GENETICS OF ATTENTION AND EXECUTIVE FUNCTIONING

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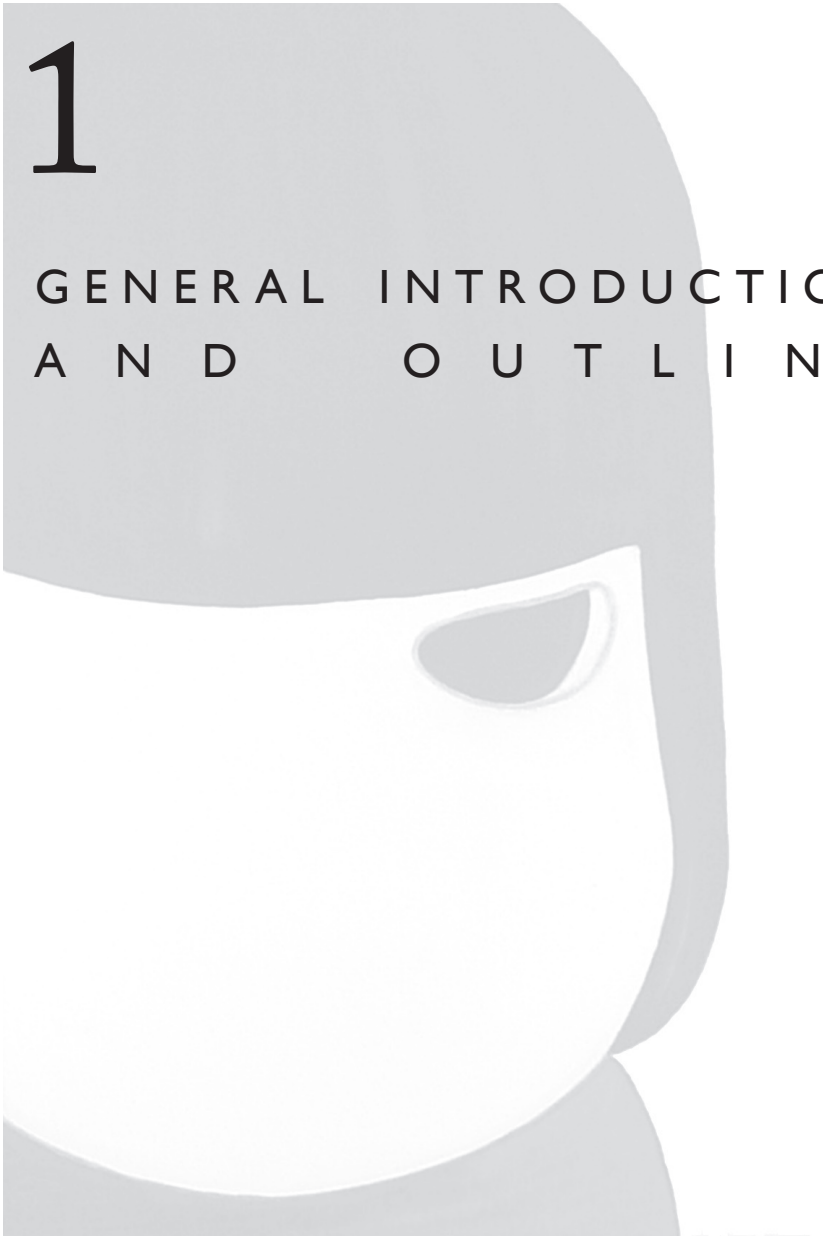
GENERAL INTRODUCTION AND OUTLINE



INTRODUCTION

This thesis focuses on the genetic aspects of attention and attention problems, executive functioning and cognition. Longitudinal data were collected in a sample of twin pairs at two time points: at age 5 (237 twin pairs), and seven years later at age 12 (172 twin pairs). At the second time point also 55 siblings of the twins, aged between 8 and 15 years, participated. Data were collected by computerised executive functioning tasks, IQ tests, and behavioral questionnaires. Questionnaires were completed by teachers, parents and children themselves. In the appendix of this thesis a detailed description of the sample and the data collection at both time points is presented.

Attention and Attention Problems

The phenotype 'attention' is normally distributed in the general population with severe attention problems being on one tail of the distribution and high levels of attention on the other (Levy et al. 1997, Hay et al. 2006). Attention skills reflect for example children's ability to sustain attention, to sit still, and to wait their turn while children with attention problems are characterised by inattentive, impulsive and hyperactive behavior. Children with severe attention problems are diagnosed with Attention Deficit/Hyperactive Disorder (ADHD). ADHD is the most common neuro-developmental disorder of childhood with prevalence's ranging from 4 to 12% in the general population (Brown et al. 2001; Faraone, 2003).
It is well established that variation in attention problems and ADHD is strongly influenced by genetic factors; the relative contribution of genes on variation in attention problems and ADHD varies between 70 and 95% (Rietveld et al. 2004; Hudziak et al. 2000; Faraone & Doyle, 2002; Nadder et al. 1998; Derks et al. 2006a). Much less is known about the aetiology of variation in attention at the other extreme of the distribution: why are some children (much) better than average? Part of the reason that the answer to this question is largely unknown, may be that the assessment of attention in a standardized way is much more advanced for attention problems than superior attention skills.

Problems of attention deficit and hyperactivity can be assessed in several ways, varying from behavior checklists, filled in by parents, teachers or children themselves, to interviews and observations by trained psychiatrists. There is a moderate to high correlation between diagnoses among the different measures of attention problems such as the Child Behavior Checklist's (CBCL, Achenbach, 1991) Attention Problem scale (AP) and DSM-IV interviewed based ADHD (Hudziak et al. 2004; Kasius et al. 1997; Derks et al. 2006b). There also is only moderate correlation between parental and teacher assessment of attention problems (Achenbach & Rescorla, 2000; Van der Ende & Verhulst, 2005), while correlations between ratings of parents are generally higher (Derks et al. 2006b). The moderate correlation between parental and teacher ratings might point to the importance of situational variation in children's behavior that preferably should be taken into account in research projects such as this one. Parents have unique information about the child's behavior in the family environment while teachers can report on problems that are specific to the classroom or other school situations (Verhulst et al. 1997; Van der Ende & Verhulst, 2005).

