The development of children's problem behaviors

a twin-singleton comparison and the influence of parental divorce

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ISBN: 978-94-6169-228-3

Cover picture by Ton Sondag, www.shelooksgreat.eu
Layout and printing by Optima Grafische Communicatie, Rotterdam, The Netherlands

This thesis was supported by the Sophia Children's Hospital Foundation, project number 483

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De ontwikkeling van probleemgedrag in de kindertijd:
een tweeling-eenling vergelijking en de invloed van echtscheiding

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. H.G. Schmidt

en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
donderdag 19 april 2012 om 9.30 uur

door

Sylvana Cornelia Catharina Robbers

geboren te Oosterhout

Promotiecommissie

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Chapter 1

General introduction

Twin-family studies have largely contributed to our understanding of the etiology of behavioral and emotional problems in childhood. From these studies we learned that almost every behavioral or psychological trait is 'heritable' to some extent. We also learned that both nature and nurture play important roles in the etiology of behavioral and emotional problems, and that these factors may act independently of one another as well as interactively (i.e., gene-environment interplay). Moreover, twin studies have given insight into the important distinction between environmental factors shared by siblings (e.g., parental socio-economic status) and those not shared by siblings (e.g., peer groups) (Boomsma, Busjahn, & Peltonen, 2002; Hudziak & Faraone, 2010). An important assumption that is made when using twin data is that results from twin samples can be generalized to singleton populations. However, the validity of this assumption needs to be examined.

This introduction will give a background of the different themes investigated in this thesis: twin-singleton differences, and the development of internalizing problems, externalizing problems, and symptoms of Attention Deficit Hyperactivity Disorder (ADHD) in twins and singletons.

Twin-singleton differences

Twins may differ from singletons in their physical and psychological development. Twins are often born premature, on average three weeks earlier than singletons, and they are generally small for gestational age (Rydhstroem & Heraib, 2001). Some authors have reported increased levels of problems in non-twin samples of preterm children and children with low birth weight, such as ADHD (Lahti, et al., 2006) and depression (Raikkonen, et al., 2008). However, low birth weight, preterm birth, or small size at birth are unlikely to have the same significance in twins as in singletons, because the etiology of these risk factors appears to be different in the two groups (Phillips, Davies, & Robinson, 2001). In twins, small size at birth results from 'crowding', rather than from an unfavorable intrauterine environment (Gruenwald, 1970). Also, various congenital abnormalities may arise as a function of two babies growing in the space of one (Hall, 2003). Twins become growth-retarded as a result of poor early placental development (Bleker, et al., 1988), as indicated by the fact that from about 24 weeks gestational age onwards placental weights of twins are smaller than those of singletons. After birth, twins generally grow well compared to singletons, and twins are almost as tall as singletons by the age of 5 years (Estourgie-Van Burk, Bartels, Van Beijsterveldt, Delemarre-Van de Waal, & Boomsma, 2006). A more likely hypothesis for twin-singleton differences in behavioral development is that the twinship may offer a favorable social environment, via interactions with, and social support of the co-twin. As a result, twins may show fewer problem behaviors than singletons (Pulkkinen, Vaalamo, Hietala, Kaprio, & Rose, 2003). It could also be that parents of twins experience more parenting stress, more financial hardships, and

less marital satisfaction than parents of singletons (Collins, 2011), which could be associated with higher levels of problem behaviors in twins than in singletons.

Studies that have compared levels of behavioral and emotional problems of twins with those of singletons have been cross-sectional, and findings were mixed. A study among 8- and 9-year-old Finnish twins and singletons showed significantly lower rates of externalizing problems (i.e., aggression and opposition) in twins (Moilanen, et al., 1999). Fewer externalizing problems were also found in 2- and 3-year-old Dutch twins compared to same-aged singletons (Van den Oord, Koot, Boomsma, Verhulst, & Orlebeke, 1995). Similarly, the level of internalizing problems (i.e., anxiety, depression, withdrawn behavior, and functional somatic complaints) in Norwegian children aged 5 to 15 years was lower in twins than in singletons, especially around the age of 12 (Gjone & Novik, 1995). In contrast, higher levels of externalizing problems in twins than in singletons were reported in an American sample of 6- to 16-year-old children (Gau, Silberg, Erickson, & Hewitt, 1992). Studies among 11- and 12-year-old Finnish twins and singletons (Pulkkinen, et al., 2003), and 5- to 15-year-old Norwegian twins and singletons (Gjone & Novik, 1995) showed no evidence for twin-singleton differences in externalizing problems. Other studies found no evidence for twin-singleton differences in internalizing problems until the age of 12 (Gau, Silberg, Erickson, & Hewitt, 1992; Pulkkinen, et al., 2003). Twin-singleton comparisons can also be performed by means of twin-family studies that include twins and their non-twin siblings. In an Australian sample, 4- to 12-year-old twins showed more ADHD symptoms than their non-twin siblings (Levy, Hay, McLaughlin, Wood, & Waldman, 1996). Although twin-singleton differences are generally not the focus of such studies, they do often not reveal twin-singleton differences (e.g., Cosgrove, et al., 2011).

In summary, the results regarding twin-singleton differences in behavioral and emotional problems have been somewhat inconsistent so far. Knowledge is lacking on twin-singleton differences and/or similarities in the development of behavioral and emotional problems in childhood.

The development of behavioral problems

Internalizing problems

General population-based longitudinal studies have shown increasing levels of problems with age in childhood. In The Netherlands, internalizing problems rose from age 4 years until early adolescence, with the number of internalizing problems being similar for boys and girls (Bongers, Koot, Van der Ende, & Verhulst, 2003). Similarly, in the United States the level of parent-reported internalizing problems increased from ages 5 to 10 years for boys and girls (Leve, Kim, & Pears, 2005). Gilliom and Shaw (2004) found increasing levels of internalizing problems in children

from ages 2 to 6 years. Levels of internalizing problems may increase in childhood for several reasons. Generally, increasing cognitive abilities in childhood enable children to self-reflect and to remember and anticipate negative life events (Fanti & Henrich, 2010; Kovacs & Devlin, 1998). Conversely, Keiley, Bates, Dodge, and Pettit (2000) reported stable levels of problems from ages 5 to 13 years for both boys and girls according to mothers and teachers. A recent study in which growth trajectories of children's internalizing symptoms were examined as predicted by interactions among maternal internalizing symptoms and children's physiological regulation, showed that trajectories decreased from ages 8 to 10 years (Wetter & El-Sheikh, 2012).

Several child and family characteristics have been found to be associated with internalizing problems in childhood, such as parental divorce (Amato, 2000; Hetherington & Stanley-Hagan, 1999), children's shy temperament and behavioral inhibition (Feng, Shaw, & Silk, 2008; Hirshfeld-Becker, et al., 2008; Muris, Van Brakel, Arntz, & Schouten, 2011), maternal depression (Feng, et al., 2008; Sterba, Prinstein, & Cox, 2007), unfavorable parenting styles (Luyckx, et al., 2011) and environmental stress (Grant, et al., 2003; Van Oort, Verhulst, Ormel, & Huizink, 2010). Twin studies have provided evidence for a moderate heritability of internalizing problems (Bartels, et al., 2004; Boomsma, Van Beijsterveldt, Bartels, & Hudziak, 2008; Boomsma, Van Beijsterveldt, & Hudziak, 2005; Van der Valk, Van den Oord, Verhulst, & Boomsma, 2003a). Bartels et al. (2004) reported that the heritability of internalizing problems decreased during childhood from 59% at age 3 to 37% at age 12, and the contribution of shared environmental influences increased over time from 13% at age 3 to 37% at age 12. Significant genetic and shared environmental influences have also been reported for anxious-depressive and withdrawn behavior at age 12 (Lamb, et al., 2010). Differences in heritabilities between boys and girls are generally negligible in childhood (Franic, Middeldorp, Dolan, Ligthart, & Boomsma, 2010). Stability in the development of internalizing problems from ages 3 to 12 years can for 43% be explained by genetic factors, and for 47% by shared environmental influences. Change in internalizing problems is mainly accounted for by nonshared environmental influences (Bartels, et al., 2004).

Externalizing problems

General population-based longitudinal studies on the development of externalizing problems in childhood show declining levels of problems over time for both boys and girls, with boys having higher mean levels of externalizing problems than girls (Bongers, et al., 2003; Keiley, et al., 2000; Leve, et al., 2005; Miner & Clarke-Stewart, 2008; Stanger, Achenbach, & Verhulst, 1997). Bongers, et al. (2003) showed that parent-rated externalizing problems decreased from age 4 years onwards for boys and girls. Leve, et al. (2005) showed that parent-rated externalizing problems from age 5 to 17 years for both boys and girls. Miner and Clarke-Stewart (2008) showed that the level of parent- and teacher-rated externalizing

problems declined between the ages of 2 and 9 years. The study of Stanger, et al. (1997) showed that the level of aggressive and delinquent problems decreased from ages 4 to 10 years. In Keiley's study (2000) maternal-rated externalizing problems decreased, whereas teacher-rated externalizing problems increased from age 5 until 13 years.

One possible reason why externalizing problems generally tend to decline during childhood is that, as children age, they rely to a lesser extent on aggressive and oppositional behaviors to communicate and control their environment (Tremblay, 2000). Family characteristics that are associated with externalizing problems include parental divorce (Amato, 2000; Hetherington & Stanley-Hagan, 1999), and unfavorable parenting styles such as rejection (Luyckx, et al., 2011; Shaw, Gilliom, Ingoldsby, & Nagin, 2003; Shaw, Lacourse, & Nagin, 2005). Genetic influences on externalizing problems are relatively large (Bartels, et al., 2004; Van der Valk, Van den Oord, Verhulst, & Boomsma, 2003b). Small increases in heritability were reported for boys from age 3 (57%) to age 12 (64%). For girls, the relative influences of genetic and environmental factors are generally stable over this period, with an estimated heritability of around 50% (Bartels, et al., 2004). Stability in externalizing problems from ages 3 to 12 years is mainly accounted for by genetic factors, while change in externalizing problems can be mainly explained by nonshared environmental influences (Bartels, et al., 2004).

Symptoms of Attention Deficit Hyperactivity Disorder

ADHD symptoms are characterized by inattentive, impulsive, and hyperactive behaviors. These kinds of problems are very common in childhood. More specifically, ADHD is regarded the most common neuro-developmental disorder in childhood that concerns about 5% of all children (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007). Both genetic and environmental factors contribute to the etiology of ADHD, and the heritability of ADHD symptoms usually varies between 50% and 80% (Derks, et al., 2008; Faraone & Doyle, 2001; Polderman, et al., 2007), but is remarkably stable throughout childhood (Rietveld, et al., 2004). Community studies on the development of ADHD symptoms in childhood report somewhat mixed findings. In an American longitudinal study of 6- to 20-year-old boys, ADHD symptoms declined with increasing age, with hyperactivity symptoms declining at a higher rate than inattention symptoms (Biederman, Mick, & Faraone, 2000). In a sample of 8- to 17-year-old Swedish twins levels of inattention remained relatively constant, whereas levels of hyperactivity-impulsivity declined with increasing age (Larsson, Lichtenstein, & Larsson, 2006). Another American longitudinal study showed that levels of ADHD symptoms were generally constant until the teen years, and declined from there (Monuteaux, Mick, Faraone, & Biederman, 2010). Similarly, mean levels of ADHD symptoms decreased after age 10 in Dutch twins (Rietveld, Hudziak, Bartels, Van Beijsterveldt, & Boomsma, 2004) and singletons (Bongers, et al., 2003). An Australian sample showed only minimal age differences in the number of ADHD symptoms in children aged 5 to 11 years (Gomez, Harvey,

Quick, Scharer, & Harris, 1999). Taking these results together, the general picture seems to be that the development of ADHD symptoms is relatively stable in childhood with a possible decrease of symptoms starting around the age of 10 years. ADHD symptoms may diminish with age as self-regulation increases during childhood, and in response to adequate treatment.

The present study

Aims and research questions

This thesis aims to extend the knowledge on developmental trajectories of problem behaviors in childhood, and to investigate whether findings from twin studies on this topic can be generalized to the population at large. Developmental trajectories of internalizing problems, externalizing problems, and ADHD symptoms are presented, for twins and singletons, and compared. Thereafter, I investigated the role of *parental divorce* with regard to the occurrence and genetic architecture of internalizing and externalizing problems in childhood. Cross-sectional studies that compared children of married versus divorced parents show higher levels of behavioral problems in children from divorced parents, but cannot provide insight into the direction or the underlying sources of the relationship between parental divorce and children's problems. As prospective studies that begin before the children's parents divorce are sparse, a unique aspect of the studies described in this thesis was that pre- as well as post-divorce problems in childhood were assessed. In order to gain more insight into the etiology of internalizing and externalizing problems in children from divorced families, I examined mean differences, variance differences, as well as possible changes in the genetic architecture of internalizing and externalizing problems between children from divorced and children from intact families.

The main research questions are:

1. a) What are the developmental trajectories of internalizing problems, externalizing problems, and ADHD symptoms during childhood? (chapters 3 and 4)
   b) Are these developmental trajectories comparable for twins and singletons? (chapters 3 and 4)
2. a) Do internalizing and externalizing problems at age 3 precede later parental divorce? (chapter 5)
   b) Do children from divorced families show more internalizing and externalizing problems at age 12 than children from intact families? (chapter 5)
   c) Does parental divorce modify the genetic architecture of pre- and post-divorce internalizing and externalizing problems? (chapter 6)

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Chapter **2**

Samples and statistical methods

Samples

We analyzed data from two longitudinal studies on the development of behavioral and emotional problems of children in The Netherlands: the Netherlands Twin Register (Boomsma, et al., 2006; Boomsma, et al., 2002), and the Zuid-Holland Study (Verhulst, Akkerhuis, & Althaus, 1985).

Netherlands Twin Registry (NTR)

The NTR was established in 1987 at the department of Biological Psychology at the VU University in Amsterdam (Boomsma, et al., 2006; Boomsma, et al., 2002). Ten thousands of twins have been invited to participate since, in a wide variety of research projects (Bartels, et al., 2007). Young twins are recruited shortly after their birth with the help of a commercial organization that visits parents of newborn children at home. Families are registered at the NTR after they complete a registration and are then sent a first survey about the twin pregnancy, health, and perinatal outcomes. The next surveys focus on growth, and problem behaviors of the children as assessed by the Child Behavior Checklist (Achenbach, 1991a; Verhulst, Van der Ende, & Koot, 1996) and Connors' short form (Conners, 1998). Data are collected when twins and triplets are 1, 2, 3, 5, 7, 10, and 12 years of age. Parents are invited to participate at each wave of data collection, regardless of their previous participation. The Teachers' Report Form (Achenbach, 1991b; Verhulst, Van der Ende, & Koot, 1997) is sent to teachers when children are 6-7, 9-10, and 12 years old, after permission is obtained from the parents. Parents provide

Table 2.1: Numbers of surveys returned by parents (NTR, d.d. June 2011)

Cohort	Q1	Q2	Q3	Q5	Q7	Q10	Q12
1986	166	110	82	101	89	103	103
1987	947	811	631	592	533	580	542
1988	999	814	658	635	601	584	529
1989	1031	795	799	710	719	636	555
1990	1197	944	943	861	801	743	683
1991	1248	990	894	867	834	756	646
1992	1345	1073	914	873	906	765	697
1993	1480	1160	1080	956	944	807	582
1994	1543	1190	999	929	895	699	481
1995	1612	1132	1057	1019	911	626	573
1996	1746	1261	1151	1046	868	550	584
1997	1687	1199	1162	1017	821	523	550
1998	1809	1482	1175	1092	683	-	527
TOTAL	16810	12961	11545	10698	9605	7372	7052

Note: Shaded cells indicate data used for this study. Each survey concerns both children of a twin pair. Due to organizational changes Q10 was not sent in 1998.

Table 2.2: Numbers of surveys returned by teachers (NTR, d.d. June 2011)

Cohort	TRF7	TRF10	TRF12
1986	-		82
1987	-	-	594
1988	-	-	540
1989	-	432	490
1990	-	991	597
1991	-	869	611
1992	592	928	566
1993	1227	959	546
1994	1165	813	487
1995	1211	720	742
1996	1169	745	565
1997	1008	977	548
1998	855	763	484
TOTAL	7227	8197	6852

Note: Shaded cells indicate data used for this study. Each survey concerns one child of a twin pair.

the names and contact details of the teachers of their twins and also of non-twin siblings in the family. After age 12, parents are contacted for consent to send their children a self-report survey at ages 14, 16, and 18 years. For this thesis, parental survey data collected at ages 3, 7, 10, and 12 years from birth cohorts 1986 until 1998 were analyzed (see Tables 2.1 and 2.2). The numbers in Table 2.1 indicate that at least one survey (from mother or father) has been returned. These questionnaires each concern both children of a twin pair. In addition, teacher data at ages 7, 10, and 12 were analyzed from children from the same birth cohorts. Table 2.2 shows the numbers of surveys that were returned by teachers. In contrast to the parental questionnaires, these surveys concern only one child from a twin pair.

Zuid-Holland Study (ZHS)

The Zuid-Holland Study is a longitudinal multi-cohort study that started in 1983 as a study on the development of behavioral and emotional problems in children (Verhulst, Akkerhuis, & Althaus, 1985). The original sample consisted of 2,600 children aged 4 to 16 years, and was randomly drawn from municipal registers that list all residents in the Dutch province of Zuid-Holland. A random sample was drawn of 100 children of each gender and age with the Dutch nationality. The sample was representative of the Dutch general population. Of the 2,447 parents reached, 2,076 (85%) responded at the initial assessment in 1983, during which data was collected via home interviews with parents. Parents were asked to give permission to contact the teacher of their child. After the initial assessment (Time 1 (T1); 1983), follow-up assessments took place in 1985, 1987, 1989, 1991, 1997, and 2007 (i.e., T2 to T7). During T1-T5 parents completed the Child Behavior Checklist, while teachers were sent

Table 2.3: Numbers of surveys returned by parents (ZHS)

Cohort	T1 1983		T2 1985		T3 1987		T4 1989		T5 1991	
	Age	N	Age	N	Age	N	Age	N	Age	N
1	4	165	6	133	8	140	10	148	12	146
2	5	168	7	138	9	140	11	143	13	142
3	6	161	8	134	10	135	12	136	14	142
4	7	163	9	139	11	136	13	141	15	137
5	8	172	10	128	12	141	14	141	16	132
6	9	159	11	138	13	131	15	140	17	129
7	10	161	12	122	14	126	16	133	18	126
8	11	161	13	131	15	135	17	134	19	-
9	12	153	14	124	16	118	18	-	20	-
Total		1463		1187		1202		1116		954

Note: Shaded cells indicate data used for this study. Each survey concerns one child.

the Teachers' Report Form (Achenbach, 1991b) to measure problem behaviors in the school context. No information from teachers was obtained at T2 owing to financial constraints. The teacher response rates were above 70% at each assessment. From age 11 years, children also completed a self-report survey. For this thesis, data were analyzed until the fifth assessment (T5). Tables 2.3 and 2.4 show the numbers of children by cohort until T5, with the shaded cells indicating the children that we included in the current study. All data from subjects who were between 6 and 12 years of age at any time point were kept in the sample. Because of the selected age range and the design of the ZHS, the singletons that we included had data from maximum four assessment waves (e.g., a child who was 6 years old at T1, was 12 years old at T4, and was excluded thereafter).

Table 2.4: Numbers of surveys returned by teachers (ZHS)

Cohort	T1 1983		T2 1985		T3 1987		T4 1989		T5 1991	
	Age	N	Age	N	Age	N	Age	N	Age	N
1	4	98	6	-	8	60	10	97	12	92
2	5	153	7	-	9	132	11	124	13	119
3	6	133	8	-	10	103	12	114	14	111
4	7	133	9	-	11	125	13	103	15	113
5	8	138	10	-	12	107	14	114	16	100
6	9	127	11	-	13	110	15	99	17	85
7	10	129	12	-	14	92	16	100	18	70
8	11	145	13	-	15	105	17	89	19	12
9	12	106	14	-	16	99	18	21	20	-
Total		1162		0		933		861		702

Note: Shaded cells indicate data used for this study. Each survey concerns one child.

Comparing twins and singletons: rearrangement of data sets

This thesis focuses on the development of problem behaviors across childhood. In order to compare twins and singletons, all data need to be structured as a function of age instead of survey year. The ZHS data were therefore restructured as a function of age. The 5 variables (T1-T5) were recoded into 7 age-specific variables (age 6-12 years) to indicate development over time. Each of the new variables indicates the original value at a specific age, e.g., internalizing problems at age 6, age 7, etc. The restructuring from 5 to 7 variables creates missing values by design, as given the design of the ZHS it is impossible for one individual to have data for each of the 7 age-specific variables. Table 2.5 illustrates the restructuring of the ZHS data. From Table 2.5 it is clear that for children who were 11 or 12 years old at T1 (i.e., birth cohorts 8 and 9) data were used from only one assessment.

In the NTR, assessments took place at specific ages. However, not all children had indeed reached the target ages during the assessments, e.g., at the time Q7 was completed, some children were still 6 years, whereas others had already turned 8 years. The exact ages of the twins were determined by the date of birth of the twins and the date of completion of the surveys. By calculating the exact ages in years of the twins at the time of completion of the surveys, 7 age-specific variables were created equal to the ones created for the ZHS. As in the ZHS, this procedure resulted in a substantial number of missing values by design (e.g., a child who has a score at age 6 automatically has a missing score at age 7).

Table 2.5: Restructuring of the ZHS data

Cohort	Age 6	Age 7	Age 8	Age 9	Age 10	Age 11	Age 12
1	T2	-	T3	-	T4	-	T5
2	-	T2	-	T3	-	T4	
3	T1	-	T2	-	T3	-	T4
4	-	T1	-	T2	-	T3	-
5	-	-	T1	-	T2		T3
6	-	-	-	T1	-	T2	-
7	-	-	-	-	T1	-	T2
8	-	-	-	-	-	T1	-
9	-	-	-	-	-	-	T1
N	**224**	**257**	**356**	**384**	**469**	**505**	**602**

Note: The dashes represent values that are missing by design. T1-T5 represent available data from the five assessment waves of the ZHS.

Statistical Methods

There are three main statistical procedures that were employed throughout this thesis: latent growth curve modeling, growth mixture modeling, and genetic modeling. Each technique is briefly introduced below.

Latent growth curve modeling (LGM)

Latent growth curves can be used to study the population's average development over time. In LGM, random effects are used to capture individual differences in development, which are summarized in the latent growth factors (McArdle & Erpstein, 1987). Latent growth curves can be determined by at least two latent growth factors: a) the intercept, which represents the initial status of the curve; b) the linear slope, which represents linear change over time. An additional growth factor to determine a quadratic slope can be used to account for quadratic change over time. Each latent growth factor has a mean and a variance. A linear growth model can be written as: Y= intercept+ (slope * time score) + residual, where Y is the observed score of an individual on a certain time point. The model allows individual differences in change over time, which are reflected in the variation of the slope factor (Muthén & Asparouhov, 2002).

Figure 2.1 visualizes a linear growth model with 7 time points (i.e., 7 assessments from ages 6 to 12 years) as applied in chapter 3 of this thesis. With this model, we determined the development of internalizing and externalizing problems with age. Latent growth curves were

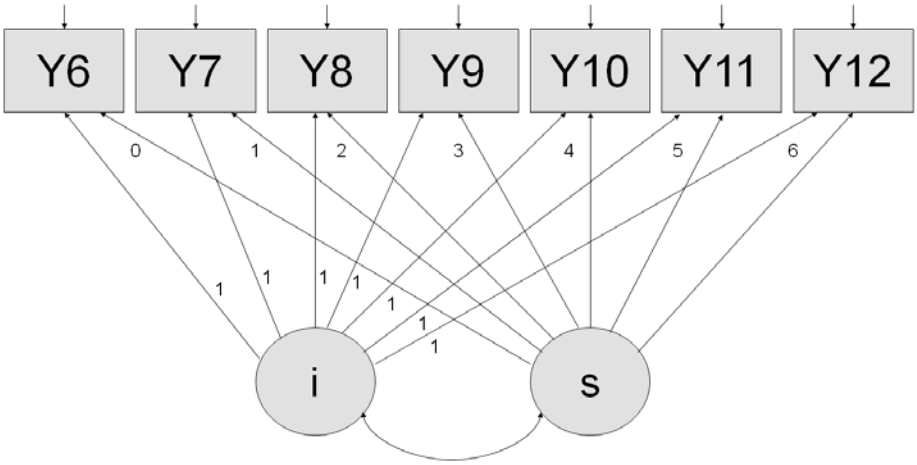

Figure 2.1: Graphical representation of the linear growth model as applied in chapter 3
Note: i = intercept; s = slope; squares Y6-Y12 = observed individual problem scores at ages 6 to 12 years.

estimated simultaneously for twins and singletons. In the parameterization of the growth model shown here, the time scores for the slope are fixed at 0, 1, 2, 3, 4, 5, and 6 to define a linear growth model with equidistant time points. In the case of a quadratic growth model, the time scores for the slope are 0, 1, 4, 9, 16, 25, and 36. The zero time score for the slope at the first time point defines the intercept as the initial status.

