment interaction/correlation

The interest in investigations of the nature-nurture interplay is to date mainstream. There are now sophisticated extended models available that allow researchers with genetically sensitive data to test interesting hypothesis about both gene-environment interaction and gene-environmental correlations (e.g., Moffitt, Caspi & Rutter, 2005).

One recent TCHAD report has shown that socioeconomic status moderates the influences of genetic and environmental effects on antisocial behavior (Tuvblad, Grann & Lichtenstein, in press). This finding was further investigated in this thesis (Paper IV) by testing whether the relationship between psychopathic personality and persistent adolescent antisocial behavior differed across neighborhood socioeconomic areas (Paper IV). No significant differences in the genetic and environmental estimates were found between adolescents in more advantaged and less advantaged socioeconomic areas (data not shown). This non-significant finding was interpreted as a replication of the main findings in different socioeconomic strata.

Future research also needs to test developmental hypothesis about different patterns of gene-environment correlations in externalizing problems. For example, a recent report from the TCHAD sample suggests that children's aggression evokes negative parenting followed by antisocial behavior - a process that might be described as evocative gene-environment correlation (Narusyte, Andershed, Neiderhiser & Lichtenstein, submitted). Similarly, when data from the fourth wave of the TCHAD sample is available one could test whether children's ADHD symptoms mediate the

association between parent-child conflict in adolescence and antisocial behavior in early adulthood. Clearly, future research that wants to enhance our understanding of the complex interplay between nature and nurture in shaping the developing individual needs to take gene-environment interaction and correlation into consideration.

STRENGTHS AND LIMITATIONS
Measurement issues

Parent-reported ADHD. Advantages of the ADHD scales used in the present thesis include its consistency with DSM symptom criteria of ADHD. Further, the different scales manifest moderate to good internal consistencies suggesting that the measures of ADHD capture systematic variance. Validity is also supported by our findings of sex and age differences that are consistent with known effects. Boys have more ADHD symptoms than girls and symptoms of inattention persist into adolescence to a greater extent than symptoms of hyperactivity-impulsivity (Biederman et al., 2000; Gaub & Carlson, 1997; Hart et al., 1995). Predictive validity is supported by moderate correlations (boys: .39; girls: .41) between the DSM-III-R based parent-report scale at age 8-9 and the externalizing scale from CBCL at age 13-14 (Forsman et al., submitted). The DSM-III-R based scale measured at age 8-9 and 13-14 are also significantly correlated with the impulsive-irresponsible dimension of the psychopathic personality measured via self-report at age 16-17 (Forsman et al., submitted). The relatively high stability coefficient reported in both the DSM-III-R based scale and the DSM-IV based symptom dimensions also provides some support for the validity of the measures (Paper I and Paper II).

There are also limitations that need to be mentioned. The reliance on parent reporting may underestimate hyperactive behavior in different settings (Martin, Scourfield & McGuffin, 2002). Parental reporting also may inflate the twin correlations. Further, both mothers and fathers could provide the parent-reported information of ADHD (even though the majority was done by mothers). Thus, parental report may potentially artificially increased the correlations in both types of twins (i.e., MZ and DZ twins) and thus overestimate the shared environmental parameters. However, the negligible shared environmental influences suggest that this limitation is not very severe. As already discussed, parental report could also lead to contrast effects. The ADHD scales did not include information about age of onset, impairment, and expression of symptoms in multiple settings. The mixture of ADHD items from DSM-III, DSM-III-R and DSM-IV may limit the DSM-IV conclusions in this thesis (Paper

II). This is partly explained by changes in measurement practice, due to the publication of DSM-IV.

Self-reported psychopathic personality. Advantages of the YPI include its focus on core psychopathic personality traits, rather than behavior consequences of these traits. Consequently, the YPI excludes behaviors such as criminal versatility and short-term relationships, which is in line with contemporary models of psychopathy (Cooke & Michie, 2001). Another advantage of the YPI is its reported psychometric functioning (Andershed et al., 2002; Skeem & Cauffman, 2003). The present thesis used confirmatory factor analyses to replicate the proposed three-factor structure. Further, the YPI manifests moderate to good internal consistencies at the dimensional level (i.e., the grandiose/manipulative, callous/unemotional, and impulsive/irresponsible dimensions) and also at the subscale level. This indicates that the YPI captures systematic variance irrespective of scale length. Convergent validity and predictive validity of YPI is also to some extent supported (Skeem & Cauffman, 2003).