Executive Functioning

Cognitive development during childhood is characterised by the increasing ability a) to hold information in mind and to process that information, b) to select relevant input from the environment, c) to inhibit inappropriate reactions, d) to maintain alertness during a certain amount of time, and e) to flexibly adapt to changing situations (Diamond, 1990). Constructs that refer to these abilities are respectively working memory, selective attention, inhibition, alertness (or sustained attention) and cognitive flexibility, and these are collectively known as executive functions. Executive functioning is essential in normal daily functioning, for example when planning a series of actions or events, or for the performance of goal directed behavior. It is also crucial in novel situations with multiple constraints, in situations that are ambigious, or during the performance of complex tasks (Pennington & Ozonhoff, 1996; Berger & Posner, 2000; Zelazo et al. 2003).

The prefrontal cortex is one of the crucial regions in the brain for executive functioning. The lateral prefrontal cortex is hypothesized to support the working

memory system, devoted to sustaining representations of information stored in the cortex's more posterior regions. The ventromedial prefrontal cortex and the anterior cingulate are systems which ensure that these representations facilitate goal-oriented behavior. The ventro medial system is the link between cognition and emotion, perhaps for improving the efficiency with which we decide among alternative actions (Fuster, 1997; Curtis et al. 2000; Bush et al. 2000; Prabhakaran et al. 2000; Smith & Jonides, 1999).

Endophenotypes

It has been suggested that children with attention problems and ADHD have impairments in executive functioning (Swaab-Barneveld et al. 2000, Slaats-Willemse et al. 2003, Pennington & Ozonoff, 1996; Tannock, 1998; Barkley, 1997; Manly et al. 2001). It has also been shown that neural systems, for example involved in working memory, are partially overlapping with neural systems that seem to be involved in neuropsychiatric disorders like ADHD (Castellanos & Tannock, 2002; Casey & Durston, 2006; Durston et al. 2006). Shaw et al. (2006) showed that children with ADHD have relative cortical thinning in regions important for attentional control (i.e., medial and superior prefrontal and precentral regions). The overlap in brain regions that affect attention problems and cognitive traits that are probably impaired in children with attention problems, has encouraged researchers to investigate not only the genetic background of attention problems itself but also the related cognitive traits. The rationale behind this approach is that these underlying cognitive traits (so called 'endophenotypes') of a certain disorder might represent simpler clues to genetic underpinnings than the disorder itself (Gottesman, 1997; Skuse, 2001; Gottesman & Gould, 2003). Criteria for useful endophenotypes are that they should co-occur with the trait of interest (Skuse, 2001), that they have to be reliable and should be heritable themselves (De Geus & Boomsma, 2001), and that they must be anchored in neuroscience (Castellanos & Tannock, 2002).

Even though heritability is a critical requirement for an endophenotype the heritability of executive functions has been investigated by only a small number of studies, and especially in children these studies are scarce. Results of adult studies showed that genetic influences explained around 50% of the variation in

several executive functions (for an overview see Doyle et al. 2005). For this thesis the genetic influences on three executive functions (working memory, selective attention, and sustained attention) were investigated in preschool children and young adolescents. In addition the genetic influences on the stability over time of these executive functions were examined.

Working Memory

Working memory (WM) refers to the capacity to simultaneously store, deal with and monitor information (Miyake & Shah, 2006; Oberauer et al. 2003; Cowan et al. 2005). Baddeley presented an influential working memory framework with three distinguishable subcomponents (Baddeley, 1992; Baddeley, 2003). The first component is the visuospatial sketch path, which manipulates visual images. The second component is the phonological loop, which stores and rehearses speech-based information. The first two components are peripheral slave systems from the third component called the central executive.

A distinction can be made between WM speed and WM capacity. WM speed (or mental speed) is the speed with which subjects can perform basic cognitive operations, like stimulus detection, stimulus perception, response selection and response execution. WM capacity refers to the fact that WM has a limited capacity that has to be distributed over the competing functions of storage and processing. Comprehension and reasoning are impaired if working memory storage, due to activities in the phonological loop or visuo spatial sketch path, increases (Myake & Shah, 1999; Fuster, 1997; De Fockert et al. 2001).

Selective Attention and Sustained Attention

Selective attention represents a system that selects task relevant input from the environment and suppresses distracting or conflicting information (Miller & Cohen, 2001; Desimone & Duncan, 1995). An example of selective attention is the well known 'cocktail party effect'; when visiting a noisy party, the goal is to attend to one single conversation while simultaneously ignore surrounding music, talks and other potential distracters. Sustained attention refers to the ability to increase and maintain response readiness during a certain time period. It requires the continuous maintenance of alertness and receptivity for a particular target

or target changes over time, the organisation of appropriate responses, and inhibition of inappropriate responses. Sustained attention can be thought of as a foundational form of attention on which other attentional functions rest (Raz & Buhle, 2006).

Psychometric Intelligence

Intelligence is described as "a very general mental capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience" (Gottfredson, 1997). In this study psychometric intelligence tests were used as a general measure of intelligence (IQ). IQ was operationalised with two well known tests, namely the Revised Amsterdam Child Intelligence Test (RAKIT, Bleichrodt et al. 1984) and the Wechsler Intelligence Scale for Children Revised (WISC-R, Van Haassen et al. 1986). Both tests are theoretically based on Thurstone's factor analysis theory (1938) and provide an index of general IQ and primary abilities such as word fluency, verbal comprehension, spatial visualization, number facility, associative memory, reasoning, and perceptual speed.