Evaluation of the growth curve models was conducted as follows. First, the model fit was evaluated with two goodness-of-fit indices (Hu & Bentler, 1999): the comparative fit index (CFI), with values of >0.95 indicating a good fit, and the root mean square error of approximation (RMSEA), with values of <0.06 indicating a good fit. Second, the intercept and slope means and variances were tested for significance. Third, a growth model in which one parameter (i.e., the means or variances of either the intercepts or the slopes) was constrained to be equal for twins and singletons, was tested against an unconstrained growth model to test for twin-singleton differences in the growth factors.

A limitation of a latent growth curve model is that it assumes that all individuals are drawn from a single population. Also, it assumes that covariates that affect the growth factors influence each individual in the same way. However, populations investigated in behavioral sciences are often heterogeneous, and the sources of population heterogeneity may not be known beforehand (Lubke & Muthén, 2005). Subgroups with different developmental patterns may remain undetected with the latent growth curve approach.

Growth mixture modeling (GMM)

GMM relaxes the single population assumption of LGM to allow for parameter differences across unobserved subpopulations, and can therefore provide a description of growth for clusters of participants within a sample (Lubke & Muthén, 2005; Muthén, 2004; Muthén & Shedden, 1999). GMM is a complex combination of mixture modeling and latent growth modeling, and is used to identify groups of individuals that resemble each other substantially more than that they resemble other individuals, resulting in subpopulations with different growth trajectories. Because GMM focuses on differences between individuals instead of variables, this method is often referred to as a person-centered approach as opposed to a variable-centered approach (such as LGM).

The subpopulations are called latent (trajectory) classes, and are represented by a categorical latent variable. The value of this variable represents the number of latent classes that is distinguished. Each latent class of participants follows a distinct developmental trajectory, and each trajectory is characterized by an intercept and slope(s). Instead of considering individual variation around a single, population average growth curve, the growth mixture model allows for different classes of individuals to vary around class-specific mean growth curves. In GMM, within-class variation with respect to the individual intercept and slope growth factors

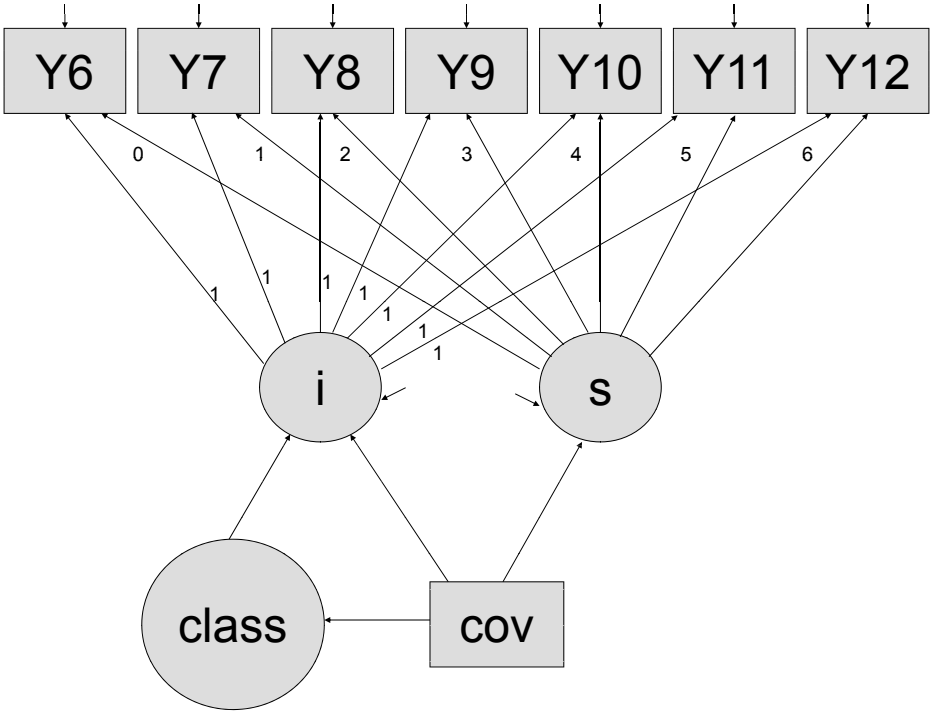

Figure 2.2: Growth mixture model as applied in chapter 4
Note: i = intercept; s = slope; class = categorical latent variable that represents the latent classes; cov = covariate; squares Y6-Y12 = observed individual problem scores at ages 6 to 12 years.

is allowed, but it is smaller than the between-class variation. A variation of GMM is latent class growth analysis (LCGA; Nagin & Tremblay, 1999), where no variation within classes is allowed.

In GMM, the goal is to find the optimal model that describes the data most parsimoniously. When performing growth mixture modeling and deciding on the best fitting model, it is necessary to compare a set of models with different numbers of classes and different within class structures (e.g., linear or quadratic slopes, fixed or free growth factor variances). The decision regarding the best fitting model may depend on fit indices (e.g., the lowest BIC value) as well as on model parsimony, theoretical justification, and interpretability (Jung & Wickrama, 2008).

In this thesis, GMM was applied to determine developmental trajectories of ADHD symptoms from ages 6 to 12 years in twins and singletons. Figure 2.2 shows the growth mixture model that was applied in chapter 4. A twin-singleton comparison was performed by comparing the number of latent trajectory classes, the shapes of the trajectories (i.e., the intercepts and slopes), and the proportions of children that were classified in each trajectory. The optimal number of classes was first determined separately for each sample. To test for twin-singleton differences in the mean intercepts and slopes of the trajectories, I fit a mixture model with the

optimal number of classes simultaneously for twins and singletons. A multi-group model was fitted with a mixture model within each group. The means and variances of the intercepts and slopes were then separately tested for equality between twins and singletons.

Genetic modeling

Almost everything that can be measured or counted in people shows variation, and scientists are concerned with explaining why differences between individuals occur. Questions like 'why aren't children from the same parents all alike' address variation within individuals and covariation between relatives (Neale & Cardon, 1992). The goal of genetic modeling is to explain inter-individual differences in psychological or behavioral traits by ascribing them to genetic and environmental influences. Twins are often used for this purpose. The basic idea of genetic modeling with twins is that if a trait is genetically influenced, monozygotic (MZ) twins must be more similar than dizygotic (DZ) twins.

In chapter 6 of this thesis, genetic modeling was applied on twin data according to the ACE-model (Neale & Cardon, 1992; Plomin, DeFries, McClearn, McGuffin, 2001). In this model, the total phenotypic variance is assumed to be the sum of the genetic, common environmental and unique environmental variance components: A, C, and E. Genetic influences are modeled latently as additive genetic effects (A), which are effects that are transmitted from parents to children, and that increase the resemblance between members of a twin pair. The proportion of phenotypic variance that can be accounted for by genetic effects is often referred to as the *heritability*. Common environmental factors (shared by family members) are also responsible for resemblance between twins, and include the unmeasured effects of factors that are shared between twin-pairs such as family structure and socioeconomic status (SES). In contrast, nonshared or unique environmental factors contribute to differences between twins, and may include for instance the effects of differential parental treatment, differential life events, and differential experiences outside the home (e.g., twins may have different friends). With structural equation modeling, the proportions of phenotypic variance explained by latent genetic and environmental factors can be estimated by maximum likelihood (Neale & Cardon, 1992). Identification of the model is obtained through the inclusion of mono- and dizygotic twins whose sharing of genetic effects differs.

The effects of A, C, and E do not need to be the same across different ages, sexes, or environments. This phenomenon is referred to as gene-environment interaction (GxE). The presence of GxE means that a single statistic (e.g., heritability) is no longer adequate to describe a whole population, because genetic effects depend on individuals' environments (Purcell, 2002). For example, the heritability of boys' antisocial behaviors was found lower in adolescents from families with lower socioeconomic status (Tuvblad, Grann & Lichtenstein, 2006, and the heritability of child and adolescent depressive symptoms was found higher

when levels of family conflict are high (Rice, Harold, Shelton & Thapar, 2006). In chapter 6, GxE was investigated by examining if the proportions of genetic and environmental variance of internalizing and externalizing problems were moderated by parental divorce. More specifically, the moderating effects of divorce, sex, and the interaction between sex and divorce on A,C, and E were investigated. The presence of GxE can be tested within a structural equation modeling approach (Purcell, 2002). An elaborate explanation of the application of this approach, as well as a graphical representation of the applied GxE model can be found in chapter 6.

When investigating GxE, a problem can be that moderators are correlated with the trait. Environmental effects can reflect genetic influences because certain experiences are influenced by genetic differences among people. This is referred to as gene-environment correlation (rGE), which is the genetic control of exposure to different environments. Gene-environment correlations can be passive (e.g., parents provide both genes and family environment to their children), evocative (e.g., children evoke reactions from other people on the basis of their genetic make-up), or active (e.g., children select and modify experiences according to their genetic make-up and their genetically influenced abilities and interests). Many environmental variables may in fact be correlated with the genetic effects on the trait rather than modifying the genetic effects on the trait (Purcell, 2002). In the study described in chapter 6, gene-environment correlations would be present when exposure to parental divorce depends on a child's genotype. To disentangle GxE and rGE, the moderators were entered in the means model to allow for a main effect of the moderators. By doing so, any genetic effects that are shared between the trait and the moderators were removed from the covariance model, resulting in GxE interactions that are not due to rGE.

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Chapter 3

A twin-singleton comparison of developmental trajectories of externalizing and internalizing problems in 6- to 12-year-old children

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Twin Research and Human Genetics, 2010, 13(1), 79-87

Abstract

Background: Research on twin-singleton differences in externalizing and internalizing problems in childhood is largely cross-sectional and yields contrasting results. The goal of this study was to compare developmental trajectories of externalizing and internalizing problems in 6- to 12-year-old twins and singletons.

Methods: Child Behavior Checklist maternal reports of externalizing and internalizing problems were obtained for a sample of 9,651 twins from the Netherlands Twin Register and for a representative general population sample of 1,351 singletons. Latent growth modeling was applied to estimate growth curves for twins and singletons. Twin-singleton differences in the intercepts and slopes of the growth curves were examined.

Results: The developmental trajectories of externalizing problems showed a linear decrease over time, and were not significantly different for twins and singletons. Internalizing problems seem to develop similarly for twins and singletons up to age 9. After this age twins' internalizing symptoms start to decrease in comparison to those of singletons, resulting in less internalizing problems than singletons by the age of 12 years.

Conclusions: Our findings confirm the generalizability of twin studies to singleton populations with regard to externalizing problems in middle and late childhood. The generalizability of studies on internalizing problems in early adolescence in twin samples should be addressed with care. Twinship may be a protective factor in the development of internalizing problems during early adolescence.

Introduction

Twins are frequently used to study causes of individual differences in problem behaviors. An important assumption of twin studies is that results from twin samples can be generalized to the general population. However, the comparability of twins to singletons is still being questioned for various reasons. For instance, increased pre- and perinatal risks among twins could result in a higher prevalence of behavioral and emotional problems in twins than in singletons (Rutter & Redshaw, 1991). Twins are born on average three weeks earlier than singletons, and their birth weight is on average lower (Rutter & Redshaw, 1991). Several authors have reported increased levels of problems such as ADHD (Lahti, et al., 2006) and depression (Raikkonen, et al., 2008) in preterm children, children with low birth weight and children with small body size at birth. However, low birth weight, preterm birth, or small size at birth are unlikely to have the same significance in twins as in singletons, because the etiology of these risk factors appears to be different in the two groups (Phillips, et al., 2001). In twins, small size at birth results from 'crowding', rather than from an unfavorable intrauterine environment (Gruenwald, 1970). From about 24 weeks gestational age onwards placental weights of twins are smaller than those of singletons. Children in multiple gestations become growth retarded, preceded by and very likely due to poor early placental development (Bleker, et al., 1988). After birth, twins grow fairly well compared to singletons, and twins are almost as tall as singletons by the age of 5 years (Estourgie-Van Burk, et al., 2006). It has also been hypothesized that twins may show fewer problems than singletons because the twinship offers a favorable social environment, via interactions with, and social support of the co-twin (Pulkkinen, et al., 2003), although there is little evidence supporting this hypothesis as yet.

Despite the importance and ongoing debate about the generalizability of twin studies, the number of studies that investigated twin-singleton differences in problem behaviors is surprisingly limited. Researchers have so far focused on comparing mean levels of externalizing and internalizing problems between twins and singletons in childhood, and their findings are mixed. For instance, a study with 8- and 9-year-old Finnish twins and singletons showed significantly lower rates of externalizing problems in twins (Moilanen, et al., 1999). Similarly, slightly less externalizing problems were found in 2- and 3-year-old Dutch twins compared to same-aged singletons (Van den Oord, et al., 1995). In contrast, higher levels of externalizing problems in twins than in singletons were reported in an American sample of 6- to 16-year-old children (Gau, et al., 1992). Also, 4- to 12-year-old twins showed more ADHD symptoms than singletons (Levy, et al., 1996) and twins showed more conduct disorders than singletons (Simonoff, 1992). Studies among 11- and 12-year-old Finnish twins and singletons (Pulkkinen, et al., 2003), and 5- to 15-year-old Norwegian twins and singletons (Gjone & Novik, 1995) showed no evidence for twin-singleton differences in externalizing problems. The level of internalizing problems in Norwegian children aged 5 to 15 years has been found to be lower in twins than in singletons, especially around the age of 12 and most pronounced for

boys (Gjone & Novik, 1995). Other studies found no evidence for twin-singleton differences in internalizing problems until the age of 12 (Gau, et al., 1992; Pulkkinen, et al., 2003).

The results of these studies may be conflicting for various reasons, such as the use of different measures, sample sizes, and age groups. A major constraint has been that all studies conducted so far are cross-sectional. Therefore, further investigation regarding whether or not results from twin samples can be generalized to singletons is needed. Information is lacking on twin-singleton differences in the longitudinal development of problem behaviors in childhood. Therefore, the aim of the present study is to compare growth curves of the development of externalizing and internalizing problems, using 6- to 12-year-old twins and singletons. In addition to cross-sectional mean differences, growth curves may yield twin-singleton differences in the overall development over time that would otherwise remain undetected. Previous studies on the normative development of internalizing and externalizing behaviors in childhood show declining trajectories of externalizing problems for both sexes (Bongers, et al., 2003; Leve, et al., 2005; Miner & Clarke-Stewart, 2008; Stanger, et al., 1997), with boys having higher mean levels of externalizing problems than girls. Regarding the development of internalizing problems in childhood, the results are somewhat mixed. Previous studies reported increasing trajectories for girls, but not for boys (Leve, et al., 2005), stable trajectories for both boys and girls (Keiley, et al., 2000), and curvilinear increasing trajectories for both boys and girls (Bongers, et al., 2003), with boys and girls having similar mean levels of internalizing problems in childhood. We expect to observe a similar decrease of externalizing problems and an increase of internalizing problems over time for twins and singletons.

Materials and methods

Subjects

Singleton sample

The singleton data used in this study were derived from an ongoing Dutch longitudinal study of behavioral and emotional problems that started in 1983. The original sample of 2,600 children aged 4 to 16 was randomly drawn from municipal registers that list all residents in the Dutch province of Zuid-Holland, and represents a general population sample (Verhulst, et al., 1985). After complete description of the study to the subjects, written informed consent was obtained. For details about the initial data collection, see Verhulst, et al. (1985). The present study uses data from the first five waves. After the first measurement in 1983, the respondents were approached again in 1985, 1987, 1989 and 1991. At study onset, 2,076 out of 2,600 invited participants (80%) responded. Response rates ranged from 80% to 85% at each measurement. For 1,964 children, within an age range of 4 to 18, mother ratings were available on at least one of the five waves of data collection. These children were all born

between 1971 and 1979. We kept all subjects in the sample who were between 6 and 12 years of age at any time point, even if mother ratings were available from only one measurement. This resulted in a final singleton sample of 1,351 children (664 boys and 687 girls). For 39% of this sample we had data from one measurement, for 26% from two measurements, for 23% from three measurements, and for 12% from four measurements. Due to the design of this study, the number of measurements of each child was not only determined by dropping out, but it was restricted by birth cohort. For example, children born in 1971 only had data at age 12, while children born in 1979 had data at multiple points in time. Attrition analyses on the initial 2,076 respondents revealed a significant effect of dropout on socio-economic status (SES), with dropouts having lower SES. There was no effect of dropout on the mean level of problems (Bongers, et al., 2003).

Twin sample

The twin data came from a longitudinal twin study on health, growth, and the development of behavioral and emotional problems. All participating families are volunteer members of the Netherlands Twin Register (NTR), established by the Department of Biological Psychology at the VU University in Amsterdam, and represent a twin family sample that is representative for the Dutch general population (Bartels, et al., 2007; Boomsma, et al., 2006). The study protocol was approved by the ethics committee of the VUMC (VU University medical center), Amsterdam. Of all multiple births in The Netherlands, 40% to 50% is registered by the NTR since 1986 (Boomsma, et al., 1992; Boomsma, et al., 2002). For the present study, data from twins born between 1986 and 1998 were analyzed. Parents of twins received surveys by mail, around the twins' 7th, 10th and 12th birthdays. The absolute response rate at each measurement was about 62%. Attrition analyses revealed that dropout was not related to problem behavior (Bartels, et al., 2007). Although most twins were aged 7, 10, or 12, there were also a substantial number of children who were older or younger than these target ages at the time of the assessments, and by calculating the exact ages in years of the twins at the moment of completion of the questionnaires data from 6 to 12 years were available for analyses. Data were available for 19,274 twins from 9,651 families. Because data obtained from twin pairs are not independent, one twin was randomly selected from each pair. This resulted in a final sample of 9,651 twins (4,728 boys and 4,923 girls). For 43% of this twin sample data were available from one measurement, for 28% from two measurements, and for 29% from three measurements. Children with longitudinal data were in general from older birth cohorts, because younger cohorts did not reach all target ages of survey collection yet (e.g., twins born in 1998 are not yet invited for age 12 participation).

Covariates

It has been documented that economic problems have an adverse influence on the behavioral and emotional development of children (McLoyd, 1998). To make sure that any observed twin-singleton difference could not be attributed to differences in SES between our samples, SES was included as a covariate. For the singleton sample, SES was scored on a six-step scale of parental occupation (Van Westerlaak, et al., 1975) with 1 indicating the lowest SES and 6 indicating the highest SES. This scale was subsequently divided into three SES levels (1 to 3 = low SES; 4 and 5 = middle SES; 6 = high SES). For 5 singletons information on SES was missing. For about two-third of the twin sample, SES was obtained from a full description of the occupation of the parents, and SES was subsequently coded according to the Dutch Standard Classification of Occupations (CBS, 2001). For the remaining twins, SES was obtained by the EPG-classification scheme (Erikson, et al., 1979), combined with information on parental education. For all twins, the level of occupation was classified into SES levels that were similar to the ones used in the singleton sample. For 73 twins SES status was unknown. For both singletons and twins we used the baseline SES status, assessed at the first measurement occasion. Because the development of problem behaviors is different for boys than for girls (Bongers, et al., 2003), we also included sex as a covariate to account for gender differences.

Instrument

For both the singletons and the twins, mother ratings of externalizing and internalizing problems were collected using the Child Behavior Checklist (CBCL/4-18; Achenbach, 1991; Achenbach, 1992). The CBCL/4-18 was developed for parents to rate the behavioral and emotional problems of their children. It consists of 120 items that are scored on a 3-point scale based on the occurrence of the behavior during the preceding 6 months: 0 if the item was not true, 1 if the item was somewhat or sometimes true, and 2 if the item was very true or often true. The good reliability and validity of the CBCL/4-18 were confirmed for the Dutch translation of the measure: Cronbach's alpha was 0.86 for the Externalizing scale and 0.83 for the Internalizing scale (Verhulst, et al., 1996). The Internalizing scale consists of the Anxious/Depressed, Somatic Complaints, and Withdrawn subscales, and consists of 31 items. The Externalizing scale consists of the Aggressive Behavior and Rule-Breaking Behavior subscales, and consists of 33 items.

Data analysis

Means and standard deviations of the problem scores were computed per age, using SPSS15. The developmental trajectories of externalizing and internalizing problems were examined using latent growth curve modeling (LGM; McArdle & Erpstein, 1987) with Mplus Version 5 (Muthén & Muthén, 1998-2007). In LGM, random effects are used to capture individual differences in development. These random effects are conceptualized as continuous latent variables, the growth factors. The growth curves were determined by two or three latent growth factors: a) the intercepts, which represent the initial status of the curve; b) the linear slopes, which represent linear change over time; and c) the quadratic slopes, which represent non-linear change. We included quadratic slopes because non-linear development of problem behaviors has been reported by earlier studies (Bongers, et al., 2003). The covariates were centered to their means. Maximum likelihood was used to estimate the growth models. We allowed for the analysis of respondents with missing data, because in LGM a person who participates only once or whose SES status is unknown, still contributes to the overall estimation of the model. We performed multi-group analyses (i.e., singletons and twins) using the grouping option in Mplus. All analyses were conducted for externalizing and internalizing problems separately.

Evaluation of the growth curve models was conducted as follows. First, we examined the model fit, which was evaluated with two goodness-of-fit indices (Hu & Bentler, 1999): the comparative fit index (CFI), with values of >0.95 indicating a good fit, and the root mean square error of approximation (RMSEA), with values of <0.06 indicating a good fit. Second, we checked if the latent growth factor means and variances were significant and if the covariates had significant influence on the growth factor means. Third, we performed likelihood-based chi-square difference tests in Mplus to test whether the growth factor means and variances were different between twins and singletons. A growth model in which the means or variances of either the intercepts or the slopes were constrained to be equal for twins and singletons, was tested against the unconstrained growth model. The linear and the quadratic slopes were jointly constrained. We tested if twin-singleton differences were different for boys and girls. This was not the case; therefore, the data were further analyzed for boys and girls together, including SES and sex as covariates.

Results

A total of 447 singletons (33%) had low SES, 444 singletons (33%) had middle SES, and 455 singletons (34%) had high SES. A total of 2,043 twins (21%) had low SES, 4,245 twins (44%) had middle SES and 3,290 twins (34%) had high SES. The twin sample had a lower proportion of low SES children than the singleton sample. Sex was equally distributed in both samples (χ^2 (1) = 0.012, p=0.91), with 51% boys in each sample. Table 3.1 shows the observed means and standard deviations for both twins and singletons for externalizing and internalizing problems, separately for boys and girls. Significant differences in these mean scores between twins and singletons were only observed for boys' externalizing problems at age 7 (p=0.03),

Table 3.1: Means and standard deviations of externalizing and internalizing problem scores for singletons (664 boys and 687 girls) and twins (4,728 boys and 4,923 girls)

	Sex	Age	Singletons			Twins		
			N	Mean	Std.	N	Mean	Std.
Externalizing	boys	6	111	9.52	8.50	274	8.80	7.18
		7	121	10.33*	7.57	3644	8.76*	7.23
		8	177	8.42	7.19	332	8.87	7.25
		9	183	8.80	7.59	1205	8.24	7.68
		10	231	8.17	7.13	1511	7.96	7.15
		11	232	8.06	7.18	809	6.92	7.11
		12	306	7.16	7.01	975	7.27	7.13
	girls	6	113	7.08	5.91	331	6.99	6.28
		7	136	5.98	5.63	3709	6.44	5.98
		8	179	7.01	6.20	370	6.76	6.32
		9	201	5.65	5.94	1378	5.75	5.80
		10	238	5.61	5.32	1561	5.67	5.99
		11	273	5.27	5.78	880	4.83	5.07
		12	296	5.44	5.49	1017	4.91	5.59
Internalizing	boys	6	111	3.52	3.59	268	4.15	3.98
		7	121	4.83	4.80	3582	4.43	4.52
		8	177	4.61	4.49	323	4.39	4.36
		9	183	5.04	5.06	1192	4.77	4.79
		10	231	5.35	5.13	1487	4.68	5.02
		11	232	5.21*	5.51	800	4.41*	5.34
		12	306	4.94*	5.56	967	4.14*	4.49
	girls	6	113	4.55	3.72	326	5.08	4.78
		7	136	4.19	4.12	3658	4.88	4.67
		8	179	5.26	4.80	364	4.62	4.29
		9	201	4.96	4.46	1354	5.20	5.27
		10	238	5.30	5.54	1545	5.07	5.24
		11	273	5.00	4.81	868	4.56	5.06
		12	296	5.40*	5.34	1007	4.58*	5.37

Note: N = number of observations; Std = standard deviation; * = significant twin-singleton mean difference (p<0.05). Due to the longitudinal design, the N's do not add up to the total number of children.

for boys' internalizing problems at age 11 (p=0.03) and age 12 (p=0.01), and for girls' internalizing problems at age 12 (p=0.02). Singletons had higher problem scores than twins at these ages.

The model fit statistics and model results for externalizing problems are reported in Table 3.2. The model fit the data well (CFI=0.99 and RMSEA=0.014). The influences of sex and SES on the intercept were significant (p<0.001) and negative for both twins and singletons, implying that children with high SES showed less externalizing problems, and that boys had more externalizing problems than girls. The effect sizes for sex differences in the intercepts of externalizing problems were moderate in both samples (Cohen's d singletons/twins = 0.50/0.38). No significant effects of sex and SES were found on the slope for both twins and singletons. Figure 3.1 shows the latent growth curves of externalizing problems for twins and singletons, corrected for sex and SES. It shows a linear decrease in externalizing problems over time. The quadratic slope was not significant for both twins and singletons, and was therefore excluded from the model. The differences between the intercept means and variances of twins and singletons were not significant ($\Delta\chi^2$ (1) = 3.345, p=0.07; $\Delta\chi^2$ (1) = 1.194, p=0.27). The linear slope means and variances were also not significantly different between twins and singletons ($\Delta\chi^2$ (1) = 0.388, p=0.53; $\Delta\chi^2$ (1) = 3.831, p=0.05).

