INTRODUCTION

Why does one adolescent show great difficulties in social interaction, while some of his classmates prefer to do nothing other than meeting up with friends? What factors underlie individual differences in withdrawn behaviour? Research questions like these can be addressed using genetically informative data, such as data from twins and their siblings (Boomsma et al., 2002). By comparing the phenotypic resemblance of monozygotic (MZ) twins with the resemblance of dizygotic (DZ) twins and non-twin siblings, the genetic and environmental influences on individual differences can be disentangled, because twins and siblings share their home environment, but MZ twins differ in their genetic relatedness as compared to DZ twins and siblings. The environmental influences can be further decomposed into influences from the environment that are shared between the family members (such as the neighbourhood they grow up in, nutrition, and socioeconomic status), and influences that are unique to each family member (such as an accident or illness, and friends or school experiences unshared with the co-twin or sibling).

Throughout development, genetic and environmental influences are subject to change. Genes can be switched on or off in the course of development due to e.g. hormonal signals (Alberts et al., 1994). Moreover, the environment a child is exposed to changes substantially: During adolescence, youth from western societies spend progressively more time at school and with peers, and less time in the home environment (Larson & Verma, 1999). Hence, the relative importance of genetic, shared environmental and nonshared environmental effects to the variance in traits can change over time, urging the study of individual differences at multiple time points in life. This thesis aims to study developmental processes from early childhood to young adulthood and focuses on two domains: the aetiology of individual differences in autistic traits and withdrawn behaviour, and the development of cognitive abilities. Within this thesis, findings from both cross-sectional and longitudinal studies are discussed. Cross-sectional twin and twin family studies can give insight in the relative importance of genetic and environmental effects at certain time points in life. Besides providing insight in the development over time, longitudinal studies can also unravel the aetiology of stability in traits. Using longitudinal data, questions such as “Why does the one child continue to show problem behaviour, while another “grows over” it?” or “What factors cause stability in cognitive abilities over time?” can be addressed.
reliability of the AQ, the heritability of autistic traits as measured using self-report AQ scores is assessed in a general population sample of 18-year-old twins and their siblings. Furthermore, the degree of partner resemblance in endorsement of autistic traits in the general population is explored. If present in the general population, assortative mating could affect the frequency of the genotypes associated to autistic traits and could consequently bias the estimate of genetic influences.

Autistic traits and withdrawn behavioural problems

Individuals with a clinical diagnosis for autism often show additional behavioural problems other than the core symptoms for autism. Clinical studies indicate an increased prevalence of affective disorder, phobia, obsessive compulsive disorder, and attention-deficit hyperactivity disorder in individuals with autism (Howlin, 2000; Lainhart & Folstein, 1994; Leyfer et al., 2006; Matson & Nebel-Schwalm, 2006). Relatives of children with autism also seem to be at increased risk for major depression, anxiety, social phobia and obsessive compulsive disorder (Bolton et al., 1998; Micali et al., 2004; Piven & Palmer, 1999; Smalley et al., 1995). However, whether these elevated risks can be partly explained by the burden of caring for an autistic child, or are due to genetic risk factors shared with the risk for autism is unclear. In this thesis, the covariance between autistic traits and a broad range of behavioural problems (as assessed using Youth Self Report (YSR) ratings (Achenbach & Rescorla, 2001; Verhulst et al., 1997) is explored. Furthermore, it is examined whether the observed covariance is of genetic or environmental origin, using multivariate genetic analyses.

After having examined the aetiology of self-reported problem behaviours in 18-year-old twins and their siblings using scores on the YSR, we aimed to study the development of behavioural problems in an earlier phase of life. We wished to focus on the development of withdrawn behavioural problems, as previous studies showed that withdrawn behaviour and behavioural inhibition are fairly common in childhood (Kagan et al., 1988) and are predictive of psychiatric disorders later in life (Caspi et al., 1996; Goodwin et al., 2004). The Netherlands Twin Register (NTR) has a long history in collecting questionnaire data concerning childhood behavioural problems (Bartels et al., 2007), using parental ratings of the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001; Verhulst et al., 1996). The CBCL and YSR are developed in parallel. Using these questionnaires in concert can provide insight in the aetiology of problem behaviours in different phases of development. This thesis reports on the development of withdrawn behavioural problems in childhood, by analysing CBCL data collected when the twins were 3, 7, 10, and 12 years old. Previous studies have shown that different raters provide different information about a child’s behaviour (Bartels et al., 2003; Bartels et al., 2004). As the NTR collects both maternal and paternal ratings of the twins’ behaviour, we could distinguish between the variance shared between the parents (representing the perception of the child’s behaviour that both parent agree on), and the variance specific to each rater.