Previous twin studies have established that general IQ is influenced by genetic factors at all ages. Heritability estimates increase from around 30% in preschool children to 80% in early adolescence and adulthood (Bartels et al. 2002; Plomin, 1999; Luciano et al. 2001; Bouchard, Jr. & McGue, 1981; Boomsma & van Baal, 1998; Posthuma et al. 2001; Petrill et al. 2004). The stability of IQ performance during childhood is mainly driven by genetic influences. Bartels et al. (2002) and Petrill et al. (2004) showed in longitudinal designs that one common factor influenced IQ performance from early childhood to adolescence, and that the influence of this genetic factor is amplified when children grow older. In this thesis the genetic relation between IQ and attention problems, and IQ and several endophenotypes associated with attention and attention problems was investigated.

Aims and Outline of this Thesis

This thesis starts with an introduction on twin studies and their potential for research on the etiology of individual differences in complex traits and behaviors.

The use of univariate, bivariate and multivariate twin analyses is illustrated with a longitudinal study on attention problems and intelligence (IQ). We investigated whether attention problems in young children can predict IQ performance in early adolescence, and whether there is a longitudinal genetic relation between these traits. Teacher ratings on attention problems and other problem behavior in young children are scarce. In chapter 3 of this thesis we investigated heritability estimates of these behaviors in young children (age 5). In addition we explored whether twin pairs that share the same teacher are differentially rated than twin pairs that are rated by different teachers, and discuss the possibility that teacher-specific styles influence the teacher's ratings.

Not much is known about the heritability of attention skills. It is the question whether the whole spectrum of attention, thus not only attention problems but also superb attention skills, shows the same amount of genetic influences as has been reported for attention problems and ADHD only. The heritability of attention as a continuous trait, varying from excellent attentional abilities to severe attention problems, was investigated in chapter 4. In addition we performed an association study between the SNAP-25 gene and the continuum of attention. A few studies in clinical samples reported significant associations for this gene and ADHD. We performed the association study in a general population sample and analysed attention as a continuous trait. The results are presented in chapter 5.

A currently often used approach to understand the genetic path ways of attention problems is to investigate the genetic background of related traits. In this thesis the genetic architecture of possible 'candidate endophenotypes' was investigated. Chapter 6 presents the heritability of working memory speed and working memory capacity, and their genetic relation among each other, and with IQ. In chapter 7 the genetic influences on selective attention, working memory and sustained attention were investigated. By using the longitudinal twin design we also examined the causes of longitudinal stability of these executive functions.

This thesis concludes with a summary and discussion, including a brief overview of other results that have been published based on this project. Finally, the appendices present a detailed description of the longitudinal sample and data collection at both time points (Appendix I), and the information brochure, invitation

letters, and informed consents that were sent to the families that participated in this study (Appendix II to VII).

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2

A LONGITUDINAL TWIN STUDY ON IQ, EXECUTIVE FUNCTIONING, AND ATTENTION PROBLEMS DURING CHILDHOOD AND EARLY ADOLESCENCE

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ABSTRACT

Variation in human behavior may be caused by differences in genotype and by non-genetic differences ("environment") between individuals. The relative contributions of genotype (G) and environment (E) to phenotypic variation can be assessed with the classical twin design. We illustrate this approach with longitudinal data collected in 5 and 12-year-old Dutch twins. At age 5 data on cognitive abilities as assessed with a standard intelligence test (IQ), working memory, selective and sustained attention, and attention problems were collected in 237 twin pairs. Seven years later, 172 twin pairs participated again when they were 12 years old and underwent a similar protocol.

Results showed that variation in all phenotypes was influenced by genetic factors. For IQ the heritability estimates increased from 30% at age 5, to 80% at age 12. For executive functioning performance genetic factors accounted for around 50% of the variance at both ages. Attention problems showed high heritabilities (above 60%) at both ages, for maternal and teacher ratings. Longitudinal analyses revealed that executive functioning during childhood was weakly correlated with IQ scores at age 12. Attention problems during childhood, as rated by the mother and the teacher were stronger predictors (r = -0.28 and -0.36, respectively). This association could be attributed to a partly overlapping set of genes influencing attention problems at age 5 and IQ at age 12. IQ performance at age 5 was the best predictor of IQ at age 12. IQ at both ages was influenced by the same genes, whose influence was amplified during development.

In this paper a longitudinal genetic study on IQ, executive functioning and attention problems during childhood, and IQ performance in early adolescence is presented. The paper starts with an introduction on twin studies and their potential for research on the etiology of individual differences in complex traits and behaviors. Next, we analyse variation in three phenotypes that are related to cognitive development. These are 1) cognitive abilities as assessed with a standardized IQ test, 2) executive functioning as measured with reaction time tasks on selective attention, working memory and sustained attention, and 3) problems on attention deficit and hyperactivity as reported with behavioral checklists by the mother and teacher of children.

In a first series of analyses the genetic and environmental influences on the phenotypes measured at ages 5 and 12 are examined. Secondly, the predictability of the phenotypes measured at age 5 for IQ performance at age 12 is analysed. Finally, the genetic and environmental mediation of the association between the phenotypes at age 5 and IQ performance at age 12 is investigated.

Twin Studies

Individual differences in complex traits (like for example intelligence) may be due to genetic or environmental factors. The influence of these factors on variation in human behavior may be additive, or may manifest itself through more complex path ways in which the influences of genes and environment interact. The relative influence of genetic factors on phenotypic variation, the "heritability", is commonly defined as the proportion of total phenotypic variance that can be attributed to genetic variance. All other, non-genetic influences on phenotypic variation are referred to as environmental influences and include the early influences of prenatal environment, the influence of the (early) home environment (environmental influences that are shared among siblings who grow up in the same family), and unique environmental influences (i.e., environmental influences that are unique to an individual and that are not shared among family members). To estimate the influences of genotype (G) and environment (E) on phenotypic variation, it is not necessary to collect genetic material (DNA) or to measure the environment. The relative importance of both sources of variation may be estimated by statistically analyzing data that have been collected

in groups of individuals who are genetically related or who do not share their genes, but who share their environment (Boomsma et al. 2002a; Martin et al. 1997). For example, data from adopted children may be compared with data from their biological and their adoptive parents. The degree of resemblance between adopted children and their biological parents informs on the importance of genetic inheritance, the resemblance of adoptive parents and their adopted children informs on the importance of cultural inheritance. Adoptions are relatively rare and the majority of studies that estimate heritability of complex traits make use of the classical twin design to unravel sources of variance.