The model fit statistics and model results for internalizing problems are reported in Table 3.2. The model fit was very good, with CFI=0.98 and RMSEA=0.019. With regard to the singletons, sex and SES had no significant influence on either the intercept or the slope estimates.

Table 3.2: LGM model fit statistics, model results with standard errors, and the influence of sex and SES on the growth factors

	Externalizing		Internalizing	
Chi-square value	133.777		171.817	
Degrees of freedom	63		57	
RMSEA	0.014		0.019	
CFI	0.99		0.98	
	Singletons	**Twins**	**Singletons**	**Twins**
Intercept mean	8.49 (0.25)	8.00 (0.08)	4.35 (0.20)	4.35 (0.08)
Intercept variance	39.75 (3.29)	35.91 (1.41)	12.55 (1.58)*	17.76 (0.89)*
Linear slope mean	-0.36 (0.05)	-0.33 (0.02)	0.41 (0.12)	0.42 (0.06)
Quadr. slope mean	n.s.	n.s.	-0.04 (0.02)*	-0.07 (0.01)*
Slope variance	0.69 (0.12)	0.42 (0.08)	0.32 (0.08)*	0.51 (0.05)*
	Singletons	**Twins**	**Singletons**	**Twins**
Intercept on sex	-3.17 (0.51)	-2.29 (0.16)	n.s.	0.62 (0.15)
Slope on sex	n.s.	n.s.	n.s.	n.s.
Quad. slope on sex			n.s.	n.s.
Intercept on SES	-1.52 (0.31)	-1.02 (0.11)	n.s.	n.s.
Slope on SES	n.s.	n.s.	n.s.	n.s.
Quad. Slope on SES			n.s.	n.s.

Note: CFI = comparative fit index; RMSEA = root mean square error of approximation; n.s. = not significant; * = significant twin-singleton difference (p<0.05).

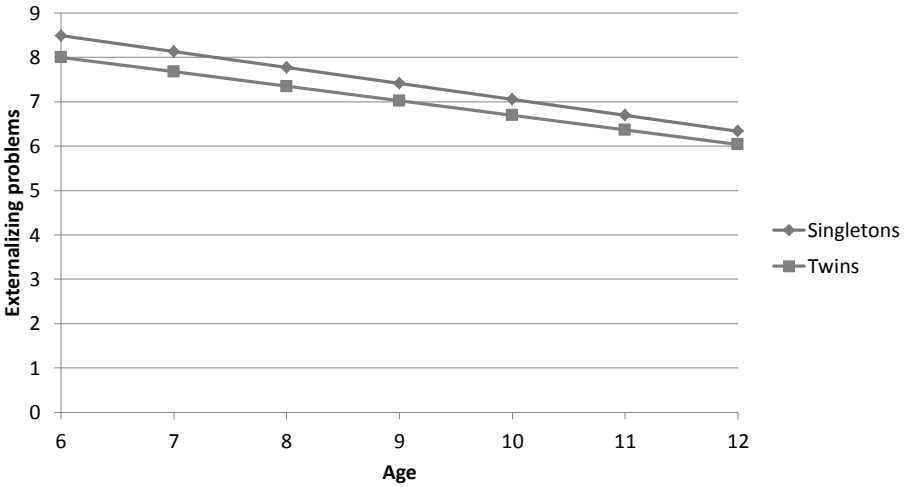

Figure 3.1: Developmental trajectories of externalizing problems for singletons and twins, adjusted for sex and SES

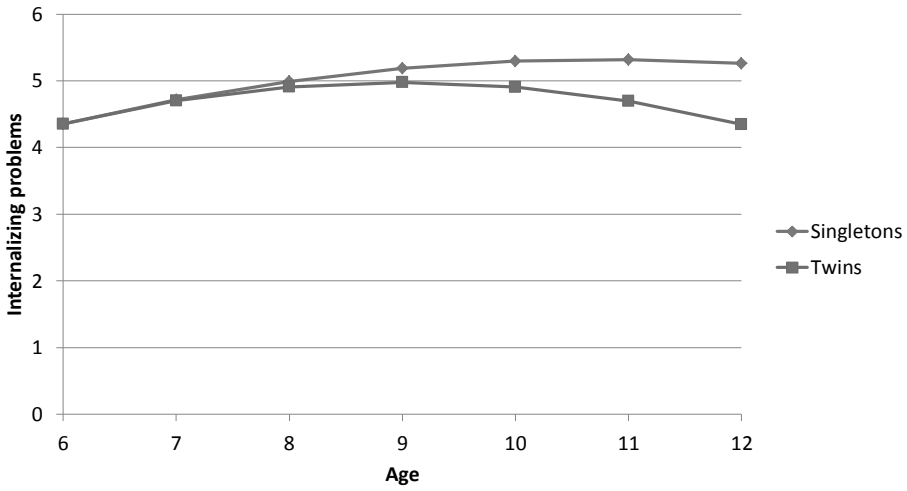

Figure 3.2: Developmental trajectories of internalizing problems for singletons and twins, adjusted for sex and SES

For the twins, there was only a significant influence of sex on the intercept ($p<0.001$), which indicated that girls had more internalizing problems than boys. The effect sizes for sex differences in the intercepts of internalizing problems were small in both samples (Cohen's *d* singletons/twins = 0.16/0.15). Figure 3.2 shows the latent growth curves of internalizing problems of twins and singletons, corrected for SES and sex. It shows a curvilinear increase of internalizing problems in singletons, with levels of problems stabilizing by the age of 12, whereas twins' levels of internalizing problems start to decrease from the age of 9 onwards,

resulting in significantly less internalizing problems than singletons by the age of 12. The intercept means of twins and singletons were identical. The development with age, as represented by the linear and quadratic slope means, was different between twins and singletons ($\Delta\chi^2$ (2) = 20.97, p<0.001). Also, twins had significantly larger intercept and slope variances than singletons ($\Delta\chi^2$ (1) =7.586, p=0.01; $\Delta\chi^2$ (1) = 4.100, p=0.04).

Discussion

This is the first study that longitudinally examined twin-singleton differences in the development of externalizing and internalizing problems in children aged 6 to 12 years. Using latent growth modeling, we estimated and compared growth curves of externalizing and internalizing problems for twins and singletons. For externalizing problems, the growth curves of twins and singletons were similar, showing a linear decrease over time. Decreasing levels of externalizing problems have consistently been found in earlier studies (e.g., Bongers, et al., 2003; Leve, et al., 2005; Miner & Clarke-Stewart, 2008; Stanger, et al., 1997). Although twins showed a tendency to have less externalizing problems than singletons overall, this difference was not significant. We also observed a trend toward a significant variance difference in the slopes of twins and singletons, with singletons having a slightly larger slope variance than twins. Because of the large sample size and the fact that these effects did not reach significance, we conclude that twins are broadly comparable to singletons with regard to the development of externalizing problems. This finding supports the generalizability of twin studies with regard to externalizing problems, and is in line with some previous cross-sectional studies that reported similar levels of externalizing problems for twins and singletons (Gjone & Novik, 1995; Pulkkinen, et al., 2003).

Internalizing problems seem to develop similarly in twins and singletons up to the age of 9, after which twins' levels of internalizing problems start to decrease in comparison to those of singletons. The lower levels of internalizing problems in twins are in accordance with the results of a previous twin-singleton comparison (Gjone & Novik, 1995). A similar trend of decreasing levels of internalizing problems after the age of 9 has been found earlier (Leve, et al., 2005). The interpretation of the larger intercept and slope variances for twins requires some caution. A general problem that may occur when mothers of twins are asked to rate their children, is that they may compare the twins' behavior. The behavior of one twin could then become the standard against which the behavior of the co-twin is rated. This is called a rater contrast effect (Eaves, 1976). Contrast effects may also result from sibling interaction, including cooperation or competition effects. These effects can result in variance differences between twins and singletons, and between monozygotic and dizygotic twins (Bartels, et al., 2007). It seems however unlikely that contrast effects have influenced the results, because both externalizing and internalizing problems are measured with the same questionnaire,

and we did not find significant variance differences for externalizing problems. Moreover, variances for monozygotic and dizygotic twins did not give any indication to the presence of contrast effects. It also seems unlikely that the difference in sample size between twins and singletons has influenced our findings, because we did not find significant variance differences for externalizing problems, and the variances remained similarly large in smaller random twin samples.

Our results did not support the hypothesis that twins' increased pre- and perinatal risks lead to higher levels of problem behaviors in twins than in singletons. This is probably because the psychological risks associated with these factors are small, and most twins are physically healthy individuals who grow up under normal circumstances (Rutter & Redshaw, 1991). The tendency of twins to have fewer internalizing problems than singletons, might be explained by the fact that twins always have someone close for support. Siblings have been found to be a source of support to each other (Furman & Buhrmester, 1985) and higher levels of sibling support have been associated with lower levels of internalizing problems (Branje, et al., 2004). Although many singletons are likely to have a sibling as well, we hypothesize that the presumed effect of sibling support is stronger for twins than for regular siblings, because twins may have a more intimate relationship with each other than regular siblings (Segal, et al., 2008). Consequently, twinship may be a protective factor to the development of internalizing problems in early adolescence. Environmental influences that are shared by twin pairs and not by other members of the family may have an effect. Twin researchers should therefore use extended twin designs that include non-twin siblings, and perform explicit tests of a special twin environment for internalizing problems.

Differences between our findings and those from earlier studies could be due to the different designs (cross-sectional versus longitudinal), different age groups, and the use of different measures. All previously conducted studies were cross-sectional. This study provides a clear picture of twin-singleton differences in the development of externalizing and internalizing problems in childhood, in addition to cross-sectional differences. Finally, we acknowledge that examining growth curves in addition to cross-sectional differences is not sufficient to fully evaluate the generalizability of twin studies with regard to these types of behaviors, but it has brought us a step further in this rather unexplored field of research.

Several limitations of the present study need to be considered. Firstly, reorganization of the data matrix as a function of chronological age created a missing data problem. Although we chose a statistical approach that can properly handle missing data, it would have been better if we had data of each respondent at each age. Secondly, we only used maternal ratings. Unfortunately, there were not enough father ratings available in the singleton sample for a reliable twin-singleton comparison. Future research should also include father ratings or teacher ratings to obtain a more complete picture of the behavior of the child, accounting for example for situational specific behavior. Thirdly, the two samples are not from the same time periods and were recruited from different regions. An earlier study that

used the same singleton data did not find evidence for clear secular differences in psychopathology over a 10-year period (1983-1993) (Verhulst, et al., 1997). Tick, et al. (2007) found increases in Dutch children's problems over a 20-year period (1983-2003), but these increases were not consistent across informants and across age. Only parent reports for children aged 6 to 16 years showed a very small increase in internalizing problems, but this increase was not reported for self-reports and teacher reports for children of the same age and not for parent reported problems in preschool children. With regard to our twin sample, we did not find any significant differences in the mean externalizing and internalizing problem scores at ages 7, 10, and 12 between twins from different cohorts. Considering these findings, it seems unlikely that cohort effects can explain twin-singleton differences. The different regions the samples have been recruited from does not limit the comparability of the samples, because we found that twins from the province of Zuid-Holland have the same externalizing and internalizing trajectories as twins from the rest of The Netherlands. Also, Tick, et al. (2007) showed that there were no significant differences in mean scale scores on the CBCL between children living in Zuid-Holland and children living elsewhere in The Netherlands.

In conclusion, our findings confirm the generalizability of twin studies with regard to the development of externalizing problems in middle and late childhood, because developmental trajectories of externalizing problems were similar for twins versus singletons. However, the generalizability of studies on internalizing problems in early adolescence in twin samples should be addressed with care. Twinship may be a protective factor for the development of internalizing problems during early adolescence. Our findings regarding internalizing problems are indicative of twin-singleton differences in adolescence. Future research should extend our findings by describing developmental trajectories of externalizing and internalizing problems from childhood to adulthood.

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Chapter 4

Trajectories of CBCL Attention Problems in childhood

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European Child and Adolescent Psychiatry, 2011, 20(8), 419-427

Abstract

Background: The first aim of this study was to identify developmental trajectories of Attention Problems in twins followed from age 6 to 12 years. Second, we investigated whether singletons follow similar trajectories.

Methods: Maternal longitudinal ratings on the Attention Problems (AP) subscale of the Child Behavior Checklist were obtained for a sample of 12,486 twins from the Netherlands Twin Register and for a general population sample of 1,346 singletons. Trajectories were analyzed by growth mixture modeling (GMM) in twins, and compared with singletons. Teacher ratings on the AP subscale of the Teachers' Report Form were available for 7,179 twins and 1,211 singletons, and were used for cross-sectional mean comparisons at each age. All analyses were conducted for boys and girls separately.

Results: We identified three linear trajectories in both boys and girls, i.e., stable low (62-71%), low-increasing (15-18%), and high-decreasing (14-21%). Singletons followed three identical trajectories, with similar class proportions. Teacher ratings yielded no differences in mean levels of Attention Problems between twins and singletons.

Conclusion: The development of Attention Problems from age 6 to 12 years can be characterized by stable low, low-increasing, and high-decreasing developmental trajectories. Twins and singletons are comparable with respect to the development of Attention Problems in childhood.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by inappropriate levels of inattention, hyperactivity, and/or impulsiveness. ADHD has a great impact on affected children and their families in terms of academic, social and behavioral dysfunction (Mannuzza & Klein, 2000; Mannuzza, Klein, Abikoff, & Moulton, 2004), and is at the moment the most common neurodevelopmental disorder of childhood with 5% of children worldwide affected. ADHD symptoms are likely to be continuously distributed in childhood through adolescence with ADHD being on the extreme tail of the distribution (Hay, Bennett, Levy, Sergeant, & Swanson, 2007; Levy, Hay, McStephen, Wood, & Waldman, 1997; Lubke, Hudziak, Derks, Van Beijsterveldt, & Boomsma, 2009; Lubke, et al., 2007; Polderman, et al., 2007). Typical presentations of ADHD symptoms in childhood are premature changes of activity, restless when calm expected, distracted by the environment, forgetful, acting out of turn, intrusions on peers, and thoughtless rule-breaking (Taylor & Sonuga-Barke, 2008).

Community studies on the development of ADHD symptoms in childhood report somewhat mixed findings. A number of them show decreases in ADHD symptoms. For example, in an American longitudinal sample of 6- to 20-year-old boys, ADHD symptoms declined with increasing age, with hyperactivity symptoms declining at a higher rate than inattention symptoms (Biederman, Mick, & Faraone, 2000). In a sample of 8- to 17-year-old Swedish twins levels of inattention remained relatively constant, whereas levels of hyperactivity-impulsivity declined with increasing age (Larsson, Lichtenstein, & Larsson, 2006). Another American longitudinal study showed that levels of ADHD symptoms were generally constant until the teen years, and declined from there (Monuteaux, Mick, Faraone, & Biederman, 2010). Similarly, mean levels of ADHD symptoms decreased after age 10 in Dutch twins (Rietveld, Hudziak, Bartels, Van Beijsterveldt, & Boomsma, 2004) and singletons (Bongers, Koot, Van der Ende, & Verhulst, 2003). An Australian general population sample showed only minimal age differences in the number of ADHD symptoms in children aged 5-11 years (Gomez, Harvey, Quick, Scharer, & Harris, 1999). The results of these studies may differ for various reasons, such as the use of different ADHD measures. Nonetheless, the general picture seems to be that the development of ADHD symptoms is relatively stable in childhood with a possible decrease of symptoms starting around the age of 10 years.

The development of ADHD symptoms can also be investigated by examining subgroups with distinct developmental trajectories. Only few studies analyzed different developmental trajectories of ADHD symptoms in school-age children. Two trajectories were identified in a high-risk sample of American children aged 7-16 years of families with parental alcoholism: one with stable low levels, and one with stable high levels, the latter containing 57% of the children (Jester, et al., 2005). In a sample of Canadian boys from low socioeconomic areas, four trajectories of hyperactivity were identified from 6 to 15 years (Nagin & Tremblay, 1999). Roughly 6% of the children in this study followed a chronic high trajectory. The other children

followed low or decreasing trajectories. In a general population sample of Dutch children aged 4-18 years, four developmental trajectories of ADHD symptoms were estimated, among which was a high trajectory with increasing scores into late childhood (Van Lier, Van der Ende, Koot, & Verhulst, 2007). Three trajectories of ADHD symptoms were identified in a sample of children aged 8-14 years who were selected from high-risk schools: one with minimal problems, one that showed an increase and then a decrease in symptoms, and one that showed a decrease and then a slight increase in symptoms (Malone, Van Eck, Flory, & Lamis, 2010). Recently, two hyperactivity-impulsivity trajectories (low, high-decreasing) and two inattention trajectories (low, high-increasing) were found in a population-based twin study (Larsson, Dilshad, Lichtenstein, & Barker, 2011). Summarizing the results of these studies, two to four trajectories of ADHD symptoms were identified. Subgroups with specific developmental trajectories of ADHD symptoms should be investigated more thoroughly by using large representative samples of school-age children.

ADHD symptoms in twins and singletons

In the current study, data from twins were analyzed to estimate developmental trajectories of Attention Problems. Twin data are frequently used to study the heritability of ADHD symptoms, which usually varies between 50 and 80% (Derks, et al., 2008; Faraone & Doyle, 2001; Polderman, et al., 2007; Rietveld, Hudziak, Bartels, Van Beijsterveldt, & Boomsma, 2004; Thapar, Harrington, Ross, & McGuffin, 2000; Wood, Buitelaar, Rijsdijk, Asherson, & Kuntsi, 2010). An important assumption of twin studies is that the results can be generalized to the general population, which mainly includes singletons. The comparability of twins to singletons is however still being questioned for various reasons, such as more pre- and perinatal problems among twins that could result in a higher prevalence of behavioral problems in twins than in singletons (Rutter & Redshaw, 1991). However, many of these problems such as low birth weight and preterm birth are unlikely to have the same significance in twins as in singletons, as the etiology of these risk factors appears to be different in the two groups (Philips, Davies, & Robinson, 2001).

Despite the uncertainty about the representativeness and possibly increased vulnerability of twins, research on twin-singleton differences in ADHD symptoms is sparse and has been cross-sectional so far. To our knowledge, there are three cross-sectional studies that compared levels of ADHD symptoms between twins and singletons. An Australian study found more ADHD symptoms in twins than in singletons aged 4-12 years (Levy, Hay, McLaughlin, Wood, & Waldman, 1996), while a study of 2- and 3-year-old Dutch twins found that twins showed slightly lower levels of ADHD symptoms than singletons (Van den Oord, Koot, Boomsma, Verhulst, & Orlebeke, 1995). In line with this study, an American study of 12- to 19-year-old twins and their non-twin siblings found some evidence for a higher prevalence of ADHD in the non-twin siblings, although this result was not consistently observed for all age groups

and in both sexes (Ehringer, Rhee, Young, Corley, & Hewitt, 2006). Whether ADHD symptoms develop differently over time for twins versus singletons has not yet been investigated.

The present study

In the current study we will extend the findings of a recent study in 7-, 10- and 12-year-old boys from the Netherlands Twin Register, that showed three mainly quantitatively different latent classes of Attention Problems at each age, i.e., high-, moderate-, and low-scoring classes (Lubke, Hudziak, Derks, Van Beijsterveldt, & Boomsma, 2009). Our aim was to identify subgroups of children with specific developmental trajectories of Attention Problems from ages 6 to 12 years. We expected to find a minimum of three relatively stable trajectories (e.g., high-, moderate-, and low-scoring) with the majority of children having low levels of Attention Problems. Trajectories were expected to reflect slightly decreasing levels of Attention Problems late in childhood, as self-regulation increases with beginning puberty (Barkley, 1997). The second aim of this study was to investigate if singletons follow similar trajectories as twins. As in general most twins are physically healthy individuals who grow up under normal circumstances, we did not expect to find large differences between twins and singletons. Finally, it has been well established that ADHD symptoms are more prevalent in boys than in girls (Biederman, 2005; Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007). Because we had two large samples of children, we were able to investigate the development of Attention Problems separately for boys and girls.

Methods

Subjects

Twin sample

All participating twins were volunteer members of the Netherlands Twin Register (NTR). The NTR represents a twin family sample that is largely representative for the Dutch general population (Bartels, et.al., 2007). For the present study, data from twins born between 1986 and 1998 were analyzed. Parents and teachers of twins received surveys by mail, around the twins' 7th, 10th and 12th birthdays. The exact ages (in years) of the twins at the time of completion of the surveys were calculated from date of birth of twins and date of completion of the surveys. The response rate at each measurement was 61-63% for mother reports. About 50% of the parents gave written permission to approach the teacher, and the subsequent teacher response rate was 74-78%. Attrition analyses revealed that, at ages 7 and 10, the level of socio-economic status (SES) was higher in families that returned the survey than in families that did not return the survey (Derks, 2006). Also, twins had higher levels of Attention Problems at ages 7 and 10 when the parents did not respond at the previous target age

(Derks, 2006). However, the effect sizes were small, and it is therefore unlikely that attrition in the Netherlands Twin Register strongly affected the results.

Twin pairs were excluded if they suffered from a severe handicap, which interferes with daily functioning. Maternal ratings were available for 9,432 male twins and 9,718 female twins. A total of 6,219 twins were part of an opposite-sex pair and were all included in the analyses. There were 6,338 twins from same-sex male pairs, and 6,748 twins from same-sex female pairs. Because data obtained from twin pairs are not independent, one twin was randomly selected from the same-sex twin pairs. It was not necessary to randomly select one twin from the opposite-sex twin pairs, because data from boys and girls were analysed separately. We excluded 215 twins for whom information on socio-economic status was unknown. The final twin sample consisted of 6,161 boys and 6,325 girls. For 42% of this sample data were available from one assessment, for 29% from two assessments, and for 29% from three assessments. The smaller proportion of children with two or three assessments partly reflects the longitudinal design of the study, because not all children had reached ages 10 and 12 years by the time we ran our analyses.

For 3,506 boys and 3,673 girls, teacher ratings were available as well. For 71% of this sample teacher data were available from one assessment, for 26% from two assessments, and for 3% from three assessments.

Singleton sample

The data from singletons that were analyzed in this study came from the Zuid-Holland study, an ongoing longitudinal study of behavioral and emotional problems that started in 1983. The sample (*N*=2,600) was randomly drawn from municipal registers that list all residents in the Dutch province of Zuid-Holland, and represents a general population (Verhulst, Akkerhuis, & Althaus, 1985). Written informed consent was obtained after complete description of the study to the subjects. After the first measurement in 1983, the respondents were approached biennially. The current study uses data from Time 1 (1983) to Time 5 (1991). Response rates ranged from 80 to 85% at each measurement. All children who were between 6 and 12 years at any assessment (i.e., born between 1971 and 1979) were included (*N*=662 boys; *N*=684 girls). Singleton data that were fully contemporaneous to the twin data were not available. However, the first assessment of twins born in 1986 was only 2 years removed in time from the fifth assessment of the Zuid-Holland study (i.e., 1993, and 1991, respectively). Attrition analyses on all participants of the Zuid-Holland study showed that dropouts had lower SES. However, dropouts did not have higher levels of behavioral problems based on the Total Problems scale of the Child Behavior Checklist (Bongers, Koot, Van der Ende, & Verhulst, 2003).

Because of the selected age range and the design of the Zuid-Holland study with assessments every two years, longitudinal data could be used from maximum four assessments (e.g., a child who was 6 years old at Time 1, was 12 years old at Time 4). For 39% of the sample,

there were data from one assessment, for 26% from two assessments, for 23% from three assessments, and for 12% from four assessments. Most of the children for whom data were available from just one assessment were already 11 or 12 years old at Time 1. Teacher ratings were available for 580 boys and 631 girls, and were obtained at Time 1, Time 3, Time 4, and Time 5. No information from teachers was obtained at Time 2 owing to financial constraints. The teacher response rates were above 70% at each assessment. For 59% of this sample teacher data were available from one assessment, for 29% from two assessments, and for 12% from three assessments. By design, teacher data were available from just one assessment for children who were between 9 and 12 years old at Time 1.

Measures

Attention Problems

For both twins and singletons, maternal ratings were collected with the Attention Problems (AP) subscale of the Child Behavior Checklist (CBCL/4-18) (Achenbach, 1991a). This scale includes 11 items such as "can't sit still", "daydreams", and "can't concentrate". It includes features of inattention, hyperactivity, and impulsivity. All items were scored on a 3-point scale, reflecting the occurrence of behavioral problems during the preceding 6 months: 0 if the item was not true, 1 if the item was somewhat or sometimes true, and 2 if the item was very true or often true. The 2-week test-retest correlation and the internal consistency of the AP scale are 0.83 and 0.67, respectively (Achenbach, 1991; Verhulst, Van der Ende, & Koot, 1996). Teacher ratings were collected using the Teachers' Report Form (TRF) (Achenbach, 1991b; Verhulst, Van der Ende, & Koot, 1997). Teachers were instructed to rate the child's behavior over the preceding 2 months. The AP subscale of the TRF consists of 20 items with the same response categories as the CBCL. The 6-week test-retest correlation is 0.83. The internal consistency coefficients are 0.90 in boys and 0.92 in girls (Achenbach, 1991b; Verhulst, Van der Ende, & Koot, 1997). The TRF includes extra items that capture situational-specific behaviors, such as "difficulty following directions", and "messy work". Ten items of the CBCL-AP scale and the TRF-AP scale overlap.