Several critics have argued that some level of psychopathic personality may be normative in adolescence and that by extending the construct to younger age groups one runs the risk of labeling some as disordered who show a normative and transient pattern of behavior (Seagrave & Grisso, 2002; Skeem & Cauffman, 2003). These issues needs to be further investigated. Future research should establish to what extent psychopathic personality is stable from adolescence into adulthood. Research should also document the predictive validity of psychopathic personality in adolescence. It is also important to appreciate that some level of comorbidity between psychopathic personality and other symptom dimensions is expected (Salekin & Frick, 2005). Thus, the etiology of different patterns of overlap (covariation) needs to be examined, preferably within a longitudinal genetically-sensitive design.
There are some problems inherent in measuring psychopathic traits through self-report. The main problems is that deceitfulness, lying, and manipulation are symptoms of the psychopathic personality, which makes it difficult to get truthful responses to questions about characteristics such as shallow affect, lack of remorse or guilt, and grandiose sense of self-worth (Andershed et al., 2002). Therefore, the YPI items were developed to assess the psychopathic traits in an indirect, rather than in a straightforward and transparent way. Furthermore, the YPI items do not frame the different psychopathic features as deficits, but instead as characteristics that should seem neutral or even appealing to those youths with psychopathic traits. This may minimize the problems

with response distortion and social desirability. The high correlations between the latent psychopathic personality factor and the latent persistent adolescent antisocial behavior suggest that the YPI measures important aspect of the psychopathic personality dimensions. Nevertheless, generalizations to the most extreme groups should be done with caution.

Self-reported antisocial behavior. Advantages of the measure of antisocial behaviors include its basis in a validated self-report scale of delinquency (Junger-Tas, Terlouw & Klein, 1994). The self-report scale used in the present thesis manifests good internal consistencies. Factor analyses of the self-report scale resulted in a single factor (Tuvblad et al., 2005, in press), which is consistent with the notion that delinquent adolescents often show a pattern of versatile offending (Klein, 1995). Although self-reports of delinquency includes instances that are not captured by official records, there could be biases, such as exaggeration and concealment.

Longitudinal study design

The longitudinal twin study design used in this thesis has a number of strengths. The use of a population-based sample increases the representativeness of the sample. The narrow age span of the sample (the difference between youngest and oldest child is less than 2 years) allows an examination of persistence and age-related changes in symptom dimensions during the development.

Problems that often apply to the longitudinal study design are attrition rate and the use of developmentally inappropriate measures. The effects of attrition in the TCHAD sample have to some extent been reported in this thesis (e.g., Paper II and Paper IV). Several non-significant associations have been reported. However, a significant association between symptoms of hyperactivity-impulsivity at age 13-14 and willingness to participate at wave 3 suggests selective attrition. The effect size of this finding and the non-significant associations (e.g., sex, family socioeconomic status) suggest that this bias is of limited importance. Further, since it is unlikely that the etiology of high ADHD scores is different from that of normal range scores (Levy et al., 1997), the generalizability may not necessarily be limited.

Another critical issue for longitudinal studies is the assumption that the phenotype under study "looks" the same across the development. This applies for example to many developmental studies of ADHD that uses the same DSM-symptoms across time. These symptoms are primarily developed for boys in middle childhood (Willoughby, 2003) and as a consequence they may not be appropriate for older populations (Thapar, 2003). Future research should allow for different behavior manifestations of ADHD in

children, adolescents and adults (Willoughby, 2003). An essential task is to identify age appropriate symptoms of ADHD, potentially by using a broader symptom pool that is more likely to capture different manifestations of ADHD and its subtypes across the development (Lahey et al., 2004). One interesting hypotheses that could be examined in a genetically sensitive design is whether the different manifestations of ADHD across age are influenced by a common genetic component (Rutter & Sroufe, 2000).

CONCLUSIONS

This thesis shows that a common genetic factor influences the development of externalizing problems from childhood to adolescence. Comorbidity between supposedly different domains of externalizing problems is also primarily explained by a common genetic factor. Nevertheless, this thesis also shows etiologic specificity in externalizing problems during the development from childhood to adolescence. The callous/unemotional and impulsive/irresponsible dimensions of the psychopathic personality are influenced by unique genetic variance and the developments of ADHD subtypes have independent genetic etiologies. Furthermore, the genetic factors that influence the association between ADHD and antisocial behavior may be partly distinct from the genetic factors that influence the association between psychopathic personality and antisocial behavior.

Thus, future research needs to consider the existence of general predisposing factors that influence a broad range of externalizing problems, but also specific predisposing factors that differentiate between different domains of externalizing problems. Identification of early emerging general and specific predisposing factors (e.g., endophenotypic markers) should be of high priority. Knowledge from such studies may not only facilitate identification of susceptibility genes, but also provide tools needed to identify effective intervention targets.

ACKNOWLEDGEMENTS

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