In the classical twin design data from monozygotic twins and dizygotic twins are used to decompose the variation of a trait into genetic and environmental contributions by comparing within pair resemblance for both types of twins. Monozygotic (MZ) twins share their common environment and (nearly always) 100% of their genes. Dizygotic (DZ) twins also share their common environment and on average 50% of their segregating genes (Hall, 2003). If MZ within twin pair resemblance for a certain trait is higher than DZ within twin pair resemblance, this suggests the presence of genetic influences on that trait. A first impression of the heritability (a^2) of a phenotype can be calculated as twice the difference between the MZ and DZ correlations: $a^2 = 2(r\text{MZ} - r\text{DZ})$. The expectation of the correlation in MZ twins equals: $r\text{MZ} = a^2 + c^2$ (where c^2 represents the proportion of the total variance attributable to common environment). The expectation of the correlation in DZ twins equals: $r\text{DZ} = ½\ a^2 + c^2$. To test how well these expectations describe the actual data and to test which model describes the data best (e.g. a model that includes genetic or common environmental influences, or both) variance components are estimated by maximum likelihood approaches (Posthuma et al. 2003). Structural relations between measured variables (traits) and unmeasured variables are often graphically represented in a path diagram, which is a mathematically complete description of a structural equation model. An example of such a model for a single trait in one twin pair is shown in Figure 1.

The variance decomposition into genetic and environmental variances for a single trait can be generalized to longitudinal and multivariate data where the variation and covariation of traits is decomposed into genetic and non-genetic sources

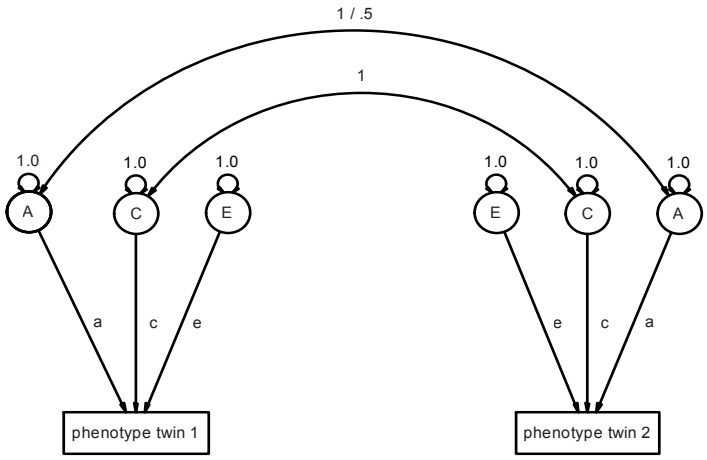


Figure 1:
The univariate ACE model represented for a twin pair.

Note:
Measured variables are presented in boxes (phenotype of twin 1 and phenotype of twin 2). The latent factors are denoted by circles representing additive genetic influences (A), shared environmental influences (C), and unique environmental influences (E). The path coefficients represent the factor loadings of the phenotype on the latent factors of the additive genetic influences (a), shared environmental influences (c), and unique environmental influences (e). The correlation between the latent factors of A is 1 for MZ twins and 0.5 for DZ twins while the correlation between the latent factors of C for MZ and DZ twins is 1.
The model represents the equation $P = aA + cC + eE$, and the variance of P equals $Vp = a^2 + c^2 + e^2$ (if latent factors are standardized to have unit variance).

(Boomsma et al. 2002a). In such data the 'cross trait-cross twin' correlations indicate how the performance of twin 1 for trait A (with longitudinal data for example at age 5) predicts the performance of twin 2 for trait B (for example at age 12), and vice versa. The pattern of 'cross trait-cross twin' correlations for MZ twins and DZ twins indicates (in a similar vein as described above) to what extent the (longitudinal) covariance between traits is influenced by genetic or environ-

mental factors. Multivariate and longitudinal studies thus offer insight into the etiology of associations between traits and the stability of traits across time. If, for example, the same set of genes influences multiple traits this constitutes evidence for genetic pleiotropy. If longitudinal stability is due to genetic factors, this indicates that the same set of genes is expressed across the life span. Additionally, multivariate and longitudinal measures increase the statistical power to detect genetic and environmental effects (Schmitz et al. 1998).

Cognitive Abilities

Intelligence has been one of the most, if not the most studied quantitative behavioral trait for more than 100 years. Historically two somewhat contrasting concepts about intelligence have been postulated. The first concept, put forward by the so-called "*g*-theorists", encompasses the idea of a single general factor *g* which accounts for the variance in test scores that is shared among subtests (Humphreys, 1985; Spearman, 1904; Jensen, 1998; Carroll, 1993). The general factor of intelligence *g*, and the specific factors are represented by Spearman's two-factor theory of abilities (Spearman, 1904).

Contrary to Spearman's two-factor theory, Thurstone (1938) postulated his multiple factor analysis theory, from which relatively independent sub-components of intelligence, so-called Primary Mental Abilities (PMA's), were obtained. However, intelligent behavior can not be explained by just these PMA's, and also evidence for *g* was found. Thurnstone's final model takes into account the presence of a general *g* factor, PMA's, and test-specific factors.

Psychometric intelligence tests consist of a number of subtests that taken together are used to infer a general IQ (intelligence quotient) score. Intelligence tests such as the Revised Amsterdam Child Intelligence Test (RAKIT, Bleichrodt et al. 1984) and the Wechsler Intelligence Scale for Children Revised (WISC-R, Dutch version, Van Haassen et al. 1986) are theoretically based on Thurstone's factor analysis theory (1938) and provide an index of general IQ and primary abilities such as word fluency, verbal comprehension, spatial visualization, number facility, associative memory, reasoning, and perceptual speed.