Socio-economic status (SES)

For the twin sample, SES was either obtained from a full description of the occupation of the parents and subsequently coded (CBS, 2001), or obtained by a nine-category classification scheme for occupations (Erikson, Goldthorpe, & Portocarero, 1979), combined with information on parental education. This information was recoded into three SES levels (i.e., low, middle, and high). For the singleton sample, SES was scored on a six-step scale of parental occupation (Van Westerlaak, Kropman, & Collaris, 1975), and was also recoded into three SES levels to allow comparison with the twin sample.

Data analysis

In order to compare growth trajectories between twins and singletons, the singleton data were reordered as a function of chronological age instead of survey year. This was done by creating age-dependent variables, equal to the ones used in the twin sample, resulting in a larger dataset with values that were missing by design (Muthén & Muthén, 1998-2007). To determine trajectories of mother-rated AP, growth mixture modeling (GMM) was used to analyze the data, separately for twins and singletons, and separately for boys and girls (Mplus Version 5) (Muthén & Muthén, 1998-2007). The trajectories were determined by latent growth factors, which model the intercepts and slopes of the individual growth trajectories. Models were tested with linear as well as quadratic effects. The latter represent a curvilinear development over time (e.g., first increasing, then decreasing). The trajectories were estimated using maximum likelihood with robust standard errors (MLR), which is robust regarding non-normality of the scores. MLR is similar to the full information maximum likelihood (FIML) method, in which missing data are not imputed, but parameters and standard errors are estimated directly using all the observed data (Wothke, 1998).

Models were fit with an increasing number of classes and different within class structures (i.e., linear and quadratic growth). There is a trade-off between within class model complexity and number of classes where more classes can compensate for a less complex within class structure (Lubke & Neale, 2008). Models with increasing numbers of classes cannot be compared with likelihood ratio tests, because in that case the test statistic does not follow a chi-squared distribution. Therefore, the optimal number of classes, and the decision between linear versus quadratic growth, was determined by the model with the smallest Bayesian information criterion (BIC). In case of small BIC differences, the more parsimonious model was chosen.

To test for twin-singleton differences in the mean intercepts and slopes of the trajectories, we fit a mixture model with the optimal number of classes simultaneously for twins and singletons. We used a group dummy variable indicating twin versus singleton as known class membership such that, effectively, a multi-group model was fitted with a mixture model within each group. The mean intercepts, mean slopes, and intercept variances were then separately tested for equality by constraining them to be equal between twins and singletons (i.e., three tests with df=3 per sex). These tests were evaluated with scaled chi-square tests using the log-likelihood values. Differences in class proportions between twins and singletons were tested by means of a standard chi-square test for cross-tables. To control for SES differences between the samples, the latent growth factors were regressed on SES. Also, class membership was regressed on SES, so that SES predicted the log odds of the probability of belonging to a given class compared with the probability of belonging to another class. Because the models were estimated conditional on SES, families without data on SES had to be excluded from the analysis.

Because of the small number of multiple assessments with teacher ratings, trajectories of teacher-rated AP could not be examined. Instead, we analyzed the age-specific mean scores with SPSS15. To test for twin-singleton differences, analysis of variance (ANOVA) was performed using two fixed factors (i.e., twin/singleton status and SES). For these analyses, a statistical significance at the level of $p<0.01$ was chosen.

Results

A total of 2,665 twins (21%) had low SES, 8,401 twins (67%) had middle SES and 1,420 twins (12%) had high SES. A total of 734 singletons (55%) had low SES, 392 singletons (29%) had middle SES, and 220 singletons (16%) had high SES. Twins and singletons were not evenly distributed over the three SES levels (χ^2 (2) = 848.26, $p<0.001$).

Table 4.1 shows the model fit statistics for the linear and the quadratic models for twins. The models were fit with within-class intercept variability, whereas all slope factor variances were fixed to zero. The intercept variances were constrained to be equal between the classes in all models. Estimating nonzero slope variances and class-specific intercept variances resulted in convergence problems for models with more than three classes, which is often an indication of overfitting (i.e., the fitted model is overly complex). For both boys and girls, a three-class linear model was the best fitting model given the LMR-LRT, BIC, and model parsimony. The quadratic models did not fit convincingly better than the linear models, as indicated by minimal BIC differences. More specifically, the BIC differences between the linear and the quadratic models were smaller than the BIC differences between the models with a different number of classes.

Table 4.2 and Figures 4.1 and 4.2 show the results for twins and singletons combined, i.e., linear three-class models, with class-specific intercept variances (BIC boys = 63945.99; BIC

Table 4.1: Growth mixture modeling model fit statistics for twins

	Classes	Linear		Quadratic	
		BIC	LMR-LRT	BIC	LMR-LRT
Boys	1	55243.60	n.a.	55235.58	n.a.
	2	54091.14	<0.001	54069.46	<0.001
	3	53449.35	<0.001	53409.63	<0.001
	4	53261.68	0.06	53210.41	0.18
Girls	1	52874.79	n.a.	52880.37	n.a.
	2	51421.16	<0.001	51425.08	<0.001
	3	50875.96	0.02	50895.03	0.22
	4	50345.62	0.10	50323.00	0.11

Note: BIC = Bayesian Information Criterion; LMR-LRT represents the *p*-value of the Lo-Mendell-Rubin likelihood ratio test (Lo, Mendell, & Rubin, 2001), which was included for comparison; n.a. = not applicable; intercept factor variances are equal across classes, slope factor variances are fixed to zero.

Table 4.2: Model results for the three-class linear model for twins and singletons

			Twins			Singletons		
			Est	*SE*	*p*-value	*Est*	*SE*	*p*-value
Boys	Class#1: stable low	I	2.06	0.10	<0.001	1.97	0.20	<0.001
		S	-0.03	0.02	0.16	0.03	0.03	0.34
	Class#2: low-increasing	I	4.04	0.19	<0.001	3.39	0.74	0.001
		S	0.83	0.14	<0.001	0.92	0.14	<0.001
	Class#3: high-decreasing	I	8.85	0.52	<0.001	8.56	0.93	<0.001
		S	-0.80	0.10	<0.001	-0.56	0.13	0.002
Girls	Class#1: stable low	I	1.13	0.08	<0.001	1.09	0.13	<0.001
		S	-0.02	0.02	0.23	0.02	0.03	0.49
	Class#2: low-increasing	I	2.66	0.19	<0.001	2.09	0.49	<0.001
		S	0.59	0.14	<0.001	0.71	0.20	<0.001
	Class#3: high-decreasing	I	6.43	0.34	<0.001	6.97	1.19	<0.001
		S	-0.60	0.07	<0.001	-0.48	0.11	<0.001

Note: BIC boys = 63945.99; BIC girls = 60683.19; I = intercept; S = linear slope; *Est* = estimated mean; *SE* = standard error; *p*-value = significance of intercept and slope means; intercept variances are freely estimated, slope variances are fixed to zero.

girls = 60683.19). The three classes differed with respect to the intercept and slope means. The results were very similar for boys and girls. The three classes were: (1) stable low (boys: 71% twins, 64% singletons; girls: 64% twins, 62% singletons); (2) low-increasing (boys: 15% twins, 15% singletons; girls: 16% twins, 18% singletons), with children whose AP scores were initially low but increased with age; and (3) high-decreasing (boys: 14% twins, 21% singletons; girls: 20% twins, 20% singletons), with children whose AP scores were initially high and decreased with age.

The intercept means of the three classes were equal between twins and singletons (boys: χ^2 (3) = 0.90, p=0.83; girls: χ^2 (3) = 0.70, p=0.87). The slope means were equal between twins and singletons (boys: χ^2 (3) = 4.82, p=0.19; girls: χ^2 (3) = 1.04, p=0.79), and the intercept variances were also equal between twins and singletons (boys: χ^2 (3) = 0.59, p=0.90; girls: χ^2 (3) = 1.83, p=0.61). Finally, the class proportions were not different for twins and singletons (boys χ^2 (2) = 1.76, p=0.41; girls χ^2 (2) = 0.15, p=0.93).

Teacher ratings

Table 4.3 presents teacher-rated AP mean scores, which are corrected for SES differences between twins and singletons. For boys, ANOVA showed that there were no main effects of twin/singleton status on levels of AP (all p values >0.01). For girls, twins had significantly lower AP scores at age 12 than singletons (p<0.001). There were no main effects of twin/singleton status on AP scores for ages 6-11 years.

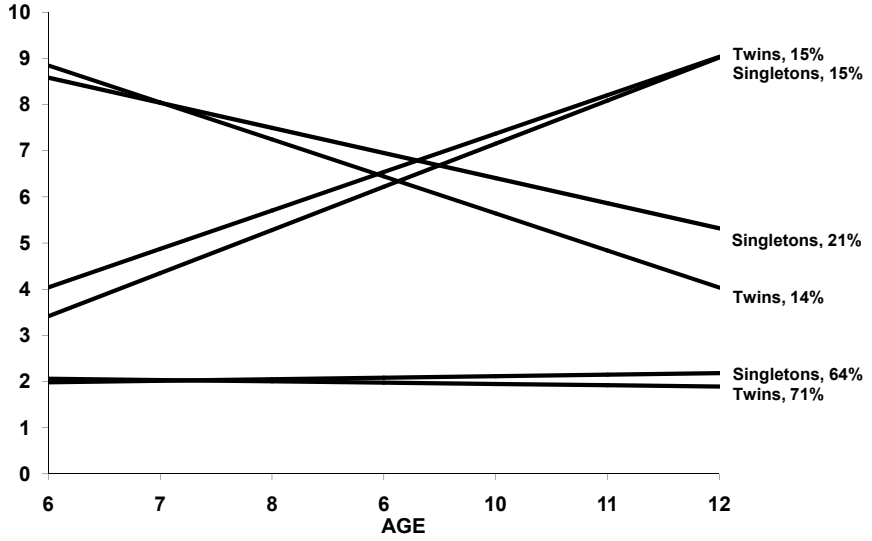

Figure 4.1: Trajectories of mother-rated Attention Problems for boys

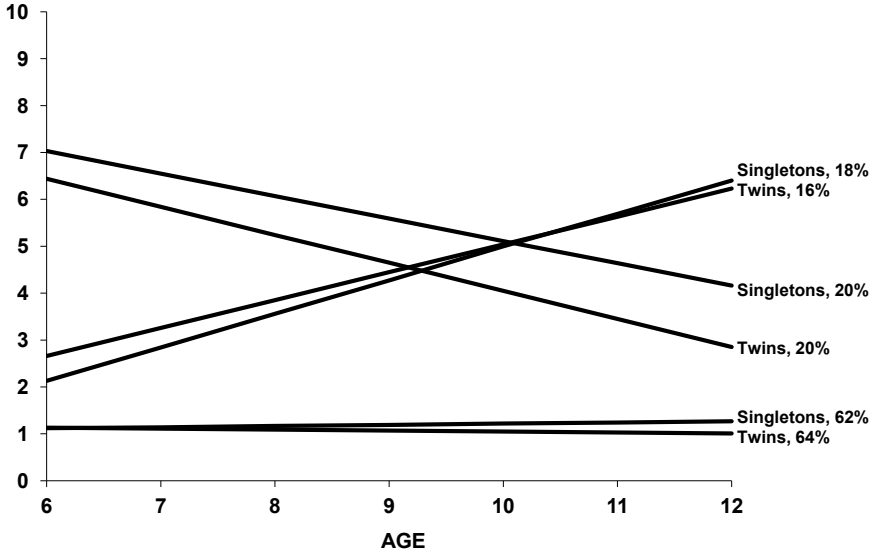

Figure 4.2: Trajectories of mother-rated Attention Problems for girls

Table 4.3: Estimated means for teacher-rated Attention Problems corrected for SES

	Age	Twins			Singletons		
		N	Mean	*SE*	*N*	Mean	*SE*
Boys	6	49	7.43	1.30	58	6.06	1.06
	7	1673	6.34	0.21	57	7.79	0.89
	8	177	7.53	0.59	100	5.72	0.74
	9	552	7.05	0.37	114	8.09	0.69
	10	1053	7.17	0.28	154	7.14	0.56
	11	367	6.62	0.44	168	7.22	0.59
	12	748	6.09	0.32	194	6.91	0.51
Girls	6	46	3.71	0.77	67	2.60	0.61
	7	1699	3.84	0.16	71	3.35	0.61
	8	177	4.42	0.55	92	4.17	0.67
	9	641	4.00	0.27	133	3.63	0.48
	10	1045	4.02	0.22	159	4.17	0.42
	11	404	3.76	0.34	200	4.68	0.41
	12	778	3.23	0.21	199	4.55	0.34*

Note: Due to the longitudinal design, the *N*'s do not add up to the total number of children; *N* = number of observations; *SE* = standard error; * = significant twin-singleton mean difference ($p<0.001$).

Discussion

In this longitudinal study, we identified three linear trajectories of mother-rated Attention Problems in boys and girls from 6 to 12 years: stable low, low-increasing and high-decreasing symptom levels. Most of the children followed the stable low trajectory, which is what we hypothesized. Further, we expected two other stable trajectories with a possible decrease late in childhood. Instead of these stable trajectories, we found a low-increasing trajectory, and a high-decreasing trajectory.

Our findings are in agreement with the study from Malone, et al. (2010) which identified three trajectories that, when considering children from middle childhood until early adolescence, included increasing and decreasing classes. Van Lier, et al. (2007) also identified a high-increasing trajectory in children from the Zuid-Holland Study using the DSM-oriented ADHD scale of the CBCL. Two earlier studies that reported a stable high trajectory included children with already elevated risk (i.e., parental alcoholism, and low-socioeconomic position) (Jester, et al., 2005; Nagin & Tremblay, 1999). It is possible that a stable high trajectory only presents in high risk populations, or populations characterized by low use of pediatric health care. In the US low-socioeconomic groups have a lower use of pediatric care, while there is no association between SES and help seeking in The Netherlands, where there are no major financial constraints to receiving professional help (Zwaanswijk, Verhaak, Bensing, Van der Ende, & Verhulst, 2003). It could also be that a stable high trajectory appears only in children with both attention deficits and hyperactivity problems. In a general population study, it may be more likely that a decreasing trajectory appears, in accordance with theory that attention

deficits diminish as self-regulation increases, and in response to adequate treatment. These reasons may explain why a stable high trajectory was not identified in our study.

It might be argued that a fourth class should be included, both for the boys and the girls. However, an additional class did not provide additional information, and appeared to split the high-decreasing trajectory into two ordered classes. This seems to be an example of a so-called 'indirect interpretation of mixture models' where classes do not represent different types of subjects, but rather approximate different parts of the joint distribution of observed data. Not including the fourth class does not change the conceptual interpretation of the modeling results.

Mean parent-rated AP scores larger than 9 (up to age 11) or 10 (age 12) are in the subclinical range, and scores larger than 12 (up to age 11) or 13 (age 12) are considered clinical (Achenbach, 1991). None of the trajectories exceeded these levels at any age. A post hoc analysis among the boys showed that 2.3% of the twins and 4.5% of the singletons had mean AP scores of 9 or higher on at least two assessments. About two-third of these children were assigned to the high-decreasing trajectory. Because DSM diagnoses of ADHD were not available, we could not investigate whether children with specific ADHD-subtypes would tend to be either in the low-increasing or high-decreasing class. However, it was found that children with a low AP-score obtained a negative ADHD diagnosis in 96% of the cases (Derks, Hudziak, Dolan, Ferdinand, & Boomsma, 2006). Furthermore, children with a high AP-score obtained a positive diagnosis in 59% (boys) and 36% (girls) of the cases. Because hyperactivity tends to decrease over time (Larsson, Dilshad, Lichtenstein, & Barker, 2011), we hypothesize that children with the hyperactive-impulsive or the combined type of ADHD would be overrepresented in the high-decreasing trajectory. Children on the low-increasing trajectory seem at risk for having high levels of ADHD symptoms later in childhood. As this risk may arise from a combination of several genetic, biological and environmental factors (Larsson, Dilshad, Lichtenstein, & Barker, 2011; Singh, 2008), further research is needed to identify specific predictors of the trajectories.

Linear growth provided the best description of the development of Attention Problems for the observed time. Attention deficits may increase during childhood as academic demands, such as demands on impulse control and response inhibition, increase. Linearity does however not mean that the regression line will go up indefinitely, but that linear models best describe the observed time (6-12 years). With longer follow-up of these children a quadratic model could provide support for declining levels of Attention Problems in adolescence.

The second aim of this study was to investigate if similar trajectories could be identified in singletons. For both boys and girls, singletons followed three trajectories identical to twins, with similar class proportions. The mean intercepts and slopes of the trajectories did not differ between twins and singletons. Therefore, we conclude that twins and singletons are comparable with respect to the development of ADHD symptoms in childhood. The findings from the teacher ratings support this conclusion, as we observed no consistent differences in the

mean AP scores between twins and singletons. This conclusion confirms the generalizability of twin studies to singleton populations with regard to ADHD symptoms in middle and late childhood. Our findings are in agreement with a cross-sectional twin-singleton comparison, in which twins were compared to their non-twin siblings, that reported no consistent differences with respect to the prevalence of ADHD (Ehringer, Rhee, Young, Corley, & Hewitt, 2006).

This is the first study that investigates trajectories of Attention Problems in middle childhood in the general population. Strengths of the study are the use of prospective data over a 6-year period, the representativeness of the samples, large sample sizes, and the use of advanced person-centered statistical analyses. Nevertheless, several limitations of this study must be considered. First, there was a modest association of non-response with SES, which may have led to underestimating the proportion of children in the high-decreasing and the low-increasing trajectories, especially in the twin sample. Also, the twin and singleton samples differed with respect to SES, with a higher proportion of twins from higher SES backgrounds. The singleton sample consists of families who were randomly selected from municipal registers, after which participation was strongly pursued, e.g., by means of home-visits, making participants (especially those from low SES) more likely to participate. In contrast, the twin sample depends on voluntary participation and families are encouraged to remain on the register, even when they do not take part in each survey for which they are approached. Secondly, the twin and singleton samples were comprised of different cohorts. For twins, birth cohort did not predict mean AP scores at ages 7, 10 and 12 (Derks, 2006). For singletons, an earlier study did not find evidence for secular changes in parent-rated AP over a 10-year period (1983-1993), but small secular changes were reported for teacher-rated AP (Verhulst, Van der Ende, & Rietbergen, 1997). Similarly, small increases in Dutch children's parent- and teacher-rated AP scores were found over a 20-year period (1983-2003) (Tick, Van der Ende, & Verhulst, 2007). As these differences were very small (Cohen's d<0.2), it is unlikely that cohort effects confound our findings. Thirdly, the twin and singleton samples were recruited from different regions of the country (data collection is nation-wide for twins, whereas for singletons a specific part of the country is included). However, an earlier study that showed there were no significant differences in CBCL scale scores between children living in Zuid-Holland and children living elsewhere in The Netherlands (Tick, Van der Ende, & Verhulst, 2007).

Conclusion

In conclusion, the development of Attention Problems in boys and girls from age 6 to 12 years can be characterized by stable low, low-increasing, and high-decreasing developmental trajectories. Our findings confirm that twins are not a more vulnerable group than singletons with respect to the development of Attention Problems in childhood, and that results from twin studies regarding ADHD symptoms can be generalized to singleton populations. As our

results and interpretations apply only to children in the age range of 6 to 12 years, future research should extend our findings by describing trajectories of Attention Problems from childhood to adulthood.

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Chapter 5

Pre-divorce problems in 3-year-olds: a prospective study in boys and girls

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Social Psychiatry and Psychiatric Epidemiology, 2011, 46(4), 311-319

Abstract

Objective: We examined to what extent internalizing and externalizing problems at age 3 preceded and predicted parental divorce, and if divorce and the time lapse since divorce were related to internalizing and externalizing problems at age 12.

Methods: Parental ratings of internalizing and externalizing problems were collected with the Child Behavior Checklist (CBCL) in a large sample (*N*=6,426) of 3-year-old children. All these children were followed through the age of 12 years, at which parents completed the CBCL again, while teachers completed the Teacher's Report Form. Children whose parents divorced between age 3 and age 12 were compared with children whose families remained intact.

Results: Girls whose parents divorced between ages 3 and 12 already showed more externalizing problems at age 3 than girls whose parents stayed married. Higher levels of externalizing problems in girls at age 3 predicted later parental divorce. Parental reports indicated that 12-year-olds with divorced parents showed more internalizing and externalizing problems than children with married parents. Levels of teacher-reported problems were not different between children with married versus divorced parents. However, children whose parents divorced between ages 3 and 12 showed more teacher-rated internalizing problems at age 12 when the divorce was more recent than when the divorce was less recent. Parental ratings of both internalizing and externalizing problems at age 12 were not associated with the time lapse since divorce.

Conclusion: Externalizing problems in girls precede and predict later parental divorce. Post-divorce problems in children vary by raters, and may depend on the time lapse since divorce.

Introduction

Each year 70,000 children in The Netherlands experience parental divorce (Spruijt, 2007). This is 1.5% of the total number of Dutch children under the age of 21. An increase in divorce rates from 24% in 1980 to 34% in 2007 (CBS, 2008) has been observed. There is a general belief that parental divorce has negative effects on the well-being of their offspring. Parental divorce is associated with children's externalizing problems, such as aggression and rule-breaking behavior, and with internalizing problems, such as anxiety and depression (Amato, 2000; Hetherington & Stanley-Hagan, 1999). On an average, children with divorced parents are emotionally, socially and academically less well adjusted than children with married parents (Amato & Keith, 1991; Kelly, 2000). However, most studies assessed children's problems using only parents as a source of information. It is known that different informants, such as parents, teachers, or children themselves may differ in their reports of problems in the same child (Achenbach, McConaughy, & Howell, 1987). Although different, these reports reflect information that may be valid in its own way. Different informants may differ in the way they perceive problems, see children in different contexts, or interact with the child in different ways (Bartels, Boomsma, Van Beijsterveldt, Hudziak, & Van den Oord, 2007). Because conclusions based on multiple informants may give a more complete picture, we chose to use information of both parents and teachers on children's problems in the present study.

The etiology behind the association between parental divorce and children's problems is still unclear. Cross-sectional studies that compared children of married versus divorced parents can not provide insight into the direction of the relationship between the experience of parental divorce and children's problems. Prospective studies that begin before the children's parents divorce are sparse, but show that some of the differences between children who experienced parental divorce and those who did not were already present before the divorce occurred. For instance, the behavior of 3-, 4- and 7-year-old boys was more problematic as early as 11 years prior to parental divorce than that of boys who did not experience parental divorce (Block, Block, & Gjerde, 1986). Because the effect was not found for girls, the authors concluded that pre-divorce stress may affect girls and boys differently. Boys and girls aged 4-11 whose parents later divorced within 4 years after initial assessment showed higher levels of anxiety, depression and antisocial behavior than those children whose parents remained married (Strohschein, 2005). Problems in parent-child relationships were found 8-12 years before divorce (Amato & Booth, 1996). Another study showed that the apparent effect of divorce on behavioral problems in 11-year-old children appeared to be sharply reduced when pre-existing problems were taken into consideration (Cherlin, et al., 1991). Finally, parents of youths diagnosed with ADHD in childhood were more likely to divorce and had a shorter latency to divorce when compared with parents of children without ADHD (Wymbs, et al., 2008). Taken together, behavioral problems may already be present in children long before the divorce actually occurs. These findings suggest that it is not the divorce per se that causes

problems in children, and they may indicate characteristics of the children or their parents that influenced the parents' marriages and the children's lives (Cherlin, Chase-Lansdale, & McRae, 1998).

Previous studies on pre- and post-divorce child problems do not sufficiently address both internalizing and externalizing problems and problems as reported by multiple informants, in particular teachers. In addition, a methodological problem in many previous studies is the lack of availability of children's age at the time of the divorce (Amato, 2001; Lansford, 2009). Lansford, et al. (2006) addressed these issues, but they measured child problems ranging only from 1 year prior to 3 years after divorce (Lansford, et al., 2006). The present study compared internalizing and externalizing problems in a large sample of 3-year-old children (*N*=6,426), who were followed through the age of 12 years. Children whose parents divorced or separated between the two time points were at both ages compared to children whose families stayed intact. Maternal, paternal and teacher reports were used to obtain information about children's behavioral problems. Because we had a large sample of children, we were able to investigate the associations between parental divorce and children's behavior problems separately for boys and girls. We expected that at the age of 12 years, boys and girls with divorced parents would show higher levels of internalizing and externalizing problems than boys and girls with married parents. More importantly, we expected that both boys and girls who had experienced parental divorce by the age of 12 years would already show higher levels of problems at the age of 3 years than those children whose parents remained married. We examined to what extent child problems at age 3 predicted parental divorce, and if child problems at age 12 were related to the time lapse since the divorce. It is sometimes assumed that children have more short-term adjustment difficulties immediately after their parents' divorce, and that these difficulties may lessen in severity following an adjustment period (Chase-Lansdale & Hetherington, 1990). Therefore, we hypothesized that children have more problems at age 12 when they experienced the divorce more recently as opposed to less recently. Furthermore, we hypothesized that higher levels of internalizing and externalizing problems at age 3 would predict parental divorce between the ages of 3 and 12 years. Finally, the prevalence of internalizing problems shows no gender differences at ages 3 and 12, whereas externalizing problems are more prevalent in boys versus girls at both ages (Bartels, et al., 2003; Van der Valk, Van den Oord, Verhulst, & Boomsma, 2001). In the current study, we expect to find similar sex patterns.