The development of cognitive abilities

One of the best studied domains in behaviour genetics is general cognitive ability, or intelligence. Both twin and adoption studies have examined genetic and environmental influences on the variance of general intelligence at multiple time points in development. While shared environmental influences explain about half of the variance in general cognitive abilities in young children, these influences gradually decrease with age and become insignificant by adolescence (Bouchard, Jr. & McGue, 2003; Deary et al., 2006; Plomin & Spinath, 2004). In concordance, the genetic influences increase, and the heritability of general intelligence may be as high as 80% in adulthood (Posthuma et al., 2002). Longitudinal studies indicate that the stability in general cognitive ability is mainly accounted for by genetic effects, while nonshared environmental effects only exert age-specific influences (Bartels et al., 2002; Bishop et al., 2003; Petrell et al., 2004). Less is known about the development of more specific cognitive abilities. Similar to general intelligence, the heritability of verbal and nonverbal abilities seems to increase with age (Posthuma et al., 2001; Price et al., 2000; Rietveld et al., 2003; Rijndijk et al., 2002; Wilson, 1986). Longitudinal analyses spanning early to middle childhood suggest that genetic effects are of main importance for the stability in both abilities in this time of development (Cardon, 1994; Rietveld et al., 2003). However, no studies have examined the stability in verbal and nonverbal abilities into later phases of development. Moreover, the developmental structure of the covariance between verbal and nonverbal abilities over time is unclear. Some cross-sectional studies suggest that the overlap between these abilities may increase with age (Posthuma et al., 2001; Price et al., 2000; Rietveld et al., 2003; Rijndijk et al., 2002; Wilson, 1986). This thesis aims to contribute to the existing literature by studying the development of verbal and nonverbal abilities over a 13-year time span, from early childhood to young adulthood.

Extra attention is devoted to verbal abilities. Verbal abilities are key components for acquiring language, and are needed for healthy social communicative functioning. Although several studies have examined the aetiology of specific verbal measures and components of language and reading at different time points in childhood (e.g. Alarcón et al., 1998; Alarcón et al., 1999; Alarcón et al., 2003; Kovas et al., 2005; Samuelsson et al., 2005), little is known about the overlap between general verbal abilities (as measured for example with the Wechsler verbal IQ scale) and more specialised verbal abilities, such as verbal learning, memory, and fluency. Moreover, it is unclear whether the overlap between these abilities, and the genetic and environ-
mental influences on this overlap, changes over time. In this thesis, the covariance between different verbal abilities is examined in two distinct phases of development: middle childhood and young adulthood.

Milestones in adolescent development: individual differences in testosterone levels and pubertal development

Puberty represents one of the most salient milestones in the development from childhood to adolescence. Secondary sex characteristics emerge, hormonal changes take place, and these changes may be related to developmental changes in cognition and behaviour. Twin studies have shown that pubertal timing is influenced by both genetic and environmental effects, with the estimated influence of genetic factors ranging between 50 to 80% (Eaves et al., 2004; Mustanski et al., 2004; Palmert & Boepple, 2001; Van den Berg et al., 2006). Studies into the aetiology of variance in testosterone levels in males reported heritability estimates ranging from 26 to 66% (Harris et al., 1998; Meikle et al., 1986; Meikle et al., 1988; Ring et al., 2005; Sluyter et al., 2000), with the subjects under study ranging from mid adolescent boys to elderly men. Only one study examined the heritability of testosterone levels in females and found that 41% of the variance in testosterone levels in 14- to 21-year-old women and their mothers was explained by genetic factors (Harris et al., 1998). This thesis aims to explore the heritability of testosterone levels in early puberty. As the variation in sex hormone levels will be related to pubertal maturation at this age, we also included testosterone-related pubertal development in the analyses. Apart from the importance of this topic from a developmental perspective, this paper was also written with a methodological interest. Until recently, methodological constraints prohibited the combined genetic analyses of continuous (such as testosterone levels) and categorical data (such as stage of pubertal development). With the development of the software package Mplus (Muthén & Muthén, 2006), and its application to the twin method (Prescott, 2004), these analyses became possible.

Research design and measures

The greater part of this thesis is based on data collected in a longitudinal twin study into the development of cognition and behavioural problems that was initiated in 1992 with the recruitment of 209 5-year-old twin pairs from the Netherlands Twin Register. The development of these twin pairs was followed at subsequent measurement occasions when the twins were 7, 10, 12, and 18 years of age. At the second to fourth measurement occasion, 92 to 94% of the original sample participated. The last assessment was completed by 122 families from the original sample. At this time point, 64 additional twin families were recruited to obtain a sufficient sample size. Complete data on all 5 measurement occasions were available for 115 twin pairs. The longitudinal twin sample consisted of 42 monozygotic male twin pairs (MZM), 44 dizygotic male twin pairs (DZM), 47 monozygotic female pairs (MZF), 37 dizygotic female pairs (DZF), and 39 dizygotic twin pairs of opposite sex (DOS). The newly recruited families who only participated at the fifth time point encompassed 13 MZM twin pairs, 12 DZM pairs, 16 MZF pairs, 9 DZF pairs and 14 DOS pairs.