Previous twin studies have established that general IQ is influenced by genetic factors at all ages. Heritability estimates increase from around 30% in preschool

children to 80% in early adolescence and adulthood (Bartels et al. 2002; Plomin, 1999; Ando et al. 2001; Luciano et al. 2001; Bouchard & McGue, 1981; Boomsma & Van Baal, 1998; Posthuma et al. 2001; Petrill et al. 2004). The stability of iq performance during childhood is mainly driven by genetic influences. Bartels et al. (2002) and Petrill et al. (2004) showed in longitudinal designs that one common factor influenced iq performance from early childhood to adolescence, and that the influence of this genetic factor is amplified when children grow older.

Executive Functioning

Working memory, selective attention, and alertness (or sustained attention) are key factors of cognitive development. Working memory refers to the capacity to simultaneously store, deal with and monitor information. It plays an important role in all forms of cognition and is essential in normal daily functioning. Most important functions are the temporary storage and manipulation of information, and the central executive which coordinates and processes information (Baddeley, 1992; Miyake & Shah, 1999; Oberauer et al. 2003; Cowan et al. 2005). Selective attention represents a system that selects task relevant input from the environment and suppresses distracting or conflicting information (Miller & Cohen, 2001; Desimone & Duncan, 1995). An example of selective attention is the well known 'cocktail party effect'; when visiting a noisy party, the goal is to attend to one single conversation while simultaneously ignore surrounding music, talks and other potential distracters. Sustained attention refers to the ability to increase and maintain response readiness during a certain time period. This capacity can be thought of as a foundational form of attention on which other attentional functions rest (Raz & Buhle, 2006). Among others working memory, selective attention, and sustained attention are collectively known as executive functions. Measures of executive functioning are often operationalized in reaction time tasks. It is argued that processing speed indexes functional efficiency and is therefore a crucial and fundamental source of developmental improvement in executive functioning (Bayliss et al. 2005; Dempster, 1981; Kail & Salthouse, 1994; Fry & Hale, 2000).

A small number of studies investigated to what extent individual differences in executive functioning may be due to genetic factors (for an overview see Doyle et

al. 2005). Results of these studies show genetic influences around 50% at all ages. For example Ando et al. (2001) examined the phenotypic variances of a spatial and verbal working memory task in a sample of young adult twins. Variance on both tasks was significantly due to genetic influences, with heritability estimates between 43% and 48%. Polderman et al. (2006) found in a twin sample of young adolescences for working memory capacity, as measured with two subtests (Arithmetic and Digit Span) of the WISC-R (Van Haasen et al. 1986) that ~50% of the variation was explained by genetic variance.

Attention Problems

Children with Attention Deficit and Hyperactivity Disorder (ADHD) are characterized by impaired attention, impulsivity and hyperactivity. It is the most common neuro-developmental disorder of childhood with prevalence's ranging from 4 to 12% in the general population (Faraone et al. 2003; Brown et al. 2001) and has a great impact on affected families in terms of academic, social and behavioral dysfunction (Mannuzza & Klein, 2000; Mannuzza et al. 2004).

Problems of attention deficit and hyperactivity can be assessed in several ways, varying from behavior checklists, filled in by for example parents, teachers or children themselves, to interviews and observations by trained psychiatrists. The overlap in diagnoses among the different measures of attention problems such as the Child Behavior Checklist's (CBCL, Achenbach, 1991a) Attention Problem Syndrome (AP) and DSM-IV interviewed based ADHD, is moderate to high (Hudziak et al. 2004; Kasius et al. 1997; Derks et al. 2006b). When multiple raters are used the situational variation in children's behavior can be taken into account. For example, teachers can report on problems that are specific to the classroom or other school situations, such as problems in the social interactions with other children, or task oriented situations, while parents have unique information about the child's behavior in the family environment (Verhulst et al. 1997; Van der Ende & Verhulst, 2005).

Attentional skills are likely to be normally distributed in the population with ADHD being on the extreme tail of the distribution (Polderman et al. in press; Levy et al. 1997). There is substantial evidence that individual differences in attention problems during childhood have strong genetic influences with heritability

estimates of 70 to 90% for impaired attention and hyperactivity (Thapar et al. 1995; Thapar et al. 2000; Bartels et al. 2004; Hudziak et al. 2000; Rietveld et al. 2004; Rietveld et al. 2003; Faraone & Doyle, 2002; Nadder et al. 1998; Nadder et al. 2001). The prevalence of ADHD tends to be higher in boys than in girls, but there is no evidence for substantial sex differences in the relative importance of genetic or environmental influences (Derks et al. 2006a). The number of studies in which the relation between psychometric IQ and attention problems is investigated is limited. Results of studies in children with ADHD showed negative correlations in most studies, however the association is weak and should be established more firmly (Cohen et al. 2000; Bonafina et al. 2000; Rucklidge & Tannock, 2001; Kuntsi et al. 2004).

Aim of the Study

Firstly, we summarize, by estimating trait heritability, the importance of genetic factors to trait variation at ages 5 and 12 years for IQ, selective attention, working memory and sustained attention, and attention problems. Secondly, we investigate whether executive functioning in early childhood predicts the outcome of IQ scores at age 12. Executive functioning, as an important index for cognitive development was operationalized as reaction time on tasks measuring selective attention, working memory and sustained attention respectively. Thirdly, it is examined whether children with attention problems at age 5 show impaired IQ scores at age 12. Problems of attention deficit and hyperactivity were assessed by behavior checklists, filled in by multiple informants, namely parents and teachers. Finally, we investigate with multivariate analyses the genetic and environmental mediation between the association of phenotypes measured at age 5 and IQ performance at age 12.

METHODS

Subjects

The sample at age 5 consisted of 237 Dutch twin pairs born between 1990 and 1992 with a mean age of 5.8 years (SD. 0.1, range 5.67 – 5.92). All subjects were registered at birth with the Netherlands Twin Registry (NTR), kept by the Department of Biological Psychology at the Vrije Universiteit in Amsterdam. Of all multiple births in the Netherlands, 40-50% is registered by the NTR (Boomsma et al. 2002b; Boomsma, 1998). The selection was based on age and a sample evenly distributed across zygosity groups. None of the children suffered from severe physical or mental handicaps. Prior to the assessment parents signed an informed consent form.