Methods

Sample and procedure

Data were used from a longitudinal twin-family study that examines causes of individual differences in health, growth, and the development of behavioral and emotional problems. All participating families are volunteer members of the Netherlands Twin Registry (NTR), established by the Department of Biological Psychology at the VU University in Amsterdam (Bartels, Van Beijsterveldt, et al., 2007; Boomsma, et al., 2006). The study protocol was approved by the ethics committee of the VUMC (VU University medical centre), Amsterdam. For the present study, data from twins born between 1986 and 1993 were analyzed. Parents of twins received surveys by mail within 3 months of the twins' 3rd, 7th, 10th and 12th birthdays; 2-3 months after these mailings, reminders were sent to the non-responders. Parents were invited to participate at each wave of data collection, regardless of their previous participation. Furthermore, surveys were sent to teachers after written permission was given by the parents. The absolute parental response rate at each measurement was 62%. The teacher response rate was 74%. Data were available for 6,426 children. There were 3,139 boys (49%) and 3,287 girls (51%).

Measures

Internalizing and externalizing problems

When the children were 3 years old, mother and father ratings were collected with the Child Behavior Checklist (CBCL/2-3) (Achenbach, 1992). The CBCL/2-3 was developed for parents to score the behavior of their 2- and 3-year-old children. It consists of 100 items that are scored on a 3-point scale that is based on the occurrence of the behavior during the 2 months prior to the survey: 0 if the problem item was not true, 1 if the item was somewhat or sometimes true, and 2 if it was very true or often true. The Internalizing scale comprised the Anxious and Withdrawn/Depressed syndromes, and consisted of 19 items; the Externalizing scale comprised the Oppositional, Aggressive, and Overactive syndromes, and consisted of 31 items (Koot, Van den Oord, Verhulst, & Boomsma, 1997). The validity and reliability of these CBCL scales have been supported by a wide variety of studies (Koot & Verhulst, 1991). For a total of 6,192 children mother ratings of internalizing problems were available. Mother ratings of externalizing problems were available for 6,190 children. Due to financial restrictions, father ratings were not collected in all birth cohorts, and problems were available for 3,657 children.

Mother and father ratings of internalizing and externalizing problems at age 12 were collected with the Child Behavior Checklist (CBCL/4-18) (Achenbach, 1991a; Verhulst, Van der Ende, & Koot, 1996), that consists of 120 items with the same three response categories as the

CBCL/2-3. Parents were instructed to rate the child's behavior over the preceding 6 months. The good reliability and validity of the CBCL/4-18 were confirmed for the Dutch version of the measure: Cronbach's alpha was 0.84 (boys) and 0.85 (girls) for the Internalizing scale, and 0.86 (boys) and 0.85 (girls) for the Externalizing scale (Verhulst, et al., 1996). The Internalizing scale consists of the Anxious/Depressed, Somatic Complaints, and Withdrawn subscales, and consists of 31 items. The Externalizing scale consists of the Aggressive Behavior and Rule-Breaking Behavior subscales, and consists of 30 items. Mother ratings of internalizing and externalizing problems at age 12 were available for 6,245 and 6,301 children, respectively. Father ratings of internalizing problems at age 12 were available for 4,839 children, and father ratings of externalizing problems were available for 4,850 children.

Teacher ratings were collected at age 12 with the Teacher Report Form (TRF) (Achenbach, 1991b; Verhulst, Van der Ende, & Koot, 1997), that consists of 120 items with the same response categories as the CBCL/2-3 and CBCL/4-18. Teachers were instructed to rate the child's behavior over the preceding 2 months. The good reliability and validity of the TRF were confirmed for the Dutch version: Cronbach's alpha was 0.86 (boys) and 0.89 (girls) for the Internalizing scale, and 0.95 (boys) and 0.94 (girls) for the Externalizing scale (Verhulst, et al., 1997). The Internalizing and Externalizing scales consist of the same subscales as in the CBCL/4-18, however, the number of items is different: the Internalizing scale consists of 36 items, and the Externalizing scale consists of 34 items. Teacher ratings of internalizing and externalizing problems were available for 2,841 and 2,885 children, respectively. Collection of TRF ratings started halfway 1986 and TRF data were available until 1993.

Socio-economic status

Socio-economic status at age 3 was included in this study as a covariate. For about two-third of the twin sample, SES was obtained from a full description of the occupation of the parents, and SES was subsequently coded according to the Standard Classification of Occupations (CBS, 2001). For the remaining twins, SES was obtained by the EPG-classification scheme (Erikson, Goldthorpe, & Portocarero, 1979), combined with information on parental education. For all twins, the level of occupation was classified into three SES levels (1=low; 2=middle; 3=high). For 122 twins (1.9% of the sample) SES status at age 3 was unknown.

Family Status

Family status for birth cohorts 1986-1991 was assessed in surveys mailed when the children were aged 12. Family status for birth cohorts 1992 and 1993 was assessed when the children were aged 10 and 12. Marital status of the parents was defined as 'married and/or living together'. There were two items in the surveys to assess the family situation. The first item was *Which of the following statements corresponds best with the twin's current family situation?* Possible answers were (1) the biological mother and the biological father are married or are living together; (2) the biological mother and the biological father have been divorced since

…;(3) the biological mother has been deceased since…;(4) the biological father has been deceased since…;(5) different family situation, namely… The parent was able to fill in the appropriate dates on the dots, or indicate any other possible family situation. The second item was *Which of the following statements corresponds best with the twin's current living situation?* Possible answers were (1) the twin lives with both biological parents; (2) the twin lives with the biological mother only; (3) the twin lives with the biological father only; (4) the twin lives with the biological mother and her partner (not the biological father); (5) the twin lives with the biological father and his partner (not the biological mother); (6) different living situation, namely… The parent was able to indicate any other possible family living situation on the dots. In order to accurately determine family status at the child's ages of 3 and 12 years, the information from both items was combined.

When parents indicated to be divorced, we needed to determine if they were already divorced when they completed the CBCL/2-3. Therefore, the date of divorce was compared to the date the parents completed the CBCL/2-3. If parents did not indicate the date they completed the CBCL/2-3, we checked whether the divorce took place before or after age 3 years of their children. If their children were younger than 4 years at the time of the divorce, we considered the parents to be divorced when they completed the CBCL/2-3.

Dataset

The original dataset consisted of 8,664 twin pairs. Twin pairs were excluded from the current study if there was a maternal or paternal death (*N*=95 twin pairs), if information on divorce could not be ascertained (*N*=261 twin pairs), if the twin pairs did not live with their biological parents (*N*=18 twin pairs), or if parents did not indicate the date of their divorce (*N*=17 twin pairs). For about half of the twin pairs in the dataset (*N*=4,424 twin pairs) no information was available at age 12, which can be explained by the presence of children from birth cohorts later than 1993 who had not yet reached the age of 12 years. The remaining dataset with 3,849 twin pairs represented a total of 7,698 children. From this sample, children were further excluded if no behavioral information was available at age 3 (*N*=1,108 children) and if parents were already divorced by the time the CBCL/2-3 was completed (*N*=164 children). The final sample consisted of 6,426 children, who were divided into two groups: (1) 5,946 (92.5%) children (2,887 boys and 3,059 girls) whose parents were still married when they reached the age of 12 years; (2) 480 (7.5%) children (252 boys and 228 girls) whose parents divorced when they were between 3 and 12 years old.

Strategy of analysis

Mean problem scores were estimated in Mplus Version 5 (Muthén & Muthén, 1998-2007) using maximum likelihood with robust standard errors (MLR). MLR adjusts for non-independence and non-normality of the scores (Muthén & Muthén, 1998-2007). For all mean comparisons, we used MLR chi-square difference testing, in which the MLR chi-square is equal to the obtained chi-square divided by the scaling correction factor (Muthén & Muthén, 2005). We allowed for the analysis of cases with missing values because: (1) not all children had both internalizing and externalizing scores at each age; (2) not for all children problem scores from all three informants were available; (3) information on socio-economic status was not available for all children. First, we tested for group differences in sex and in socio-economic status, and for sex differences in the internalizing and externalizing problem scores at ages 3 and 12. Then, we tested if the mean problem scores differed between the two groups of offspring of divorced and non-divorced parents at both age 3 and 12 years.

To examine if internalizing and externalizing problems at age 3 predicted parental divorce, we carried out continuous-time survival analyses (Cox regressions) in Mplus while again controlling for the dependency between the scores of twins and for socio-economic status. The estimator used in these analyses was again MLR. A non-parametric baseline hazard function was applied. Survival time was considered 'the number of months from completion of the CBCL/2-3 to the actual divorce'. We created this variable by means of the child's age in months at the time of the divorce. We tested for interaction effects of sex with the predictors, i.e., the internalizing and externalizing problem scores at age 3. The results are presented as the log odds of the incremental probability of divorce for a one unit change in the predictors.

To examine the association between the time lapse since divorce and internalizing and externalizing problems at age 12, regression analyses were conducted with the number of months from completion of the CBCL/2-3 to the actual divorce as the predictor variable (divorce interval). For these analyses, children were selected whose parents divorced between ages 3 and 12. Data from boys and girls were analyzed simultaneously with sex and SES added as additional predictors in the model, and we tested for interaction effects of divorce interval with sex. We again used MLR to control for the dependency between twins. For all analyses, a statistical significance at the level of $p<.05$ was chosen.

Results

For parent-reported internalizing problems the scores ranged from 0 to 28 at age 3, and from 0 to 49 at age 12. The scores for parent-reported externalizing problems at age 3 ranged from 0 to 55; at age 12 these scores ranged from 0 to 50. Teacher-reported internalizing problems at age 12 ranged from 0 to 37, and teacher-reported externalizing problems at age

12 ranged from 0 to 52. The age 3 problem scores correlated moderately with the parent-reported problem scores at age 12 (r=0.26-0.44). The TRF scores correlated moderately with the CBCL ratings at age 12 (r=0.24-0.38). Sex was equally distributed between the two groups of children (χ^2 =2.768, p=0.10). No sex differences were found for internalizing problems at both ages. For externalizing problems, boys had higher problem scores than girls at both ages and according to all informants (p-values <0.001).

Tables 5.1 (mother ratings), 5.2 (father ratings), and 5.3 (teacher ratings) display the means and standard errors of the internalizing and externalizing problem scores at age 3 and age 12 per group. All means are within the normal range (Koot & Verhulst, 1991), and were corrected for the dependency between twins and for socio-economic status at age 3.

The mean problem scores of children with married parents were compared with those of children whose parents divorced between the ages of 3 and 12. Divorced parents reported more internalizing and externalizing problems in their 12-year-old children than married parents (p-values <0.05). However, according to the teachers, there was no significant difference

Table 5.1: Means and standard errors of internalizing and externalizing problems at age 3 and 12 of married and divorced children as rated by the mother

		Married until age 12	Divorced between age 3 and 12	MLR χ^2 diff.	p-value
Age 3 Internalizing	Boys	4.54 (0.08)	4.67 (0.24)	0.124	0.72
	Girls	4.45 (0.09)	4.85 (0.34)	1.639	0.20
Age 3 Externalizing	Boys	16.49 (0.23)	17.08 (0.74)	0.426	0.51
	Girls	14.52 (0.21)	17.04 (0.82)	11.438	<0.001
Age 12 Internalizing	Boys	4.18 (0.11)	5.92 (0.47)	37.956	<0.001
	Girls	4.32 (0.10)	6.27 (0.50)	62.256	<0.001
Age 12 Externalizing	Boys	6.98 (0.16)	8.36 (0.53)	10.066	<0.01
	Girls	4.71 (0.11)	7.06 (0.45)	125.024	<0.001

Note: The means of the internalizing and externalizing problem scores are corrected for SES at age 3 and for the dependency between twins.

Table 5.2: Means and standard errors of internalizing and externalizing problems at age 3 and 12 of married and divorced children as rated by the father

		Married until age 12	Divorced between age 3 and 12	MLR χ^2 diff.	p-value
Age 3 Internalizing	Boys	4.37 (0.10)	4.28 (0.28)	0.058	0.81
	Girls	4.27 (0.10)	4.88 (0.41)	3.164	0.08
Age 3 Externalizing	Boys	15.46 (0.25)	16.07 (0.76)	0.441	0.51
	Girls	13.82 (0.23)	16.38 (0.92)	11.575	<0.001
Age 12 Internalizing	Boys	3.45 (0.11)	5.46 (0.57)	23.411	<0.001
	Girls	3.25 (0.09)	5.18 (0.54)	102.630	<0.001
Age 12 Externalizing	Boys	6.21 (0.16)	7.72 (0.77)	4.150	0.04
	Girls	4.02 (0.11)	5.90 (0.54)	77.567	<0.001

Note: The means of the internalizing and externalizing problem scores are corrected for SES at age 3 and for the dependency between twins.

Table 5.3: Means and standard errors of internalizing and externalizing problems at age 12 of married and divorced children as rated by the teacher

		Married until age 12	Divorced between age 3 and 12	MLR χ^2 diff.	p-value
Age 12 Internalizing	Boys	4.58 (0.18)	5.21 (0.60)	1.682	0.19
	Girls	4.31 (0.16)	4.98 (0.56)	0.303	0.58
Age 12 Externalizing	Boys	6.16 (0.27)	6.68 (0.96)	1.611	0.20
	Girls	2.69 (0.17)	2.74 (0.66)	0.005	0.94

Note: The means of the internalizing and externalizing problem scores are corrected for SES at age 3 and for the dependency between twins.

in the level of internalizing and externalizing problems between children of married versus divorced parents. At age 3, girls whose parents later divorced showed more externalizing problems than girls whose parents stayed married (p<0.001 for both mother and father ratings). Boys whose parents divorced after age 3 did not show more externalizing problems at age 3 than boys whose parents stayed married. Children whose parents divorced after age 3 did not show more internalizing problems at age 3 than children whose parents stayed married. Mother and father ratings showed the same pattern of results.

Continuous-time survival analyses were carried out to examine if the levels of problems at age 3 predicted divorce. The survival time, which was the number of months in which parental divorce took place, ranged from 0 to 102 months, indicating that parental divorce took place at a maximum child age of 12.5 years. The mean number of months between age 3 and parental divorce was M = 49.78 (SD = 27.64), which corresponds with the child's age of 8 years. A total of 21% of the 'divorcing' children experienced parental divorce between the ages of 4 and 6, and 75% of these children had experienced parental divorce by the age of 10. Sex of the child did not significantly predict parental divorce (p=0.15), when entered in the model as a sole predictor. All sex interactions significantly predicted divorce (p<0.05), except for the interaction of sex with mother ratings of internalizing problems (p=0.68). Mother and father ratings of externalizing problems and father ratings of internalizing problems were, therefore, further analyzed per sex. The survival analyses indicated that the level of girls' externalizing problems significantly predicted parental divorce (log odds mother ratings = 0.025, SE=0.008, p<0.01; log odds father ratings = 0.039, SE=0.010, p<0.001). Internalizing problems and boys' externalizing problems did not significantly predict parental divorce.

Next, the association between divorce interval and child problems at age 12 was investigated. There was a main effect of divorce interval on teacher-rated internalizing problems (β=0.03, p=0.04), implying that children who had experienced parental divorce more recently had more internalizing problems than children who had experienced the divorce less recently. The interactions with sex were only significant for mother-rated externalizing problems (β=0.04, p=0.04): for boys there was a trend to show fewer externalizing problems at age 12 if the divorce was more recent (β=-0.04, p=0.06), while for girls this effect was not significant.

Discussion

In numerous studies over the past decades, children of divorced parents have been reported to show more behavioral problems than children of married parents (Amato & Keith, 1991; Hetherington & Stanley-Hagan, 1999). Our study yielded similar results: when boys and girls from married and divorced families were compared at the age of 12 years, we found that divorced parents reported more problems in their children than married parents. However, teacher ratings of internalizing and externalizing problems did not reveal any significant differences between children from married and divorced parents. This finding is in line with an earlier study in Chinese children that found that teachers reported less differences between children of married and divorced parents than their parents did (Liu, et al., 2000). This inconsistency between parental and teacher reports may indicate that children differ in the context in which they manifest their behavioral problems, divorced parents may over-report children's problems or they may be more sensitive to them, or teachers and parents differ in their knowledge of normative child behaviors. When compared with teachers, mothers have less knowledge of normative child behaviors on which to base their judgments, which may result in more immoderate assessments of children's behaviors (Campbell, 2002; Miner & Clarke-Stewart, 2008). Over-reporting could be due to parental characteristics, such as anxiety or depression (Fergusson, Lynskey, & Horwood, 1993), to parents' concern about their children's mental health, or to their own distress associated with the divorce (Liu, et al., 2000). Our results seem in contrast with findings that divorced parents may tend to underestimate their children's problems (Amato & Keith, 1991). As the long-term impact of divorce could be different between the sexes (Pirkola, et al., 2005), it would be interesting to extend our study with adult behavioral and emotional problems of these children.

We found evidence for pre-divorce externalizing problems in 3-year-old girls. This finding suggests that at least part of the higher levels of parent-reported externalizing problems in 12-year-old girls is not likely to be caused by the parental divorce, but by conditions that existed well before the divorce occurred. Furthermore, not only were the mean levels of problems of girls whose parents divorced between the ages of 3 and 12 higher than those of girls whose parents stayed married, but girls' externalizing problems also significantly predicted later parental divorce. Our finding is in line with earlier research that showed that marital conflict predicted changes in children's behavior, but that at the same time children's behavior also predicted an increase in marital conflict (Jenkins, Simpson, Dunn, Rasbash, & O'Connor, 2005). Unfortunately, our results do not provide any insight into the reasons why girls and not boys showed pre-divorce externalizing problems and why only girls' behavior problems predicted parental divorce. It could be the case that increased levels of externalizing problems are more notable in girls than in boys, and may evoke more familial stress. In contrast with our hypotheses, we did not find evidence for pre-divorce internalizing problems. The higher

levels of internalizing problems in children of divorced parents at age 12 appear to be due, at least in part, to the parental separation.

An often-mentioned and investigated explanation for pre-divorce problems in children is the presence and the level of marital conflict and familial stress preceding the actual marital break-up (Bryner, 2001; Kelly, 2000). An overwhelming number of studies have demonstrated associations between marital conflict and childhood problems (Cummings & Davies, 2002). Parental conflict appears to be a more important predictor of child psychopathology than the divorce itself (Kelly, 2000). Although the maximum time interval to divorce in our study was large (9 years), it is possible that part of the observed pre-divorce externalizing problems in girls is due to marital conflict. Another explanation for pre-divorce problems may be found in genetics. Parental divorce increases the likelihood that offspring will divorce (Amato, 1996) and it has been suggested that divorce risk is heritable (McGue & Lykken, 1992). The heritability of divorce risk could be due to genetic transmission of personality traits that make individuals liable to divorce. A study from the Minnesota Twin Registry showed for example that for women and men, respectively, 30 and 42% of the association between personality and divorce was accounted for by genetic factors (Jockin, McGue, & Lykken, 1996). An association between personality and divorce has been found in many studies. For example, extraversion and neuroticism appear to be positively related to risk of divorce (Eysenck, 1980; Kelly & Conley, 1987). Like divorce risk, internalizing and externalizing problems are influenced by genetic factors. These explain about 50% of the variance of internalizing and externalizing problems at ages 3 and 7, indicating an inborn vulnerability to child psychopathology (Bartels, et al., 2004; Van der Valk, et al., 2001). Because both divorce risk and problem behaviors have a strong genetic basis, a likely hypothesis is that the association between divorce and internalizing or externalizing problems does not exist because divorce causes these problems or vice versa, but because genetically influenced correlated factors account for the association. A number of studies addressed this possibility (D'Onofrio, et al., 2007; D'Onofrio, et al., 2006; O'Connor, Caspi, DeFries, & Plomin, 2000; O'Connor, Caspi, DeFries, & Plomin, 2003) and found evidence for genetic factors influencing the associations between parental divorce and offspring problems. Our findings with regard to girls' externalizing problems endorse the results of these behavioral genetic studies. We suggest that a shared genetic tendency in a family to exhibit increased levels of externalizing behaviors, could contribute to parents' marital distress and divorce, and to children's behavioral problems.

Children showed more teacher-rated internalizing problems at age 12 when the divorce was more recent as opposed to less recent. However, this association was not observed for parent-rated problems at age 12. Therefore, the belief that children have more short-term adjustment difficulties immediately after their parents' divorce, and that these difficulties may lessen in severity following an initial adjustment period, may have limited validity. Alternatively, shortly after divorce parents may be less sensitive to the behavioral and emotional problems of their offspring. To the best of our knowledge, there are no other studies that

have used an indicator of children's ages at the time of their parents' divorce, and that have accounted for the time lapse to the divorce in their analyses. Further research is therefore needed to explore these effects.

Powerful and unique aspects of this study are the large number of participating families, the accurate measurement of the time lapse to the divorce, the large time span between the two behavioral assessments, and the use of multiple informants. Beside these strong aspects, some limitations of the current study need to be mentioned. First, the use of twins for studies of normal behavioral development is still a topic of debate, because the behavioral development of twins and singletons could be different. However, a recent study confirmed the generalizability of results from twin studies to singletons with regard to externalizing problems in middle and late childhood. Twin-singleton differences in internalizing problems were only found in early adolescence (Robbers, et al., 2010). In addition, the general level of problem behaviors in twins at age 3 is broadly comparable to that in singletons (Van den Oord, Koot, Boomsma, Verhulst, & Orlebeke, 1995). Second, we can not determine whether the observed frequency of divorce in our twin sample is representative for the general population. However, when considering that in general about one-third of all marriages end in divorce, the divorce frequency observed in our sample does not seem to be outside the range of normal expectation. Third, we derived divorce status at age 3 from information collected at a later time (i.e., at age 7, 10 and 12). Although unlikely, this may have caused unreliability of divorce status at age 3 in some cases due to recall bias. Fourth, the classification system to determine socio-economic status was not the same for all children. However, we believe we adequately combined the two classification systems, to retrieve a representative measure of socio-economic status. Finally, it would be informative to include other covariates, such as the level of marital conflict at several time points.

Conclusion

Externalizing problems in girls precede and predict later parental divorce. Post-divorce problems in children vary by raters, and may depend on the time lapse since the divorce. Future research should prospectively measure both marital conflict, timing of divorce, and pre- and post-divorce child problems using multiple raters to increase our understanding of the etiology of pre-divorce problems in children. In addition, it is of interest to extend our study with adult behavioral and emotional problems in offspring from divorced families.

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Chapter 6

Childhood problem behavior and parental divorce: evidence for gene-environment interaction

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Social Psychiatry and Psychiatric Epidemiology, 2012. Advance online publication. doi: 10.1007/s00127-011-0470-9

Abstract

Objective: The importance of genetic and environmental influences on children's behavioral and emotional problems may vary as a function of environmental exposure. We previously reported that 12-year-olds with divorced parents showed more internalizing and externalizing problems than children with married parents, and that externalizing problems in girls precede and predict later parental divorce. The aim of the current study was to investigate whether genetic and environmental influences on internalizing and externalizing problems were different for children from divorced versus non-divorced families.

Methods: Maternal ratings on internalizing and externalizing problems were collected with the Child Behavior Checklist in 4,592 twin pairs at ages 3 and 12 years, of whom 367 pairs had experienced a parental divorce between these ages. Variance in internalizing and externalizing problems at ages 3 and 12 was analyzed with biometric models in which additive genetic and environmental effects were allowed to depend on parental divorce and sex. A difference in the contribution of genetic and environmental influences between divorced and non-divorced groups would constitute evidence for gene-environment interaction.

Results: For both pre- and post-divorce internalizing and externalizing problems, the total variances were larger for children from divorced families, which was mainly due to higher environmental variances. As a consequence, heritabilities were lower for children from divorced families, and the relative contributions of environmental influences were higher.

Conclusion: Environmental influences become more important in explaining variation in children's problem behaviors in the context of parental divorce.

Introduction

Previous studies in twins and adoptees showed a substantial heritability in internalizing and externalizing problems over childhood (Bartels, et al., 2004; Boomsma, Van Beijsterveldt, & Hudziak, 2005; Haberstick, Schmitz, Young, Hewitt, 2005; Huizink, Van den Berg, Van der Ende, & Verhulst, 2007). Bartels, et al. (2004) showed that the heritability of internalizing problems decreased during childhood from 59% at age 3 to 37% at age 12, and the contribution of shared environmental influences increased over time from 13% at age 3 to 37% at age 12. For externalizing problems, small increases in heritability were observed for boys from age 3 (57%) to age 12 (64%), whereas for girls the influences of genetic (50%) and environmental factors remained stable over this period. Significant genetic and shared environmental influences have also been reported for anxious-depressive and withdrawn behavior at age 12 (Lamb, et al., 2010).