The first to fourth assessments were carried out by three researchers, who all reported on these data in their PhD theses (Bartels, 2003; Rietveld, 2003; Van Baal, 1997). A fifth assessment when the twins were 18 years of age enabled the follow-up of these children into young adulthood. At this time point, siblings of the twins were also included in the study, and collaboration with the Department of Paediatric Endocrinology of the VU medical centre was sought. Medical PhD student Frederiek Estourgie – van Burk collected data on the physical development of the twins and their siblings, while I conducted the psychological test protocol, including the follow-up study of behavioural problems and cognition. In this chapter I will briefly describe the measures that were used for the data analyses in this thesis. Additional information on the longitudinal data collection and on the other measures that were collected as part of the psychological test protocol at the fifth measurement occasion can be found in appendix I.

Autistic traits and behavioural problems

When the twins were 18 years of age, the twins and their siblings filled out the Autism-Spectrum Quotient (AQ; Baron-Cohen et al., 2001). At this time point, all participants also filled out the Dutch Health and Behavior Questionnaire, a large self-report questionnaire including questions about health, wellbeing, leisure activities and behavioural problems (Bartels et al., 2007). Within this questionnaire, problem behaviour was assessed using the Youth Self Report (Achenbach, 1991; Verhulst et al., 1997), a widely used screening and assessment instrument to measure a broad range of behavioural problems.

Cognitive abilities

At all time points, data on psychometric intelligence were collected. At age 5, 7, and 10 years, the twins completed 6 subtests of the Revised Amsterdamse Kinder Intelligentië Test (RAKIT; Bleichrodt et al., 1984). At age 12, the twins completed the Wechsler Intelligence Scale for Children-revised (WISC-R; Van Haassen et al., 1986). At age 18, the twins and their siblings completed 11 subtests of the Wechsler Adult Intelligence Scale-Third edition (WAIS-III; Wechsler, 1997). At all ages, the performance on the intelligence tests could be decomposed into verbal IQ and nonverbal IQ scores. At the fifth measurement occasion, performance on additional verbal tasks was also assessed. Tasks included the California Verbal Learning Test (CVLT; Mulder
et al., 1996) to measure verbal learning and memory, and a test of verbal letter fluency and category fluency. In another twin family project conducted at the NTR (Van Leeuwen et al., 2007), similar data were collected in 9-year-old twins and their siblings. This provided us with the opportunity to compare the aetiology of different verbal abilities in middle childhood and young adulthood.

**Hormones and pubertal development**

At age 12 and 18 years, the twins (and when the twins were 18 also including the siblings) were asked to fill out a self-report questionnaire assessing their pubertal development, based on the Tanner (Marshall & Tanner, 1969; Marshall & Tanner, 1970) scales. Girls were asked whether they had experienced their menarche, and to rate their stage of breast development and pubic hair growth. Boys were asked about genital development and pubic hair development, and about the size of their testes. The different stages of pubertal development were illustrated by sketches (at the assessment at age 12) or by photographs (assessment age 18). At both measurement occasions, subjects were also asked to collect saliva samples (on 2 consecutive days, just before lunch) for the assessment of biologically active testosterone levels.

**Outline of this thesis**

This thesis starts with an examination of the reliability and the diagnostic validity of the Dutch translation of the Autism-Spectrum Quotient (Baron-Cohen et al., 2001). Moreover, chapter 2 evaluates the factor structure underlying autistic traits in a large student and general population sample. In chapter 3, the genetic and environmental influences on individual differences in autistic traits are explored in 18-year-old twins and their siblings, and it is tested whether there is evidence for assortative mating for autistic traits in the general population. Chapter 4 discusses an analysis of the genetic and environmental covariation between autistic traits and behavioural problems, as indexed by the Youth Self Report (Achenbach & Rescorla, 2001; Verhulst et al., 1997). The development of withdrawn behavioural problems in childhood is examined in chapter 5, by performing a longitudinal multi-informant twin study into withdrawn behaviour spanning age 3, 7, 10, and 12 years.

Chapter 6 focuses on the stability of verbal and nonverbal intelligence from early childhood to young adulthood. In this chapter, longitudinal IQ data, collected when the twins were 5, 7, 10, 12 and 18 years, are analysed. The genetic and environmental architecture underlying stability in verbal and nonverbal IQ is explored, and it is examined whether the association between these abilities becomes stronger with age. In chapter 7, sources of covariation between verbal IQ and other verbal abilities (that is, verbal learning, verbal memory and verbal fluency) are studied in two independent samples of 9-year-old and 18-year-old twins and their siblings. By including these two samples, we examined whether the pattern of covariation, and the origins of this overlap, were different in middle childhood and late adolescence. The empirical study of development is concluded in chapter 8, with an examination of the genetic and environmental influences on testosterone levels and its relation to pubertal development when the twins were 12 years of age.

In chapter 9, the results from the preceding chapters are summarised and integrated with the existing literature on these topics. Future directions in the study of autistic traits, withdrawn behavioural problems, and cognitive abilities are considered.
REFERENCES