Of the original sample of 237 twin pairs, 172 twin pairs participated again when they were 12 years old (mean age = 12.42, SD = 0.16). Five extra dizygotic female twin pairs were recruited, which made a total of 177 twin pairs at age 12. The parents were invited by mail for participation of their children in the continuing study entitled 'Genetics of Attention'. After two weeks the parents were contacted by phone and asked if they were willing to participate. Prior to the assessment parents and children signed an informed consent form.

Zygosity

In the same sex twin pairs, zygosity was determined on the basis of DNA polymorphisms. DNA samples were collected by buccal swabs at home and were returned to the university. DNA isolation from buccal swabs is a relatively easy lab procedure with the advantage of being a non-invasive technique from which high-yield of high-quality DNA can be obtained (Meulenbelt et al. 1995; Min et al. 2006). In the same sex twin pairs, zygosity was assessed using 11 highly polymorphic microsatellite markers. Genotyping was performed blind to familial status and phenotypic data. At age 5 there were 125 monozygotic twin pairs (MZ) and 112 dizygotic twin pairs (DZ) and in the sample and at age 12 there were 97 MZ twin pairs and 80 DZ twin pairs.

Instruments

Psychometric iq

At age 5 iq was assessed with the rakit, a Dutch intelligence test (Bleichrodt et al. 1984). The following 6 subtests were employed: Exclusion: This measures reasoning by assessing the child's ability to induce a relationship between four figures, and to determine that one of the figures is deviant; Discs: This subtest measures spatial orientation and speed of visualization; Hidden Figures: This subtest relates to transformation of a visual field, and convergence/flexibility of closure; Verbal Meaning: This is a vocabulary index and a measure of passive verbal learning; Learning Names: This subtest measures active learning and remembering meaningful pictures; Idea Production: This subtest measures verbal fluency. Raw scores on these subtests were standardized, and the sum of standardized scores was transformed to a total iq score. The six subtests represents the shortened version of the rakit which has been shown to correlate 0.93 with the full scale iq score (Bleichrodt et al. 1984).

At age 12 iq was assessed with the Wechsler Intelligence Scale for Children Revised (wisc-r, Dutch version, Van Haassen et al. 1986). The following 6 subtests were employed: Similarities: This measures verbal abstract reasoning. Subjects describe why two things are similar or alike; Vocabulary: This subtest measures knowledge of word meanings, language development and verbal fluency; Arithmetic: This measures verbal mathematical reasoning skills, concentration and short time memory for meaningful information; Digit Span: This subtest involves a child's ability to remember a sequence of numbers (both backwards and forwards). It measures concentration and short-term auditory memory for non-meaningful information; Block Design: This subtest measures visual abstract ability, spatial analysis and abstract visual problem-solving; Object Assembly: This measures visual analysis and the ability to assemble separate elements into a whole.

Standardized scores of this shortened form of the wisc correlate 0.94 with standardized iq scores based on all subtests of the wisc-r (Sattler, 1982; Sattler, 1992) and the concurrent validity with the rakit is 0.86 (Bleichrodt et al. 1984).

Executive Functioning Tasks

To assess selective attention, working memory and sustained attention the Amsterdam Neuropsychological Tasks (ANT, De Sonneville, 1999) were used. The ANT consists of a series of tasks, designed especially for measuring a diverse range of executive functions in children as young as 5 years. When the children were 5 years old they were visited at home where trained testers administered the executive functioning tasks on a laptop. In addition six subtests of the RAKIT were assessed. The children were tested individually. The entire test battery took ~2 hours including breaks. When the children were 12 years old they visited the Vrije Universiteit for the assessment. Tasks were similar as at age 5 but adjusted for age (for example consonant stimuli instead of pictures, and more trials per task). Children were tested at the same time, in separate rooms by separate experimenters. The entire test battery at this time took ~4 hours, including breaks.

Selective Attention, Working Memory, and Sustained Attention Tasks at age 5

Selective Attention

In this task a fruit basket is presented with four pieces of fruit. Two pieces of fruit are aligned in a vertical fashion (top and bottom) and two pieces in a horizontal fashion (left and right). Subjects have to give a yes-response if the target fruit is shown at one of the two relevant locations (the top or bottom location of the vertical axis). They have to give a no-response if the target fruit is shown but at an irrelevant location (left or right of the horizontal axis), or if the target fruit is absent altogether. The display with the target fruit on the vertical axis is the target signal; the display with the target fruit on the horizontal axis is the distracting signal, and the display that contains only the four non-target fruits is the non-target signal. The three signal types were presented in a random order (28 target signals, 14 distracting signals, and 14 non-target signals). Following a response, the next signal was presented 1200 ms later, preceded the last 500 ms by a warning signal (small fixation cross).

Working Memory

In this task children were presented with an image of a house with four animals presented simultaneously in the windows and the door opening. Subjects were instructed to press the yes-key when the signal contained an animal from the memory set, and to press a no-key when this was not the case. On each trial the animals occupied different positions. The task consisted of two parts. In part 1 the memory set contained one animal and in part 2 two animals. In each part 20 target and 20 non-target signals were presented in random order. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation square).

Sustained Attention

During this task a house with three windows is continuously present on the screen. In each trial one animal is presented randomly in one of the windows. Subjects are instructed to press the yes-key when they detect a target animal and the no-key when a non-target animal is presented. The task consisted of 20 series of 12 trials (i.e., 240 trials). In each serie 6 target and 6 non-target signals were presented in random order. To keep the children alert a beep sound was presented in case of an error. Following a response, the next stimulus was presented after 250 ms.