In addition to differences in heritability as a function of age and sex, genetic effects may also be conditional on environmental exposures, a process often referred to as gene-environment interaction (GxE) (Franic, Middeldorp, Dolan, Ligthart, & Boomsma, 2010). For the current study we were interested in the moderating role of parental divorce on the genetic architecture of internalizing and externalizing problems in children. The experience of parental divorce is often associated with higher mean levels of internalizing and externalizing problems in children (Amato, 2000; Hetherington & Stanley-Hagan, 1999; Robbers, et al., 2011). So far, little is known about a possible interaction effect of parental divorce on sources of variation in internalizing and externalizing problems.

In disadvantageous environments, heritabilities may differ from those in advantageous environments. So far, there is empirical support for both higher and lower heritabilities of child problem behaviors in the context of disadvantageous environments. Lower heritabilities in disadvantageous environments can result from the suppression of genetic effects by environmental exposures that push or predispose a child to show behavioral problems (Bronfenbrenner & Ceci, 1994; Raine, 2002; Shanahan & Hofer, 2005). Several studies reported that heritabilities are lower in disadvantageous environments. For instance, Hicks, et al. (2009) showed that the heritability of internalizing problems in 17-year-olds was lower in the context of greater environmental adversity, which included parental divorce (Hicks, DiRago, Iacono, & McGue, 2009). Also, it has been reported that the heritability of adolescent depressive symptoms was lower at higher levels of parental negativity (e.g., frequency of conflicts, punitiveness, parent-child disagreement) (Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007). Another study showed that the heritability of conduct problems in children aged 5 to 17 years dropped from 77% to 0% at high levels of family dysfunction (Button, Scourfield, Martin, Purcell, & McGuffin, 2005). The heritability of boys' antisocial behavior was lower in adolescents from families with lower socioeconomic status (Tuvblad, Grann, & Lichtenstein, 2006). A lower heritability does, however, not necessarily imply less genetic

variance. Heritability is a ratio (genetic variance divided by total phenotypic variance), so enlarged environmental variance may result in a lower heritability, even when the absolute amount of genetic variance remains the same. For instance, Feinberg, et al. (2007) showed that the amount of non-shared environmental variance was higher at high levels of parental negativity, whereas the absolute amount of genetic variance remained stable.

Alternatively, when genetic effects are triggered or amplified by disadvantageous environments, heritabilities will increase (McGue, 2010; Shanahan & Hofer, 2005). South and Krueger (2008) reported a higher heritability of internalizing problems when marital quality was lower, suggesting that persons with a genetic predisposition to internalizing problems may be more likely to express this predisposition in the context of a problematic marriage. Similarly, the heritability of child and adolescent depressive symptoms was higher when levels of family conflict were high (Rice, Harold, Shelton, & Thapar, 2006). The heritabilities of adolescent depressive symptoms and externalizing problems were higher when adolescents had experienced more stressful life events (Hicks, South, DiRago, Iacono, & McGue, 2009; Lau & Eley, 2008), and Feinberg, et al. (2007) reported that the heritability of antisocial behavior was greater at low levels of parental warmth. Regarding these previous studies that report higher as well as lower heritabilities in the context of disadvantageous environments, it is obvious that GxE findings with regard to child and adolescent psychopathology are mixed.

We previously reported in this journal that parental divorce was preceded and predicted by higher levels of externalizing problems in girls at age 3 (Robbers, et al., 2011). Furthermore, parental reports indicated that children at age 12 years with divorced parents showed more internalizing and externalizing problems than children with married parents. The aim of the current study was to investigate whether genetic and environmental influences on internalizing and externalizing problems are modified by parental divorce. Therefore, we compared the genetic architecture of internalizing and externalizing problems at ages 3 and 12 between children from divorced and non-divorced families. We expected to find the genetic architecture of pre- and post-divorce internalizing and externalizing problems to be influenced by parental divorce. However, as earlier GxE findings are mixed we could not formulate a specific hypothesis about the direction of effects.

A unique aspect of this study is that all families were still intact at age 3, and a subgroup of children experienced parental divorce between ages 3 and 12 years. This way, we were able to investigate variation in pre-divorce and post-divorce internalizing and externalizing problems in children. Another unique aspect is the large sample size of 4,592 twin pairs. Because the genetic architecture of child problem behaviors may be different for boys and girls (Bartels, et al., 2004), and because the moderating effect of parental divorce may depend on sex (Van der Aa, Boomsma, Rebollo-Mesa, Hudziak, & Bartels, 2010), we took divorce, sex, age, and the interaction of sex by divorce into account as moderators.

Methods

Sample and procedure

All participating families are members of the Netherlands Twin Registry (NTR) (Bartels, et al., 2007; Boomsma, et al., 2006). For the present study, data from surveys mailed and collected within three months of the twins' 3rd and 12th birthdays of twins born between 1986 and 1996 were analyzed. In general, reminders were sent to non-responders two to three months after the first mailing. The response rate was 73% at age 3 and 61% at age 12 (Boomsma, et al., 2007). For 5,017 twin pairs data were available at age 12 (i.e., survey returned by at least one parent). From this dataset, twin pairs were excluded if one or both of the children suffered from a severe handicap (*N*=175), if information on divorce or date of divorce could not be determined (*N*=25 twin pairs), if there was a maternal or paternal death (*N*=66 twin pairs), if there was an irregular family situation (e.g., the twins did not live with either of their biological parents; *N*=39 twin pairs), if parents were already divorced when the child was 3 years old (*N*=116 twin pairs), and when information on zygosity was missing (*N*=4 twin pairs).

The study sample consisted of 4,592 twin pairs (52% girls), of whom 367 (8%) had experienced a parental divorce between the ages 3 and 12. There were 1,722 monozygotic (MZ) twin pairs, and 2,870 dizygotic (DZ) twin pairs, from which there were 1,386 same-sex DZ twin pairs. For 3,895 twin pairs mother ratings on internalizing and externalizing problems were available at both target ages. For 52 twin pairs, mother ratings were missing at age 12, but information on divorce status was available. For 645 twin pairs, mother ratings on internalizing and externalizing problems were missing at age 3. Twin pairs were not excluded from the study when data on internalizing or externalizing problems were missing on one of the target ages. Attrition analyses showed that drop-out after age 3 was not related to problem behaviors at age 3 (Boomsma, et al., 2007).

Zygosity was determined for 852 (27%) same-sex twin pairs by DNA analyses or blood group polymorphisms. For all other same-sex twin pairs, zygosity was determined by discriminant analyses using longitudinal questionnaire items on physical resemblance.

Measures

Divorce Status

Divorce status for birth cohorts 1986-1991 was assessed in surveys mailed when the children were aged 12 years. Divorce status for birth cohorts 1992 and 1993 was assessed when the children were aged 10 and 12 years. For birth cohorts 1994-1996 we assessed divorce status at ages 7, 10, and 12 years. There were two items in the surveys to assess divorce status. The first item was *Which of the following statements corresponds best with the twin's current fam-*

ily situation? Possible answers were: (1) the biological mother and the biological father are married or are living together; (2) the biological mother and the biological father have been divorced since …; (3) the biological mother has been deceased since…; (4) the biological father has been deceased since…; (5) different family situation, namely… The second item was *Which of the following statements corresponds best with the twin's current living situation?* Possible answers were:(1) the twins live with both biological parents; (2) the twins live with the biological mother only; (3) the twins live with the biological father only; (4) the twins live with the biological mother and her partner (not the biological father); (5) the twins live with the biological father and his partner (not the biological mother); (6) different living situation, namely… The information from both items was combined to classify divorce status at ages 3 and 12 years. When parents indicated to be divorced, we deduced divorce status at age 3 from date of divorce.

Internalizing and externalizing problems

At age 3, parental ratings were collected with the Dutch translation of the Child Behavior Checklist (CBCL/2-3) (Achenbach, 1992), which is a reliable and validated instrument to measure internalizing and externalizing problems in young children (Koot, Van den Oord, Verhulst, & Boomsma, 1997). It consists of 100 items that are scored on a 3-point scale that is based on the occurrence of the behavior during the 2 months prior to the survey: 0 if the problem item was not true, 1 if the item was somewhat or sometimes true, and 2 if it was very true or often true. The Internalizing scale (INT3) covers anxious, withdrawn, and depressed behaviors, and consisted of 19 items; the Externalizing scale (EXT3) measures oppositional, aggressive, and overactive behaviors, and consisted of 31 items.

Parental ratings at age 12 were collected with the Dutch translation of the Child Behavior Checklist (CBCL/4-18) (Achenbach, 1991; Verhulst, Van der Ende, & Koot, 1996), that consists of 120 items with the same three response categories as the CBCL/2-3. Parents were instructed to rate the child's behavior over the preceding 6 months. The Internalizing scale (INT12) measures anxious, depressed, and withdrawn behaviors, as well as functional somatic symptoms, and consists of 31 items. The Externalizing scale (EXT12) consists of 30 items and measures aggressive and rule-breaking behaviors. Sumscores were used in the analyses.

The good reliability and validity of the CBCL were confirmed in our sample: Cronbach's alpha's were 0.79 (INT3), 0.92 (EXT3), 0.87 (INT12), and 0.90 (EXT12). The reliability estimates were not different between boys and girls. For the present study, only mother ratings were used. Missing data were not replaced by father ratings.

Strategy of analysis

The models for GxE analyses are based on an extension of the classical twin design, in which the relative contributions of genetic and environmental factors to individual differences in internalizing and externalizing problems can be inferred from the different levels of genetic relatedness between MZ and DZ twins. MZ twins are genetically (nearly) identical, while DZ twins share on average 50% of their segregating genes. We can use this difference in similarity to estimate different portions of variance. Individual differences may be due to additive genetic (A), shared environmental (C), and nonshared environmental (E) factors (Neale & Cardon, 1992). Shared environmental factors are responsible for resemblance between members of a twin pair, whereas nonshared environmental factors contribute to differences between members of a twin pair. Additive genetic factors are correlated 1.0 in MZ twins, because it is assumed that MZ twins share (nearly) 100% of their genes. On average, additive genetic factors are correlated 0.5 in the DZ twins. By definition, shared environmental factors are correlated 1.0 in both MZ and DZ twins, assuming that the environment shared by a twin pair does not depend on zygosity. This is referred to as the equal environments assumption. Nonshared (or unique) environmental factors are uncorrelated, and may also include measurement error.

Genetic structural equation modeling in Mx (Neale, Boker, Xie, & Maes, 2006) was used with the raw data maximum likelihood procedure for estimation of parameters. First, means, variances and twin correlations for INT3, INT12, EXT3, and EXT12 were estimated. Sex, divorce status, and their interaction, were coded as dummy variables (i.e., 0 and 1), and included as fixed effects in the models. To assess whether they significantly influenced means and variances of INT3, INT12, EXT3, and EXT12, we tested whether constraining each regression weight (i.e., β_D, β_S, β_{S*D}) at zero led to a significant deterioration of model fit. By including the mean effects in the genetic models, gene-environment correlations were controlled for (Purcell, 2002). Gene-environment correlations are present when exposure to parental divorce depends on a child's genotype.

The pattern of twin correlations provides a first indication of the magnitude of genetic and environmental influences. If genes contribute to individual differences, the MZ correlations are higher than the DZ correlations. More specifically, there must be an effect of genes when the MZ correlation is about twice as large as the DZ correlation, because MZ twins share twice as many genes as DZ twins. Shared environmental influences are present if the MZ correlations are less than twice as high as the DZ correlations, because this means that the DZ twins are more alike than we would expect on the basis of their shared genes. There are non-shared environmental effects when the MZ correlation is smaller than 1. An indication for GxE is provided when the difference between the MZ and DZ correlations differs between the divorced and non-divorced groups.

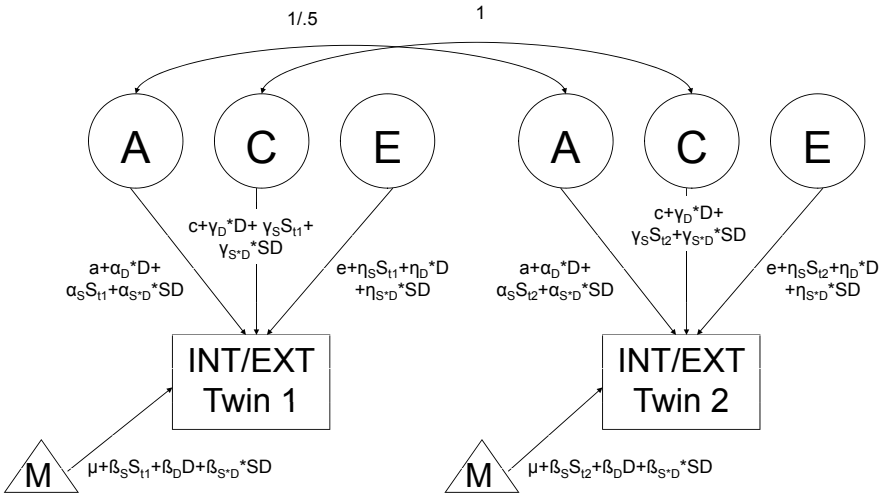

Figure 6.1: Genetic model for pre- and post-divorce internalizing and externalizing problems with moderating effects of sex and divorce status

Note: effect of divorce status (β_D), of sex (β_S), and their interaction (β_{S*D}) on internalizing and externalizing problems; the triangle (M) represents the INT/EXT residual score; A = additive genetic score; C = shared environmental factor; E = unique environmental factor; a = genetic path coefficient; c = shared environmental path coefficient, e = unique environmental path coefficient; D = divorce status; S_{t1} = sex twin 1; S_{t2} = sex twin 2; α_D = moderation effect of divorce status on A; γ_D = moderation effect of divorce status on C; η_D = moderation effect of divorce status on E; α_S = moderation effect of sex on A; γ_S = moderation effect of sex on C; η_S = moderation effect of sex on E; α_{S*D} = moderation effect of sex * divorce status on A; γ_{S*D} = moderation effect of sex * divorce status on C; η_{S*D} = moderation effect of sex * divorce status on E. Additive genetic factors are correlated 1.0 in MZ twins and 0.5 in DZ twins. Shared environmental factors are correlated 1.0 in both MZ and DZ twins.

Next, sex, divorce status, and their interaction were included as moderators on the genetic architecture of INT3, INT12, EXT3, and EXT12, according to the method as proposed by Purcell (2002). There were 9 moderation effects to be tested for each outcome (Figure 6.1): the effect of divorce status (D) on A (α_D), on C (γ_D), and on E (η_D), the effect of sex (S) on A (α_S), on C (γ_S), and on E (η_S), and the effect of sex * divorce status (S*D) on A (α_{S*D}), C (γ_{S*D}), and E (η_{S*D}). In all models the effects of sex, divorce status and their interaction were included as fixed effects. We assessed the significance of the moderation effects by testing whether fixing them at zero resulted in a significant deterioration of model fit. Each moderation effect was separately tested. Assuming that the latent factors A, C and E have unit variance, the expectation for the phenotype equals:

$$P = (a + \alpha_D *D + \alpha_S *S + \alpha_{S*D} *SD) + (c + \gamma_D *D + \gamma_S *S + \gamma_{S*D} *SD) + (e + \eta_D *D + \eta_S *S + \eta_{S*FS} *SD)$$

Nested models were compared by χ^2 tests, in which the χ^2 statistic is computed by subtracting the value of -2LL (log-likelihood) for the full model from that for a reduced model ($\chi^2 = -2LL_1$-

($-2LL_0$)). This statistic is χ^2 distributed with degrees of freedom (df) equal to the difference in the number of parameters estimated in the two models ($\Delta df = df_1 - df_0$). In addition to the χ^2 test statistic, Akaike's Information Criterion was computed. The AIC is obtained as: 2k – 2ln(L), where k is the number of parameters in the model, and L is the maximized value of the likelihood function for the estimated model. Thus, with a smaller number of parameters (k) AIC will be lower, and indicates a better model fit. Because all nested models were compared to the full model, the order in which the regression weights were tested, did not influence the results. We calculated the genetic and environmental variance components from the parameter estimates for the path coefficients from the best fitting models, such that, for instance, the unstandardized genetic variance equals a^2 in the group that did not experience divorce. The unstandardized genetic variance in the group of children who experienced divorce is equal to $(a + \alpha_D)^2$. The standardized variance components were computed by dividing the unstandardized variance components by the total variances. The standardized genetic variance components are referred to as the heritabilities. We defined $p<0.05$ as statistically significant in all analyses.

Results

Tests of mean effects and twin correlations

In Table 6.1, means of internalizing and externalizing problems at ages 3 years (pre-divorce) and 12 years (post-divorce) are presented conditional on sex and divorce status. Mean effects of divorce status were significant at age 12 (INT12 β_D= 1.39; EXT12 β_D=1.65), showing that children from divorced families had significantly higher mean scores than children from non-divorced families. Mean effects of sex were significant for all outcomes (INT3 β_S=-0.17; INT12 β_S=0.30; EXT3 β_S=-1.41; EXT12 β_S=-0.83). Boys had higher mean scores for INT3, EXT3, and EXT12, and girls had higher mean scores for INT12. Variances (see Table 6.2, column *Total variance*) were larger in children from divorced families (INT3: β_D=3.23, $\chi^2(1)$=21.93, $p<0.05$; INT12: β_D=3.97, $\chi^2(1)$=10.06, $p<0.05$; EXT12: β_D=4.14, $\chi^2(1)$=4.34, $p<0.05$), although for EXT3 this effect

Table 6.1: Maximum likelihood estimates of means of INT3, INT12, EXT3, and EXT12, conditional on sex and divorce status

	INT3	INT12	EXT3	EXT12
Boys, non-divorced	3.71	3.96	13.71	6.54
Boys, divorced	3.90	5.42	14.34	7.88
Girls, non-divorced	3.54	4.26	12.24	4.66
Girls, divorced	3.83	5.61	13.69	6.62

Note: Means are based on sumscores. As the scales have a different number of items at ages 3 and 12 years, these means can not be compared over time.

Table 6.2: Unstandardized and standardized estimates of A, C, and E for internalizing and externalizing problems at ages 3 and 12, conditional on sex and divorce status

		Standardized			Unstandardized			Total variance
		A	C	E	A	C	E	
INT3	Non-divorced	0.57	0.21	0.22	9.32	3.41	3.68	16.40
	Divorced	0.49	0.18	0.33	9.32	3.41	6.13	18.85
INT12	Boys, non-divorced	0.37	0.25	0.39	9.31	6.29	9.79	25.39
	Boys, divorced	0.03	0.60	0.38	1.08	23.53	14.81	39.43
	Girls, non-divorced	0.37	0.25	0.39	9.31	6.29	9.79	25.39
	Girls, divorced	0.25	0.54	0.21	10.98	23.53	9.32	43.83
EXT3	Boys, non-divorced	0.34	0.51	0.15	41.78	61.43	17.96	121.17
	Boys, divorced	0.34	0.51	0.15	41.78	61.43	17.96	121.17
	Girls, non-divorced	0.41	0.42	0.17	41.78	43.27	17.96	103.01
	Girls, divorced	0.31	0.56	0.13	41.78	74.58	17.96	134.32
EXT12	Boys, non-divorced	0.60	0.18	0.22	28.17	8.44	10.34	46.95
	Boys, divorced	0.51	0.15	0.33	28.17	8.44	18.16	54.79
	Girls, non-divorced	0.47	0.29	0.24	13.38	8.44	6.89	28.72
	Girls, divorced	0.44	0.28	0.28	13.38	8.44	8.69	30.52

Note: A = genetic variance; C = shared environmental variance; E = nonshared environmental variance; INT3 = internalizing problems at age 3; INT12 = internalizing problems at age 12; EXT3 = externalizing problems at age 3; EXT12 = externalizing problems at age 12.

was only significant for girls (β_{S*D}=14.77, $\chi^2(1)$=8.83, p<0.05). For EXT12, the variance was lower in girls than in boys (β_S=-7.11, $\chi^2(1)$=179.25, p<0.05). Twin correlations for INT3, INT12, EXT3, and EXT12 are presented in Table 6.3. The pattern of MZ and DZ correlations revealed genetic, shared environmental, and nonshared environmental influences on internalizing and externalizing problems at ages 3 and 12. There was no indication for genetic influences on INT12 for the divorced group as the MZ correlation (r=0.60) was not significantly greater than the DZ correlation (r=0.63) (χ^2 (1)=0.29, p=0.59). Because the correlational structure of the data was not identical for children from married and divorced families, it was justified to start genetic modeling with divorce status as a moderator on the genetic and environmental path coefficients.

Table 6.3: Twin correlations for INT3, INT12, EXT3, and EXT12, conditional on divorce status

		INT3	INT12	EXT3	EXT12
Non-divorced	MZ	0.77	0.67	0.84	0.81
	DZ	0.49	0.47	0.65	0.51
Divorced	MZ	0.64	0.60	0.83	0.74
	DZ	0.47	0.63	0.67	0.51

Note: All correlations are significant (p<0.05).

Table 6.4: Model fitting results

	-2LL	df	χ^2	Δdf	P value	AIC
INT3						
1. Full model	49595.425	9170				
2. Drop α_S	49595.441	9171	0.02	1	0.90	-1.98
3. Drop γ_S	49595.785	9171	0.36	1	0.55	-1.64
4. Drop η_S	49595.425	9171	0.00	1	1.00	-2.00
5. Drop α_D	49595.919	9171	0.49	1	0.48	-1.51
6. Drop γ_D	49596.605	9171	1.18	1	0.28	-0.82
7. Drop η_D	49611.601	9171	16.18	1	<0.05	14.18
8. Drop α_{S*D}	49596.323	9171	0.90	1	0.34	-1.10
9. Drop γ_{S*D}	49595.770	9171	0.35	1	0.56	-1.66
10. Drop η_{S*D}	49595.681	9171	0.26	1	0.61	-1.74
11. Best model	49599.014	9178	3.59	8	0.89	-12.41
INT12						
Full model	53473.134	9169				
Drop α_S	53473.134	9170	0.001	1	0.98	-2.00
Drop γ_S	53473.298	9170	0.16	1	0.69	-1.84
Drop η_S	53473.257	9170	0.12	1	0.73	-1.88
Drop α_D	53477.596	9170	4.46	1	<0.05	2.46
Drop γ_D	53486.132	9170	13.00	1	<0.05	11.00
Drop η_D	53491.299	9170	18.17	1	<0.05	16.17
Drop α_{S*D}	53478.876	9170	5.74	1	<0.05	3.74
Drop γ_{S*D}	53473.184	9170	0.05	1	0.82	-1.95
Drop η_{S*D}	53530.904	9170	57.77	1	<0.05	55.77
Best model	53474.517	9173	1.38	4	0.85	-6.62
EXT3						
Full model	65767.171	9170				
Drop α_S	65767.356	9171	0.19	1	0.67	-1.82
Drop γ_S	65771.173	9171	4.00	1	<0.05	2.00
Drop η_S	65768.344	9171	1.17	1	0.28	-0.83
Drop α_D	65767.278	9171	0.11	1	0.74	-1.89
Drop γ_D	65767.174	9171	0.003	1	0.96	-2.00
Drop η_D	65767.942	9171	0.77	1	0.38	-1.23
Drop α_{S*D}	65767.798	9171	0.63	1	0.43	-1.37
Drop γ_{S*D}	65771.040	9171	3.87	1	<0.05	1.87
Drop η_{S*D}	65769.275	9171	2.10	1	0.15	0.10
Best model	65772.972	9177	5.80	7	0.56	-8.20
EXT12						
Full model	56000.290	9169				
Drop α_S	56034.084	9170	33.79	1	<0.05	31.79
Drop γ_S	56001.914	9170	1.62	1	0.20	-0.38
Drop η_S	56047.502	9170	47.21	1	<0.05	45.21
Drop α_D	56000.291	9170	0.00	1	0.99	-2.00
Drop γ_D	56000.393	9170	0.10	1	0.75	-1.90
Drop η_D	56021.178	9170	20.89	1	<0.05	18.89
Drop α_{S*D}	56000.300	9170	0.01	1	0.92	-1.99
Drop γ_{S*D}	56003.112	9170	2.82	1	0.09	0.82
Drop η_{S*D}	56035.104	9170	34.81	1	<0.05	32.81
Best model	56017.810	9174	17.52	5	<0.05	7.52

Note: -2LL = -2 log likelihood; *df* = degrees of freedom; χ^2 = chi-square difference test; Δ*df* = degrees of freedom of χ^2-test; full model = ACE model including all moderation effects; best model = ACE model including only significant moderation effects; due to a combination of effects, the best model is not always a better fitting model than the full model.

Table 6.5: Parameter estimates of the best models with their 95% confidence intervals

	Moderation effects	Path coefficients
INT 3	η_D = 0.56 (0.32 – 0.82)	a = 3.05 (2.89 – 3.22) c = 1.85 (1.56 – 2.09) e = 1.92 (1.85 – 1.99)
INT12	α_D = -2.01 (-4.06 – -0.33) γ_D = 2.34 (1.58 – 3.00) η_D = 0.72 (0.38 – 1.08) α_{S*D} = 2.27 (0.86 – 3.82) η_{S*D} = -0.80 (-1.01 – -0.59)	a = 3.05 (2.77 – 3.31) c = 2.51 (2.21 – 2.77) e = 3.13 (3.00 – 3.26)
EXT3	γ_S = -1.26 (-1.73 – -0.80) γ_{S*D} = 2.06 (0.76 – 3.44)	a = 6.46 (6.10 – 6.82) c = 7.84 (7.40 – 8.27) e = 4.24 (4.10 – 4.38)
EXT12	α_S = -1.65 (-1.92 – -1.39) η_S = -0.59 (-0.77 – -0.42) η_D = 1.05 (0.67 – 1.46) η_{S*D} = -0.72 (-1.00 – -0.45)	a = 5.31 (5.06 – 5.55) c = 2.91 (2.56 – 3.21) e = 3.22 (3.03 – 3.40)

Note: see note Figure 6.1

Model fitting results

Table 6.4 presents the model fitting results for internalizing and externalizing problems at ages 3 and 12 years. The parameter estimates of the best fitting models are presented in Table 6.5. For INT3, the best fitting model showed divorce status significantly modified the nonshared environmental variance (η_D = 0.56). For INT12, the best fitting model included the effects of divorce status on all three variance components (α_D=-2.01; γ_D=2.34; η_D=0.72). Also, the genetic and nonshared environmental variance were modified by sex * divorce status ($\alpha_{S*D=}$2.27; η_{S*D}=-0.80). For EXT3, sex modified the amount of shared environmental variance (γ_S=-1.26), as did sex * divorce status (γ_{S*D}=2.06). For EXT12, the best fitting model showed that sex significantly modified the genetic and nonshared environmental variance (α_S=-1.65; η_S=-0.59). The nonshared environmental variance was also modified by divorce status (η_D=1.05) and by sex * divorce status (η_{S*D}=-0.72).

Differences in estimates of ACE

From the parameter estimates of the best fitting models, the standardized and unstandardized contributions of genetic and environmental influences were calculated, which are presented in Table 6.2. For INT3, the nonshared environmental variance was larger in children from divorced families than in children from non-divorced families, resulting in a lower heritability for children from divorced families (0.49 vs 0.57). For INT12, the amount of shared environmental variance was larger in boys and girls from divorced families, resulting in lower heritabilities than in children from non-divorced families. Boys from divorced families also

showed less unstandardized genetic variance and more nonshared environmental variance. For EXT3, the amount of shared environmental variance was higher for girls from divorced families than for girls from non-divorced families, resulting in a lower heritability for girls from divorced families (0.31 vs 0.41). For EXT12, boys, and to a lesser extent girls, from divorced families showed more nonshared environmental variance than boys and girls from non-divorced families. Also, boys showed more genetic variance than girls. This resulted in lower heritabilities for children from divorced families.

Overall, genetic factors explained at least 25% of the total variances, except for INT12, for which the heritability was estimated near zero for boys from divorced families. With regard to INT12 and EXT3 (girls only), shared environmental influences were relatively more important for children from divorced families. Nonshared environmental influences were more important for children from divorced families with respect to INT3 and EXT12.

To summarize, parental divorce was associated with higher levels of psychopathology and larger variances of internalizing and externalizing problems. The differences in variance were environmental in origin, and resulted in lower heritabilities for children from divorced families and for children whose parents would later divorce.

Discussion

The present study contributes to the field of GxE interaction research by investigating whether the genetic architecture of internalizing and externalizing problems differed between children living in intact versus divorced families. Children's behavioral problems were assessed pre-divorce (at age 3 years) as well as post-divorce (at age 12 years). Although age-specific genetic and environmental influences (Bartels, et al., 2004) may have contributed to a somewhat different pattern of interaction effects at ages 3 and 12 years, we showed that at both ages heritabilities were slightly lower for children from divorced families than for children from intact families. These results support the hypothesis that genetic influences are less important in the context of parental divorce (Bronfenbrenner & Ceci, 1994; Raine, 2002; Shanahan & Hofer, 2005), which is consistent with findings from several other studies (Button, et al., 2005; Feinberg, et al., 2007; Hicks, et al., 2009; Tuvblad, Grann, & Lichtenstein, 2006). However, as the absolute amounts of genetic variance were similar between children from divorced and intact families (except for boys' internalizing problems at age 12), genetic effects were not suppressed by the experience of parental divorce. Heritabilities were lower for children from divorced families because for these children there was more environmental variance. This finding emphasizes the importance of considering both the relative and the absolute contributions of genes and environment (i.e., the standardized and unstandardized estimates of genetic and environmental variances) when studying GxE. A sole focus on

standardized estimates (i.e., heritabilities) may provide a limited picture of what is going on, and can even lead to misinterpretation (Feinberg, et al., 2007).

One of the unique aspects of this study is the assessment of pre-divorce as well as post-divorce problems. Although we did not find evidence for higher mean levels of pre-divorce internalizing problems at age 3 in this study as well as in our earlier report (Robbers, et al., 2011), our present results show a larger nonshared environmental variance for pre-divorce internalizing problems. Thus, pre-divorce environmental factors increase heterogeneity in children's internalizing problems without significantly increasing mean levels of internalizing problems.

Our findings are in agreement with previous studies that showed increasing environmental variances of internalizing problems with age (Bartels, et al., 2004; Boomsma, Van Beijsterveldt, & Hudziak, 2005), which may likely be explained by mounting environmental influences as a result of children's transition to school, during which they develop social relations with other children, and must cope with several new demands. Our study shows that shared environmental influences become even more important for children of divorced families, which may be an expression of the impact of divorce on family dynamics, such as family relationships. It may also partly reflect children's understanding of the family situation or twins' shared acces to possible support in relationships outside the family. More research is needed to define which specific environmental factors are of interest in explaining the effects of parental divorce on variation in children's problem behaviors.

The significant moderation of the shared and nonshared environment by divorce status indicates a greater heterogeneity in internalizing and externalizing problems among children with divorced parents. This underlines the importance of focusing on etiologies of individual differences in the effects of parental divorce instead of focusing on general mean effects.

The ways in which children cope with stressors associated with parental divorce, such as spending less time with the noncustodial parent, parents beginning new romantic relationships, and the intensity, frequency, and style of parental conflict (Button, Scourfield, Martin, Purcell, & McGuffin, 2005; Huizink, Van den Berg, Van der Ende, & Verhulst, 2007), may be important mediators and moderators of the relation between parental divorce and behavioral problems (Compas, et al., 2001). One could hypothesize that exposure to parental conflict could enhance shared environmental effects, while coping strategies would be more likely to enhance genetic effects.

There seems to be a stronger GxE effect for internalizing problems than for externalizing problems, because divorce moderated genetic effects on internalizing problems, but not those on externalizing problems. One possible explanation for this difference is that additive genetic factors are the main source of stability in externalizing problems over time, whereas most of the stability in internalizing problems can be explained by shared environmental factors (Bartels, et al., 2004). The high genetic contribution to stability in externalizing problems results from the fact that a subset of genes is active at multiple ages throughout childhood. Also, heritability estimates of externalizing problems are generally more similar at different

ages during childhood than heritability estimates of internalizing problems (Bartels, et al., 2004).

GxE approaches to human behavior are still at the initial stages of inquiry (McGue, 2010). Research to the role of the environment in genetic expression may be complicated if the population is heterogeneous in the type of GxE interactions (Shanahan & Hofer, 2005). Some interactions may apply only to subgroups of the population, that differ for instance in their social experiences or that have specific genetic variants. For researchers interested in identifying specific genes associated with externalizing or internalizing problems, our results suggest that greater efficiency in detecting associations with specific genes could be obtained by limiting samples to children who have not experienced parental divorce, because then the relative influence of genetics is largest.

Besides some powerful aspects of this study, such as the large number of participating families, there are some important limitations. Firstly, the observed rate of parental divorce in our twin sample (i.e., 10%) is not representative for the general population. In a large prospective study of Dutch adolescents, about 20% had experienced parental divorce before the age of 12 years (Oldehinkel, Ormel, Veenstra, De Winter, & Verhulst, 2008). Non-response could be related to divorce status. Non-responders are not necessarily unwilling to return the questionnaire, but as parental divorce often involves change of address, surveys could have been sent to wrong addresses when the families moved without informing the NTR. Secondly, divorced parents may over-report children's problems or they may be more sensitive to them. Over-reporting could be due to parental characteristics such as anxiety or depression (Fergusson, Lynskey, & Horwood, 1993), to parents' concern about their children's mental health, or to their own distress associated with the divorce (Liu, et al., 2000). Part of the increased environmental variance found in children from divorced families could therefore be due to over-reporting. However, earlier studies to the effects of rater bias and unreliability showed that these effects distort the estimates of the shared en nonshared environmental factors to a small degree only. For both the internalizing and the externalizing scale, rater bias accounted for at most 13% of the variance, and measurement error and unreliability accounted for less than 11% of the variance (Bartels, et al., 2003, 2007). Thirdly, as younger children may be differently affected by parental divorce than older children and adolescents (Hetherington & Stanley-Hagan, 1999), our results can not be generalized to children of other ages. The heritability estimates obtained in our moderation analyses control for common variance between the moderators and child behavioral problems. Therefore, our estimates may not be directly comparable to studies that only estimate heritability.

In conclusion, environmental influences become more important in explaining variation in children's problem behaviors in the context of parental divorce. Replication of these GxE effects is necessary. It would be interesting to extend our study with adult data of these children, in order to investigate if the experience of parental divorce in childhood also affects variability in problem behaviors in adulthood.

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Chapter 7

General discussion

In this thesis I investigated the development of internalizing problems, externalizing problems, and ADHD symptoms during childhood, in twins and singletons. One assumption that is made when using twin data is that results from twin samples can be generalized to singleton populations. In this thesis, the validity of this assumption was examined. An important life event for children as they grow up is parental divorce, and I investigated the influence of parental divorce on degrees of internalizing and externalizing problems at the ages of 3 and 12 years. Because life events such as parental divorce can also act as modifiers of the genetic architecture of complex traits, I also looked at the interaction of parental divorce and the influence of genetic factors on internalizing and externalizing problems.

The data for this thesis come from two large longitudinal studies: the Netherlands Twin Register (NTR; VU University, Amsterdam) and the Zuid-Holland Study (ZHS; Erasmus Medical Center, Rotterdam). The NTR supplied data on twins and the ZHS data on singletons. Based on these data, latent growth curves were estimated for internalizing and externalizing problems for twins and singletons (chapter 3). Growth mixture modeling was used to determine developmental trajectories of ADHD symptoms for twins and singletons (chapter 4). The influence of parental divorce on levels of internalizing and externalizing problems was investigated with regression and survival analysis (chapter 5). Finally, the influence of parental divorce on the genetic architecture of internalizing and externalizing problems was examined (GxE, chapter 6). The results are discussed below, as well as the strengths and limitations of the studies, and implications and suggestions for future research.

Comparing twins to singletons

Internalizing problems

We studied the development of internalizing problems from ages 6 to 12 years in chapter 3. The main finding was that these problems develop similarly for twins and singletons up to age 9. After this age twins' levels of internalizing problems started to decrease, whereas in singletons they stabilized. This resulted in a lower level of internalizing problems for twins than singletons by the age of 12 years. In early adolescence, twinship may be a protective factor to the development of internalizing problems. This may be explained by the premise that twins have someone close for support. Siblings, in general, have been found to be a source of support to each other (Furman & Buhrmester, 1985). As twins appear to have a more intimate relationship with each other than regular siblings (Segal, Chavarria, & Hoven Stohs, 2008), they could be a greater source of support to each other than regular siblings. Higher levels of sibling support have been associated with lower levels of internalizing problems (Branje, Van Lieshout, Van Aken, & Haselager, 2004). Sibling support is present at younger ages as well, but may be stronger in early adolescence (Branje, et al., 2004). This may explain

why twins show less internalizing problems than singletons by the age of 12 years and not already at a younger age. Also, given that conflicts in sibling relationships predict internalizing problems (Moser & Jacob, 2002), one could hypothesize that twin-pairs may experience less conflicts in their relationships than other sibling pairs, which may explain the lower levels of internalizing problems in twins.

Externalizing problems

The development of externalizing problems from ages 6 to 12 years was similar for twins and singletons. Externalizing problems decreased steadily with age for both twins and singletons, and their developmental trajectories were not significantly different with respect to the initial levels of problems and the developmental course with age. Although decreasing levels of externalizing problems in childhood have consistently been found in earlier studies (e.g.,Bongers, Koot, Van der Ende, & Verhulst, 2003; Leve, Kim, & Pears, 2005; Miner & Clarke-Stewart, 2008; Stanger, Achenbach, & Verhulst, 1997), our findings are innovative as developmental trajectories for twins and singletons had not yet been compared. The main finding that externalizing problems develop similarly for twins and singletons up to age 12 is in agreement with earlier cross-sectional studies among 11- and 12-year-old Finnish twins and singletons (Pulkkinen, et al., 2003) and 5- to 15-year-old Norwegian twins and singletons (Gjone & Novik, 1995) that reported no evidence for twin-singleton differences in externalizing problems. Although other cross-sectional twin-singleton comparisons have shown some mixed results (i.e., lower or higher levels of externalizing problems in twins than in singletons (Moilanen, et al., 1999; Van den Oord, et al., 1995, Gau, et al., 1992), my longitudinal study contributes to a further confirmation of the generalizability of twins to singletons with respect to externalizing problems.

ADHD symptoms

Chapter 4 reports on three trajectories of mother-rated CBCL Attention Problems in boys and girls from 6 to 12 years: stable low, low-increasing and high-decreasing symptom levels. The Attention Problems scale of the CBCL covers both attention problems and hyperactivity symptoms, and will be further referred to as ADHD symptoms. The finding of these three trajectories is in agreement with the study from Malone and colleagues (2010) which identified three trajectories that, when considering children from middle childhood until early adolescence, also included increasing and decreasing trajectories. Although a stable high trajectory is often postulated (Jester, et al., 2005; Nagin & Tremblay, 1999), the data did not support the presence of this trajectory in the general population. This issue is further

discussed in chapter 4. Both the shapes of the trajectories (i.e., the initial levels of problems and the developmental course) and the proportion of children in each trajectory were similar for twins and singletons. Teacher ratings further supported the comparability of twins and singletons with respect to ADHD symptoms. This knowledge is important, especially in the light of recent findings regarding a causal relationship between ADHD symptoms and birth weight (Groen-Blokhuis, et al., 2011). In an earlier cross-sectional twin-singleton comparison, in which adolescent twins were compared to their non-twin siblings, also no differences with respect to the prevalence of ADHD were found (Ehringer, Rhee, Young, Corley, & Hewitt, 2006). However, an earlier cross-sectional Australian study found more ADHD symptoms in twins than in singletons aged 4 to 12 years (Levy, et al., 1996), and a study of 2- and 3-year-old Dutch twins found that twins showed slightly lower levels of ADHD symptoms than singletons (Van den Oord, et al., 1996). For the first time, we now confirmed the comparability of twins and singletons with respect to ADHD symptoms by a person-centered approach (i.e., growth mixture modeling). A person-centered approach focuses on differences between individuals instead of variables, and allows for differences across unobserved subpopulations. By providing a description of the development of ADHD symptoms for clusters of twins and singletons, this study gives further support to the generalizability of twin studies on ADHD(-symptoms).

Can results from twin studies be generalized to singletons?

Twins and singletons were comparable in their development of externalizing problems and of ADHD symptoms from ages 6 to 12 years. They were also comparable in their development of internalizing problems until the age of 9 years. From age 9 years onwards, twins' and singletons' trajectories of internalizing problems began to drift apart, with twins showing less problems than singletons. So, twin studies on externalizing problems and ADHD symptoms in middle and late childhood are very likely generalizable to the general population, but for twin studies on internalizing problems the generalizability is debatable in late childhood and early adolescence, but well accepted in early and middle childhood.

The generalizability of studies on internalizing problems in early adolescence in twin samples should be addressed with care, because I did not only find mean differences between twins and singletons, but also larger individual differences (i.e., larger variances) among twins than among singletons. Such results should be interpreted cautiously pending replication and further investigation of the course of these differences into adolescence and adulthood. It is intriguing that differences were found for internalizing problems only. One could hypothesize that internalizing problems are more affected by supportive sibling relationships than externalizing problems or ADHD symptoms, but this idea is not supported by earlier research (Branje, et al., 2004). Sibling influences are likely to be domain specific and further research is needed to examine the differential effects of sibling support in twin-pairs versus other sibling

pairs. The current findings support the hypothesis that twins' increased pre- and perinatal risks do not lead to higher degrees of problem behaviors (Phillips, Davies, & Robinson, 2001).

Parental divorce

Levels of internalizing and externalizing problems

Chapters 5 and 6 focused on differences between children from divorced and intact families with regard to mean levels of internalizing and externalizing problems, as well as differences in the underlying sources of individual differences (i.e, variance differences). These two studies were performed with data from the NTR and included only twins. Numerous studies over the past decades have reported that children of divorced parents show more behavioral problems than children of married parents (Amato, 2001; Amato & Keith, 1991; Hetherington & Stanley-Hagan, 1999). However, only few of these studies included children's pre-divorce behaviors, which are important to understand the direction of the relationship between parental divorce and children's problems. A unique feature of this study was that children's internalizing and externalizing problems were assessed pre-divorce (at age 3 years) as well as post-divorce (at age 12 years) using a large sample of twins.

This study yielded the following results: according to both mothers and fathers, children from divorced families had more internalizing and externalizing problems than children from intact families when these two groups were compared at the age of 12 years. However, teacher ratings of internalizing and externalizing problems did not reveal any significant differences between these two groups of children. This interesting finding may be indicative of several underlying processes, for example that children differ in the context in which they manifest their behavioral problems. It could also be that divorced parents over-report children's problems or that they are more sensitive to them as a result of their problems, such as depressive symptoms (Fergusson, Lynskey, & Horwood, 1993). However, Van der Toorn (2009) showed that maternal depressive symptoms do not bias maternal ratings of child's internalizing problems to a serious degree. Bartels, et al. (2007) reported that about 70% of the total variance in internalizing problems from ages 3 to 12 years is agreed upon by both mothers and fathers, and 1 to 17% of the total variance is rater-specific variance reflecting real behavior instead of bias or error. These rater-specific components are probably larger for teacher data.

Furthermore, there was some support for pre-divorce parent-rated externalizing problems in 3-year-old girls. This finding suggests that part of the higher levels of parent-reported externalizing problems in 12-year-old girls may be caused by factors that existed before the divorce occurred. Such factors may include parental conflict (Jenkins, Simpson, Dunn, Rasbash & O'Connor, 2005), familial stress (Booth & Amato, 1991), and family violence (Mänty-

maa, 2011). It is intriguing that girls and not boys showed pre-divorce problems, and that this effect was only found for externalizing problems. It could be the case that increased levels of externalizing problems are more notable in girls than in boys, and may therefore evoke more familial stress.

Genetic architecture of internalizing and externalizing problems

To get a more comprehensive insight into the interplay between children's problem behavior and parental divorce, genetic analyses and within pair comparisons were done with a focus on gene-environment interaction (GxE, chapter 6). We used the classical twin design to examine GxE interaction by investigating whether the amounts of genetic and environmental influences on internalizing and externalizing problems differed between children living in intact versus divorced families. At both ages (i.e., 3 and 12 years) heritabilities of internalizing and externalizing problems were slightly lower for children from divorced families than for children from intact families. However, the absolute amounts of genetic variance were similar between children from divorced and intact families, which implies that genetic effects were not suppressed by environmental factors. Heritabilities were lower for children from divorced families due to more environmental variance (which also increases the total variance). Thus, environmental factors get more important in explaining variability in children's problem behavior in the context of parental divorce. The larger total variances in children of divorced families emphasizes the great diversity of children's responses with respect to parental divorce.

The findings differed by age and by gender. Age-sensitive mechanisms include developmental changes in gene expression, and epigenetic modifications (Lenroot & Giedd, 2011). An earlier developmental twin study examining anxiety and depression from childhood to early adulthood found evidence of new genetic risk factors in early adolescence (Kendler, Gardner, & Lichtenstein, 2008). Also, genetic innovations and age-specific shared environmental influences account for some change in internalizing and externalizing problems from ages 3 to 12 years (Bartels, et al., 2004). A recent study of Vendlinski and colleagues (2011) concluded that GxE may follow a diathesis-stress pattern for some aspects of genetic risk but a bio-ecological pattern for other aspects, even when the outcome and the environmental risk factors are the same. High levels of psychosocial adversity may reduce the impact of some genes while simultaneously allowing expression of other genes that raise the liability for internalizing or externalizing problems (Vendlinski, Lemery-Chalfant, Essex, & Goldsmith, 2011). Such processes may, at least partly, explain why the genetic variances remained relatively unchanged by the experience of parental divorce (except for boys' internalizing problems). It may be too simplistic to expect the GxE effects for a given phenotype to be in

the same direction for all exposed individuals. This is also what Vendlinski and colleagues (2011) concluded in their article.

The conclusion that twins are comparable to singletons with regard to the development of externalizing problems, but not fully comparable with regard to internalizing problems, has implications for the interpretation of the results in chapters 5 and 6. As these two studies included only twins, mean levels of internalizing problems at age 12 could have been underestimated. In addition, the presumed more intimate relationship of twins as compared to other sibling pairs may have moderated the effects of parental divorce, such that twinship may be a protective factor in the association between children's adjustment and parental divorce. However, as I found no twin-singleton differences in levels of externalizing problems, twinship is not likely to bias the association between parental divorce and children's adjustment to any serious degree. The results presented in chapters 5 and 6 are innovative and valuable in emphasizing the importance of environmental influences on the development of problem behavior before and after an important life event. Replication of the reported GxE effects is necessary, and the study could be extended with adult data of these children, in order to investigate if the experience of parental divorce in childhood also affects variability in problem behaviors in adulthood.

Limitations

As data came from two different longitudinal data sets, the results presented in this thesis should be considered in light of differences and similarities between them. Important similarities of the NTR and the ZHS include the longitudinal design with assessments from early childhood to adulthood, use of the same measurement instrument (i.e., the Child Behavior Checklist) on multiple assessments, and the use of multiple raters (i.e., mothers, fathers and, teacher). Despite these essential similarities, the two samples were not fully comparable. The main differences between the samples relate to time frame, the use of different birth cohorts, response rates, selective attrition, and socio-economic status.

As the two samples are not from the same time periods, secular changes should be taken into consideration. Secular changes can include changing family structures with rising divorce rates, mothers who work more often nowadays than 20 years ago, changing ethnic distributions, overall economic growth, new media that have changed leisure activities of children, and the constantly changing and developing education system in The Netherlands. Data were used from twins born between 1986 and 1998, whereas the children from the ZHS were born between 1971 and 1979. An earlier study did not find evidence for clear secular differences in psychopathology over a 10-year period (1983-1993) (Verhulst, Van der Ende, & Rietbergen, 1997). Tick, Van der Ende, and Verhulst (2007) found increases in Dutch children's parent-reported internalizing problems over a 20-year period (1983-2003),

but these increases were very small and not consistent across age. There were no significant differences in the degrees of externalizing and internalizing problems at ages 7, 10, and 12 between twins from different birth cohorts. Furthermore, birth cohort did not predict mean scores of CBCL Attention Problems at ages 7, 10 and 12 (Derks, 2006). For these reasons, it is unlikely that secular changes or cohort effects had any meaningful implications for the results described in this thesis.

The response rates were lower for the NTR than for the ZHS, which is probably due to the different strategies that were used to retain the participants. As higher SES families may be more likely to remain in the study, the response rate difference may reflect a higher level of selective attrition in the twin sample. To overcome the difference in SES between the two samples, I took SES into account in most of the analyses. Non-response could be related to divorce status in the twin sample. Given that the observed rate of parental divorce in the NTR (10%) is lower than in the general population (20%) (Oldehinkel, et al., 2008), divorced families may be less likely to continue their participation in the NTR. The premise that parents of twins are less likely to divorce is not supported by recent research (Collins, 2011). Problematic families may be underrepresented in the NTR in comparison to the ZHS, which implies that twins' levels of behavioral problems may have been underestimated.

Finally, the NTR recruits families from any place in The Netherlands, whereas the participants of the ZHS were recruited in the province of Zuid-Holland. Because twins from the province of Zuid-Holland had the same externalizing and internalizing trajectories as twins from the rest of The Netherlands, this difference does not limit the comparability of the samples. Further, Tick, et al. (2007) showed that there were no significant differences in mean scale scores on the CBCL between children living in Zuid-Holland and children living elsewhere in The Netherlands. As The Netherlands is a small country, regional differences were not expected.

Despite their differences, the above considerations lead to the conclusion that the NTR and the ZHS provide a solid basis for a series of meaningful twin-singleton comparisons, because of the similarities in their longitudinal designs. Other limitations should be mentioned as well. In the ZHS no data are available about siblings in the families. Therefore, a number of children labeled as singletons will in fact be one of a twin-pair. Given that approximately 2% of all children are twins, the number of misclassifications was small. Nevertheless, when a pure singleton sample was used, twin-singleton differences may have been slightly larger than the differences reported in chapters 3 and 4. Perhaps, it would be more appropriate to speak of the current study as a twin-general population comparison instead of a twin-singleton comparison.