Selective Attention, Working Memory, and Sustained Attention Tasks at age 12

Selective Attention

In this task a fixed display with two different consonants was presented on one of two diagonals, the top-left to bottom-right or the top-right to bottom-left diagonal. The task contained three manipulations: 1) location of the consonants: relevant or non-relevant diagonal 2) presence of a target: target or non target letter present, and 3) memory load: in part 1, one target letter, in part 2, three target letters (of which one could appear). Subjects had to give a yes-response when a target appeared on the relevant diagonal (the top-left to bottom-right one). The target was one consonant ('l') in part one and three consonants ('g', 'r', or 't') in part 2. A no-response was required when a target letter appeared on the

non-relevant diagonal or when a non-target letter appeared on one of the two diagonals. The task consisted of two parts with each 120 trials. The presentation of stimuli was balanced so that an equal number of yes- and no-responses was required. A stimulus appeared for 300 ms. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation cross).

Working Memory

In this task memory load, operationalized as target set size, increased from one to three target letters. The computer screen showed a fixed display of four consonants arranged in a square, from which subjects had to detect one or more target letters. For Load 1 the target signal requiring a yes-response was 'k' (40 trials; 50% target signal). For Load 2, target signals were 'k' + 'r' (72 trials; 36 complete target sets, 18 trials one target signal, 18 trials no target signals) and for Load 3 target signals were 'k' + 'r' + 's' (96 trials; 48 complete target sets, 16 trials one target signal, 16 trials two target signals, 16 trials no target signals). Children were instructed to press the yes-button only when a complete set of target letters was present. In all other instances a no-response was required. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation square).

Sustained Attention

During this task a square with 3, 4 or 5 dots is presented on the screen. Subjects are instructed to press the yes-key when they detect 4 dots and the no-key when 3 or 5 dots are presented. The task consisted of 50 series of 12 trials (i.e., 600 trials). In each serie 4 target and 8 non-target signals were presented in random order. To keep the children alert a beep sound was presented in case of an error. Following a response, the next stimulus was presented after 250 ms.

In all tasks, at both ages, responses were made by pressing the left or right mouse button. A yes-response was made with the preferred hand, a no-response with the non preferred hand. Prior to the experiments, the children were given verbal instructions in which both speed and accuracy were emphasized. Twelve practice trials were provided for each task to ensure instructions were well understood.

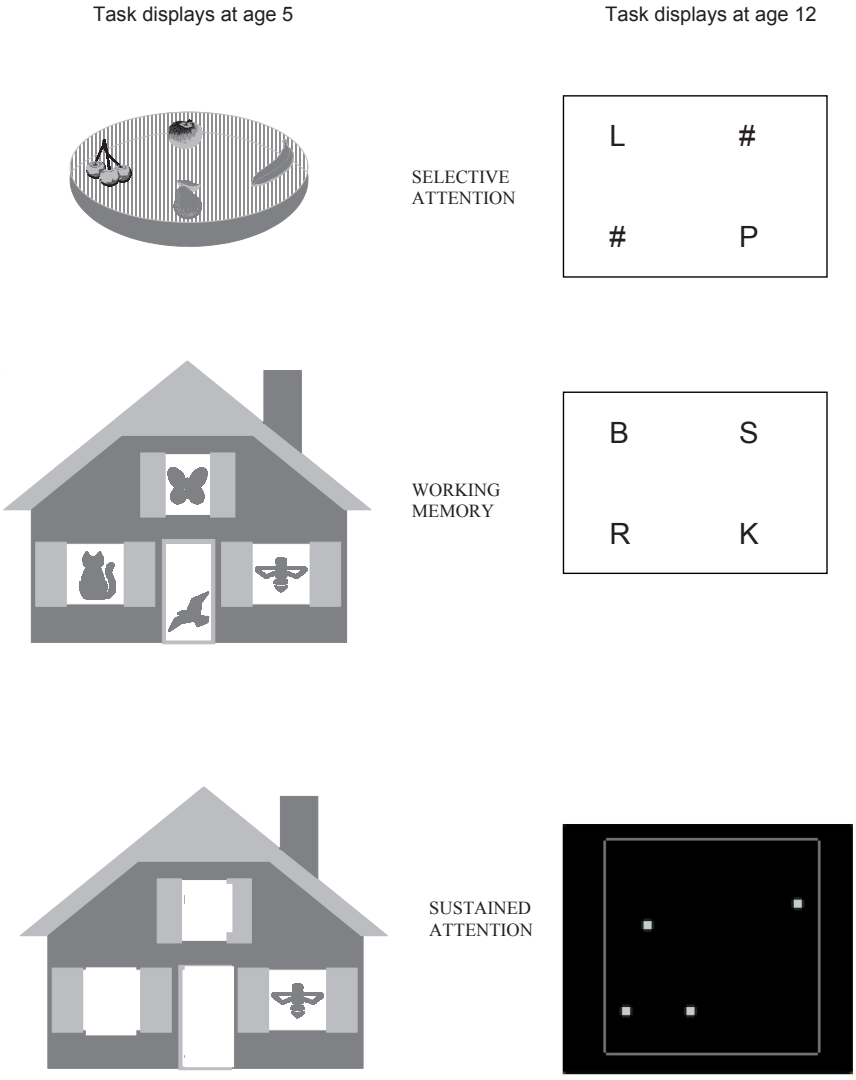


Figure 2:
An example of stimuli and task displays of respectively the Selective Attention task, the Working Memory task and the Sustained Attention task, at age 5 (left part) and age 12 (right part)

Dependent measures were reaction times (RT) for hits, correct rejections, false alarms and misses, and accuracy (percentage of misses and false alarms). Reaction times at age 5 had to be generated between 200 and 6000 ms. post stimulus onset. Reaction times before 200 ms. were not considered to be the result of a cognitive evaluation and were automatically replaced by trials of a similar type. Figure 2 shows an example of each task display, at age 5 and at age 12.

Behavioral Checklists

Behavioral data on Attention Problems (AP) at age 5 were adapted from 5 items on AP of the Devereux Child Behavior Rating Scale (DCB, Spivack & Spotts, 1966), filled in by the parents. Parents are instructed to rate the severity of their child's behavior over the last six months on a 5 point scale. The DCB is described in detail by Van Beijsterveldt et al. (2004). After permission of the parents, the Teacher's Report Form (TRF, Achenbach, 1991b) was filled in by the teachers. The TRF AP scale contains 20 problem items. Teachers are instructed to rate the child's behavior over the last two months on a three point scale.