In the light of our findings with regard to the development of internalizing problems, data on sibling relationships of twins and singletons would have made a valuable contribution to this study. Also, it would have been very interesting to refine the findings on twin-singleton differences and similarities in developmental trajectories, to see if there are any subgroups of twins that deviate from the general picture, for example by distinguishing between children

with low and normal birth weight or take into account maternal age. Mothers of twins are generally slightly older than mothers of singletons and problem behaviors may decrease with increasing maternal age (Orlebeke, Knol, Boomsma & Verhulst, 1998). Therefore, a statistical control for maternal age as a confounding variable in both samples would have been of interest. Unfortunately, data on birth weight, gestational age, and maternal age were not available in the ZHS. Also, a recent meta-analysis of perinatal risks in twins, showed that IVF twins had an increased risk of preterm birth and low birth weight compared to naturally conceived twins (McDonald, 2010). However, given that IVF and naturally conceived twins have the same degrees of internalizing problems, externalizing problems, and attention problems (Van Beijsterveldt, Bartels, & Boomsma, 2011), a possible difference between the ZHS and the NTR in the number of IVF conceived children is not likely to have biased the results.

There were also no data in the ZHS on family situation and parental divorce. Therefore, we could not include data from the ZHS in the studies on parental divorce. It would have been very interesting to compare the two samples with respect to the prevalence of parental divorce and children's responses to divorce. In this way, a more complete twin-singleton comparison could have been performed.

Recommendations and considerations for future research

Recommendations for future research include ideas for further studies refining and extending the current findings for twin-singleton differences, for mixture modeling and for studies of GxE interactions.

Twin-singleton differences

The generalizability of twins to singletons should be more elaborately tested. What we do not know yet is how twin-singleton differences and similarities in development of internalizing, externalizing and ADHD symptoms further develop over adolescence and into adulthood. In adolescence, self-report data may or may not confirm the findings from teachers and parents reported so far. It is worth to further study the etiology of the differences in internalizing problems that appear in early adolescence, and to investigate whether these differences were unique for a subgroup of twins. With such insights, twin studies can take the apparent limited generalizability of internalizing problems into account, for instance by controlling for the presumed moderating role of the sibling relationship. Future research should also focus on long-term trajectories (into adulthood) of twins and singletons of several different childhood psychopathologies, such as anxiety disorders.

The extended twin design, a design that includes not only twins, but also their additional siblings, can be used to further study the role of sibling relationships in twin families. Such data have been collected by the NTR from teachers of twins and their siblings and from adolescents at ages 14, 16, and 18. This enables the assessment of the magnitude of twin-specific shared environmental influences, or environmental influences specific to twin pairs that lead them to be more similar than non-twin siblings (e.g., environmental influences that siblings of the same age are more likely to share, such as having more friends in common) (Cosgrove, et al., 2011). With the above design one can test for a special twin environment for internalizing problems in early adolescence, for instance by comparing twin-twin covariances to twin-sibling covariances of internalizing problems.

Twin-singleton comparisons in which twins are compared to their non-twin siblings should, however, be distinguished from twin-singleton comparisons in which twins are compared to singletons from a general population sample. The representativeness of singletons from extended twin families with respect to child problem behaviors deserves further scientific attention, as it is uncertain to what degree extended families with twins and additional siblings are representative for families with multiple non-twin children from the general population. It would be interesting to perform a comparison of a range of child behavioral problems between 'regular singletons' (with or without additional siblings) and singletons that have twin siblings.

Mixture modeling

There is a growing interest among researchers in the use of (growth) mixture modeling techniques. In the meantime, quantitative psychologists and statisticians are still working on the validation of GMM, for instance with respect to the application of model fit criteria. When regarding studies on children's behavioral development that apply mixture modeling, it is important to consider the different ways in which researchers apply mixture modeling to their data. There is the 'simple' latent class growth analysis (LCGA), where no variation across individuals is allowed within classes, and there is the more complex growth mixture model (GMM) where within-class variation of individuals is allowed for the latent trajectory classes. In addition to these two main lines of mixture models, there can be various in-between forms. For instance, researchers may solve model convergence problems by making parameter constraints on the original GMM. As a result of this variety in mixture model applications, it could very well be the case that researchers with other opinions or preferences with regard to mixture modeling find a different mixture solution for a given data set. For instance, if I would have fit a mixture model to the Attention Problems data with variance constraints on the growth factors (i.e, no within class variation with respect to the intercepts and slopes) I would have distinguished three parallel trajectories. Without constraints on the growth fac-

tors I found three non-parallel trajectories (i.e., low, low-increasing, high-decreasing). Hence, parameter constraints can have serious consequences for the possible model solutions and subsequent interpretations and conclusions. The choice for LCGA, GMM, or an in-between form should always be based on the Bayesian Information Criterion and on model parsimony. Researchers should monitor the modeling process carefully and keep a detailed logbook of the outcomes of the different mixture models that need to be tested in order to identify the best fitting model. The modeling process includes testing and comparing models with and without covariates, as the results can be different depending on the inclusion of covariates.

As a result of the apparent lack of uniformity in the application of GMM, it may very well be the case that different researchers would come to different conclusions while working with the same data. Obviously, this is a very undesirable situation, and it emphasizes the importance of replication of any mixture modeling results. Researchers who apply GMM should be aware of their own role in the decision making process that leads to the choice of the best mixture model, and of the sensitivity and complexity of this statistical framework.

Despite these methodological issues, GMM is a valuable tool for researchers interested in individual differences in abnormal and normal development, and a promising tool for the investigation of interactions of biological and environmental processes contributing to risk and protective factors for psychopathology.

GxE interactions

There has been an explosion of interest in studying GxE interactions, and these can be studied in various ways. Because in this study genetic influences were modeled latently I found evidence for a statistical moderation by which environmental influences became more important. For researchers interested in identifying specific genes associated with externalizing or internalizing problems, our results suggest that greater efficiency in detecting associations with specific genes could be obtained by limiting samples to children who have not experienced parental divorce, because then, the relative influence of genetics is the largest.

Given that the impact of parental divorce may stretch over many years, including several years before the divorce actually occurs, future research should focus on the longitudinal impact of genetic and environmental risk on children's behavioral development. We still know too little about the impact of specific genetic risk factors over time, particularly during childhood and adolescence. Discovering such risk factors is, however, a big challenge, especially given the complexity of the pathways stretching from a specific gene or environmental influence to its effects on observable behavior. Identifying changing genetic risk factors would have implications both for research (e.g., molecular genetic studies) and for treatment and prevention (Kendler, Gardner, & Lichtenstein, 2008). Also, further understanding of epi-

genetic mechanisms by which the environment affects gene expression is very important for the development of effective interventions (Lenroot & Giedd, 2011).

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Samenvatting

(Dutch Summary)

In dit proefschrift is de ontwikkeling van gedrags- en emotionele problemen van tweelingen en eenlingen in de leeftijd van 3 tot 12 jaar onderzocht. In **hoofdstuk 1** wordt een introductie gegeven op de thema's van dit proefschrift: verschillen en overeenkomsten in de gedragsontwikkeling van tweelingen en eenlingen, de ontwikkeling gedrags- en emotionele problemen in de kindertijd en de invloed van echtscheiding. Een aanname die wordt gemaakt in tweelingonderzoek is dat tweelingen representatief zijn voor de algemene bevolking. De validiteit van deze aanname is in dit proefschrift onderzocht door het vergelijken van ontwikkelingstrajecten van gedrags- en emotionele problemen van tweelingen en eenlingen.

Voor dit proefschrift werd gebruik gemaakt van de gegevens van twee grote longitudinale bevolkingsstudies: het Nederlands Tweelingen Register (NTR; Vrije Universiteit Amsterdam) en de Zuid-Holland Studie (ZHS; Erasmus Universiteit Rotterdam), welke in **hoofdstuk 2** worden toegelicht. Tevens worden in dit hoofdstuk de gebruikte statistische technieken uitgelegd. Voor alle studies beschreven in dit proefschrift geldt dat gedrags- en emotionele problemen zijn gemeten met de Nederlandse vertaling van de Child Behavior Checklist (CBCL), een gevalideerde vragenlijst waarmee vaders en moeders het gedrag van hun kind(eren) beoordelen. Leerkrachtbeoordelingen zijn verzameld met de Teachers' Report Form (TRF). De gebruikte subschalen van zijn: Externaliserende Problemen, Internaliserende Problemen, en Aandachtsproblemen.

In **hoofdstuk 3** zijn de ontwikkelingstrajecten van internaliserende en externaliserende problemen van tweelingen en eenlingen in de leeftijd van 6 tot 12 jaar met elkaar vergeleken. Moederbeoordelingen van het gedrag van 9.651 tweelingkinderen en 1.351 eenlingen zijn geanalyseerd door middel van latente groeimodellen. Uit deze modellen bleek dat externaliserende problemen afnamen naarmate kinderen ouder werden. Er werd geen verschil gevonden tussen tweelingen en eenlingen in het beginniveau van externaliserende problemen (de intercept) of in de verandering in externaliserende problemen over tijd (de slope). Deze resultaten bevestigen de generaliseerbaarheid van de uitkomsten van tweelingstudies met betrekking tot externaliserend gedrag bij kinderen van 6 tot 12 jaar. De ontwikkeling van internaliserende problematiek vertoonde tot de leeftijd van 9 jaar een lichte stijging, en was tot die leeftijd vergelijkbaar voor tweelingen en eenlingen. Na deze leeftijd daalden de niveaus van internaliserende problematiek voor tweelingen, terwijl de niveaus van eenlingen ongeveer gelijk bleven. Dit resulteerde in significant minder internaliserende problematiek bij tweelingen dan bij eenlingen op de leeftijd van 12 jaar. De resultaten van tweelingstudies naar internaliserend gedrag in de late kindertijd en de vroege adolescentie kunnen op basis van de huidige resultaten niet worden gegeneraliseerd naar de algemene bevolking. Aanvullend onderzoek (op basis van meerdere beoordelaars) is nodig om de oorzaken van het gevonden tweeling-eenling verschil te kunnen verklaren. Mogelijk is het hebben van een tweelingbroer of - zus een beschermende factor in de ontwikkeling van internaliserende problemen in de vroege adolescentie.

In **hoofdstuk 4** is door middel van een latente klasse-analyse van groeimodellen onderzocht of ontwikkelingstrajecten van symptomen Attention Deficit Hyperactivity Disorder (ADHD) vergelijkbaar zijn voor tweelingen en eenlingen van 6 tot 12 jaar. Moederbeoordelingen van ADHD symptomen van 12.486 tweelingkinderen en 1.346 eenlingen zijn geanalyseerd, en leerkrachtbeoordelingen van 7.179 tweelingkinderen en 1.211 eenlingen. Er werden drie ontwikkelingstrajecten geïdentificeerd: (1) een stijgend traject met een laag beginniveau van ADHD symptomatologie, (2) een dalend traject met een hoog beginniveau van ADHD symptomatologie, (3) een stabiel traject op een laag niveau van ADHD symptomatologie. Tweelingen en eenlingen verschilden niet met betrekking tot de beginniveaus van de trajecten (de intercepts), de ontwikkeling over de tijd (de slopes), en de verdeling van de kinderen over de trajecten. De meeste kinderen volgden het stabiele lage traject. Volgens de leerkrachtrapportages was er geen verschil tussen tweelingen en eenlingen in de gemiddelde scores van ADHD symptomatologie op alle leeftijden. Op basis van deze resultaten kunnen we concluderen dat tweelingen vergelijkbaar zijn met eenlingen met betrekking tot de ontwikkeling van ADHD symptomen in de leeftijd van 6 tot 12 jaar. Deze kennis is relevant voor de generaliseerbaarheid van de resultaten van tweelingstudies over ADHD.

In **hoofdstuk 5** is de invloed van scheiding op internaliserende en externaliserende problemen bij kinderen onderzocht. Hierbij is speciaal gekeken of internaliserende en externaliserende problemen al vóór een scheiding aanwezig waren. Gedragsrapportages van moeders, vaders en leerkrachten werden geanalyseerd voor in totaal 6.426 kinderen (allen tweelingen) op de leeftijden van 3 en 12 jaar. Alle geïncludeerde kinderen maakten op 3-jarige leeftijd nog deel uit van een intact gezin. Ongeveer 10% van deze kinderen maakte tussen hun 3e en 12e jaar een scheiding van de ouders mee. Kinderen uit gezinnen met gescheiden ouders werden vergeleken met kinderen uit intacte gezinnen. Via de datum van de scheiding kon worden bepaald of de niveaus van internaliserende en externaliserende problemen op 12-jarige leeftijd afhankelijk waren van de tijd die was verstreken sinds de scheiding. De resultaten lieten zien dat meisjes waarvan de ouders later zouden gaan scheiden op 3-jarige leeftijd verhoogde niveaus van externaliserende problemen hadden. Tevens waren externaliserende problemen van meisjes voorspellend voor het plaatsvinden van een scheiding. Deze resultaten benadrukken dat gedrags- en emotionele problemen van kinderen geen direct gevolg van een echtscheiding hoeven te zijn. Leerkrachten rapporteerden geen verschillen in de niveaus van internaliserende en externaliserende problemen tussen 12-jarige kinderen van gescheiden ouders en kinderen van intacte gezinnen, terwijl ouders hogere niveaus van internaliserende en externaliserende problemen rapporteerden indien een scheiding had plaatsgevonden. Leerkrachten rapporteerden wel meer internaliserende problemen indien de scheiding recentelijker had plaatsgevonden dan wanneer de scheiding al langer geleden had plaatsgevonden.

In **hoofdstuk 6** is onderzocht of de mate waarin individuele verschillen in internaliserende en externaliserende problemen kunnen worden verklaard door genetische factoren,

afhankelijk is van het meemaken van een scheiding (gen-omgevingsinteractie). Hiertoe zijn moederbeoordelingen van internaliserend en externaliserend gedrag geanalyseerd van 4.592 tweelingparen op de leeftijden van 3 en 12 jaar, waarbij alle geïncludeerde kinderen op 3-jarige leeftijd nog deel uitmaakten van een intact gezin. De spreiding in internaliserende en externaliserende problemen op 12-jarige leeftijd was groter bij kinderen die een scheiding hadden meegemaakt. Tevens bleek dat voor deze kinderen de spreiding in internaliserende en externaliserende problemen ook groter was op 3-jarige leeftijd, nog voordat de scheiding had plaatsgevonden. Door middel van genetische analyses bleek dat het verschil in de spreiding was toe te schrijven aan omgevingsinvloeden, welke in grotere mate bijdroegen aan individuele verschillen bij kinderen van gescheiden ouders dan bij kinderen uit intacte gezinnen. Dit resulteerde in een relatief kleinere rol van erfelijke factoren in de ontwikkeling van internaliserende en externaliserende problemen bij kinderen met gescheiden ouders dan bij kinderen uit intacte gezinnen. De resultaten tonen aan dat omgevingsinvloeden een belangrijke rol spelen bij het verklaren van gedragsverschillen bij kinderen die een scheiding hebben meegemaakt.

In **hoofdstuk 7** worden de bevindingen van de verschillende studies bediscussieerd. Sterke aspecten van de beschreven studies betreffen onder andere de longitudinale designs van zowel het NTR als de ZHS, de grote aantallen onderzochte kinderen, het gebruik van gevalideerde meetinstrumenten, en de toepassing van geavanceerde statistische technieken. Mede hierdoor dragen de uitkomsten van dit proefschrift bij aan de kennis omtrent de generaliseerbaarheid van de resultaten van tweelingstudies, en de effecten van echtscheiding op gedrags- en emotionele problemen van kinderen.

Dankwoord

De afgelopen 5,5 jaar waarin ik aan mijn proefschrift heb gewerkt waren enerverend, leerzaam, verrassend, vaak uitdagend en regelmatig frustrerend. Het is overduidelijk dat zonder de hulp en ondersteuning van een heleboel mensen, dit mooie boekje hier nu niet zou hebben gelegen. Een oprecht woord van dank is daarom zeer op zijn plaats.

Ik wil graag de vele duizenden ouders en leerkrachten bedanken die, soms jarenlang, vragenlijsten hebben ingevuld ten behoeve van het Nederlands Tweelingen Register en de Zuid-Holland Studie. Zonder die belangeloze inzet is zulk mooi onderzoek niet mogelijk.

Mijn promotoren en copromotoren, Frank, Dorret, Floor en Meike, bedankt voor jullie vertrouwen en inzet gedurende de afgelopen 5,5 jaar. Ik heb zeer veel geleerd van jullie uiteenlopende wetenschappelijke kennis. Ik ben erg blij dat ik de kans heb gekregen om op beide afdelingen, bij zowel VU als EMC, te mogen werken, dit heb ik als een luxe ervaren. Floor, je hebt me echt door de eindfase heengesleept. Ik waardeer het enorm dat ik altijd bij je terecht kon en dat je me wist te motiveren wanneer dat hard nodig was. En je hebt me ook nog eens binnengesleept bij het gaafste orkest van Rotterdam, de KRPH, waardoor mijn leven in Rotterdam een erg fijne draai heeft gekregen.

Ook de overige leden van de promotiecommissie wil ik hartelijk bedanken voor het lezen en beoordelen van mijn proefschrift. In het bijzonder Anja Huizink, die als initiator van dit project 5,5 jaar lang op allerlei manieren haar inzet en betrokkenheid heeft getoond.

Gitta Lubke, dank voor de leerzame tijd die ik heb mogen doorbrengen op de afdeling Quantitative Psychology bij de University of Notre Dame. Jouw expertise op het gebied van mixture modeling is indrukwekkend. Ik ben dan ook erg blij dat je als co-auteur betrokken was bij hoofdstuk 4 van mijn proefschrift. Special thanks to Stephen, Melissa, Laura and Manshu for their support and friendship during my stay at Notre Dame.

Alle ex-collega's van de afdeling Biologische Psychologie (VU) wil ik bedanken voor de gezellige en leerzame tijd. Lieve dames van het NTR (Thérèse, Michelle, Louise, Jacqueline, Cyrina), het was me altijd een genoegen om met jullie te werken! Ik heb me altijd erg thuisgevoeld bij BioPsy, ook nog nadat ik naar Rotterdam vertrokken was. Marleen, wat was het fijn om met jou een kamer te delen in mijn eerste jaar, en Jenny, wat een gave reis hebben we gemaakt in Zuid-Korea! Tinca, dank voor je inzet voor mijn 'attention paper'. Toos, erg bedankt voor het aanleveren van alle databestanden en voor je inzet als co-auteur bij meerdere van mijn proefschrifthoofdstukken.

Wat heb ik een gezellige tijd gehad op de Westzeedijk! Al mijn lieve (ex-)collega's van de afdeling Kinder- en Jeugdpsychiatrie wil ik bedanken voor hun steun en luisterend oor. Inge, Hanneke en Joni, wat waren we een mooi HIJS-cluppie, en wat fijn dat ik nog steeds voor allerlei zaken bij jullie terecht kan. Andrea, Brittany, Anneke, Sabine, Willem, Linda, Janneke, wat prijs ik mij gelukkig om met jullie allemaal mijn kamer te hebben gedeeld, ik denk nog vaak terug aan alle gezellige theekransjes. Jan, dank voor je inzet als co-auteur van hoofdstuk 3 van dit proefschrift en dat ik altijd met vragen bij je binnen kon lopen. Sofia, your scientific

insights are amazing, and our discussions were always very inspiring and helpful. Thanks for discussing, reading, and reviewing my work, and for being a friend.

Mijn collega's bij Yulius ben ik dankbaar voor alle getoonde belangstelling, de luisterende oren en het begrip voor het gegeven dat het soms erg lastig is om een baan te combineren met afrondende proefschriftwerkzaamheden. Ik voel me erg thuis bij Yulius en hoop nog lang zo prettig met iedereen te mogen samenwerken. Esther, wat leuk dat we weer collega's zijn, je belangstelling en optimisme doen me goed!

Niels en Elise, wat ben ik blij met jullie als paranimfen. Niels, lieve Jul, fijn dat ik altijd met jou kon sparren en dat we onze promotiebeslommeringen zo goed met elkaar konden delen, al dan niet tijdens een gezellig etentje met Hannah. Lieve Elise, mijn leven in Rotterdam is een stuk leuker geworden sinds ik jou heb leren kennen. Dank voor je steun en je luisterend oor, je bent een kanjer.

Ik prijs mij gelukkig met veel lieve vrienden en vriendinnen, die ieder op hun eigen manier mij enorm tot steun zijn geweest, en mijn soms eindeloze klaagzangen hebben moeten aanhoren. In het bijzonder wil ik Marloes, Annelies en Wendy noemen, jullie zijn werkelijk schatten. Ik weet dat jullie net zo opgelucht zijn als ik nu dit boekje hier ligt. Ik heb echt enorm veel aan jullie gehad!

Ton, bedankt voor de tijd die je hebt gestoken in het maken van de coverfoto's. Het is prachtig geworden! Tante Rina en mama, bedankt voor het beschikbaar stellen van Liliane en Liliane.

Tot slot wil ik mijn familie bedanken, mijn lieve broertje, opa, oma en de allerliefste ouders van de hele wereld die altijd voor mij klaarstaan. Zonder jullie ben ik nergens, dank voor jullie liefde en steun!

Sylvana

Curriculum vitae

Sylvana Robbers werd op 4 maart 1983 geboren te Oosterhout en groeide op in Rijen. In 2001 haalde ze haar VWO diploma aan het Cambreur College in Dongen en in datzelfde jaar begon zij met haar studie Pedagogische Wetenschappen aan de Radboud Universiteit Nijmegen. In 2004 vervolgde zij haar studieloopbaan met de 2-jarige research master Behavioral Science. In het kader van haar onderzoeksstage en scriptie heeft zij in 2006 3 maanden doorgebracht bij de University of Denver om onderzoek te doen naar de ontwikkeling van romantische relaties in de adolescentie, waar zij in het najaar van 2006 op afstudeerde. Tijdens haar studie heeft zij gewerkt als assistent laborant monstervoorbereiding bij Analytico B.V. te Breda. Van oktober 2006 tot december 2010 was zij als junior onderzoeker verbonden aan het Erasmus MC – Sophia Kinderziekenhuis te Rotterdam, waar zij haar promotieonderzoek uitvoerde binnen de afdeling Kinder- en Jeugdpsychiatrie (hoofd: prof. dr. Frank C. Verhulst), in samenwerking met de afdeling Biologische Psychologie van de Vrije Universiteit Amsterdam (hoofd: prof. dr. Dorret. I. Boomsma). Het eerste jaar van dit promotietraject was haar standplaats de Vrije Universiteit Amsterdam, waar zij betrokken was bij de dataverzameling van het Nederlands Tweelingen Register. Vanaf oktober 2007 werkte zij vanuit het Erasmus MC aan haar promotieonderzoek, waarvan de bevindingen zijn beschreven in dit proefschrift. Tevens is zij van januari tot december 2010 voor 1 dag in de week wederom betrokken geweest bij de dataverzameling van het Nederlands Tweelingen Register. Van december 2010 tot december 2011 heeft zij voor 1 dag in de week gewerkt voor de Hogeschool InHolland in Den Haag als projectcoördinator van een studie naar de effectiviteit van synchrone coaching van leerkrachten in het basisonderwijs. Sinds juni 2011 is Sylvana werkzaam als senior onderzoeker bij de Yulius Academie te Rotterdam, waar zij zich momenteel bezighoudt met onderzoek naar veiligheidsbeleving binnen het speciaal (cluster 4) onderwijs.

PhD Portfolio

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD Student: Sylvana Robbers
PhD period: 10/2006 – 12/2010
Erasmus MC Department: Child & Adolescent Psychiatry
Promotor(s): Prof. Dr. F. C. Verhulst
Prof. Dr. D. I. Boomsma

1. PhD training

Courses	Year	Workload (ECTS)
Moleculaire genetica, VU Amsterdam	2006	6
Genen en gedrag, VU Amsterdam	2007	6
Genetica van psychiatrische aandoeningen, VU Amsterdam	2007	6
Genetic modeling with Mx, VU Amsterdam	2007	1
Biomedical English writing and communication, Rotterdam	2007	4
Models for longitudinal and incomplete data, Rotterdam	2008	0.8
Conceptual foundation of epidemiologic study design, NIHES, Rotterdam	2008	0.7
Regression analyses, NIHES, Rotterdam	2008	0.9
Principles of genetic epidemiology, NIHES, Rotterdam	2008	0.7
Modern statistical methods, NIHES, Rotterdam	2008	4.3
Mixture modeling, University of Notre Dame	2009	10
Workshop 'Updaten professionele mondigheid'	2009	0.2

Conferences and symposia	Year	Workload (ECTS)
The 37th Annual Meeting of the Behavior Genetics Association, Amsterdam, poster presentation	2007	2
The Society for Research in Child Development Biennial Meeting, Denver, poster presentation	2009	2
Symposium Epidemiologie, Rotterdam	2009	0.2
Symposium Generation R, Rotterdam	2010	0.2
The 40th Annual Meeting of the Behavior Genetics Association, Seoul, oral presentation	2010	2
The 13th International Congress on Twin Studies, Seoul, oral presentation	2010	2

2. Teaching activities

Activity	Year	Workload (ECTS)
Supervising practicals, Erasmus MC Rotterdam	2007-2009	1.5
Supervision bachelor thesis, Erasmus MC Rotterdam	2009	1.5
Supervision master thesis, Erasmus MC Rotterdam	2010	3