At age 12 attention problems were assessed with the TRF. Parental data on AP were assessed with the CBCL (Achenbach, 1991a) as part of an ongoing survey conducted by the NTR every two years. The CBCL is a standardized questionnaire for parents to report the frequency and intensity of behavioral and emotional problems of their children. The AP scale of the CBCL contains 11 problem items, of which 10 items overlap with the TRF AP scale. Parents are instructed to rate the child's behavior over the last six months with 0 if the behavior is not true, 1 if the behavior is sometimes or somewhat true, and 2 if the behavior is very or often true.

Analyses

Descriptives

Structural equation modeling, as implemented in Mx (Neale et al. 2003), was used to perform the analyses. In Mx all available data, also when certain observations for subjects are missing, can be included. Therefore the data of all subjects at age 5 and at age 12, regardless of whether they participated once or twice,

were included in the longitudinal analyses. Mx provides parameter estimates by maximizing the raw data likelihood. The goodness of fit of different models is evaluated by hierarchic likelihood ratio (χ^2) tests. Specifically, the χ^2 statistic is computed by taking twice the difference between the log-likelihood of the full model and the log-likelihood of a reduced model ($\chi^2 = -2(LL_0 - LL_1)$). The associated degrees of freedom are computed as the difference in degrees of freedom between the two hierarchic models (Neale & Cardon, 1992).

Means, variances, phenotypic correlations and twin correlations were obtained with maximum likelihood estimation in a saturated model under the assumption that means, variances and phenotypic correlations were the same for first born and second born twins and for mz and dz twins. A saturated model is fully parameterized and provides a baseline model against which subsequent, more parsimonious, models are compared.

Genetic Analyses

The different degree of genetic relatedness between monozygotic (mz) twins and dizygotic (dz) twins (mz twins share all their genes while dz twins share on average half of their segregating genes) was used to estimate the genetic and environmental contributions to the (co)variance of the variables. The total variation can be decomposed into sources of additive genetic variance (A), common environmental variance (C) and unique environmental variance (E). A is due to additive effects of different alleles, C is due to environmental influences shared by members of a family, and E is due to environmental influences not shared by members of a family. E also includes measurement error and is therefore always included in the models.

As pointed out in the introduction the pattern of 'cross trait-cross twin' correlations for mz twins and dz twins indicates to what extent the longitudinal covariance between traits is influenced by genetic or environmental variance. A decomposition of the longitudinal covariance structure into genetic (A) and environmental (C, E) covariance matrices was considered by means of a bivariate model with two observations; the phenotype at age 5 and the phenotype at age 12. The longitudinal model contained two latent factors for A, C and E respectively, of which the variances were constrained to be one. The first observation

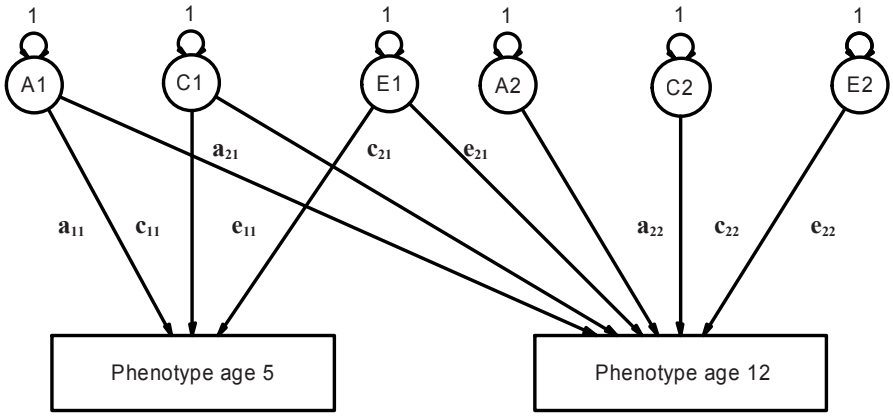


Figure 3:
The bivariate (longitudinal) model represented for one individual

Note:

Phenotype age 5:

$P = (a_{11}A_1 + c_{11}C_1 + e_{11}E_1)$

$V_P = (a_{11}^2) + (c_{11}^2) + (e_{11}^2)$

h² age 5 is $\frac{a_{11}^2}{a_{11}^2 + c_{11}^2 + e_{11}^2}$

Phenotype age 12:

$P = (a_{21}A_1 + a_{22}A_2 + c_{21}C_1 + c_{22}C_2 + e_{21}E_1 + e_{22}E_2)$

$V_P = (a_{21}^2 + a_{22}^2) + (c_{21}^2 + c_{22}^2) + (e_{21}^2 + e_{22}^2)$

h² age 12 is $\frac{a_{21}^2 + a_{22}^2}{a_{21}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{22}^2 + e_{21}^2}$

Genetic covariance is $(a_{11} \times a_{21})$

Genetic correlation is r_g is $\frac{a_{11} \times a_{21}}{\sqrt{a_{11}^2} \times \sqrt{a_{21}^2 + a_{22}^2}}$

loaded on the first latent factors A, C and E. The sum of squared estimates of factor loadings (i.e., $(a_{11}^2)+(c_{11}^2)+(e_{11}^2)$) represented the phenotypic variance at

age 5. The second observation loaded on both factors and the phenotypic variance of this observation consisted of the sum of the respective squared factor loadings (i.e., $(a_{21}^2+a_{22}^2)+(c_{21}^2+c_{12}^2)+(e_{21}^2+e_{22}^2)$). The covariance between both observations is derived by multiplying the factor loadings of both phenotypes on the first latent factors. The total covariance is the sum of those products (i.e., $(a_{11} \times a_{21})+(c_{11} \times c_{21})+(e_{11} \times e_{21})$). The longitudinal bivariate model is shown in Figure 3.

The longitudinal bivariate model can be extended to a longitudinal multivariate model. In this model an unconstrained decomposition of the covariance structure of multiple phenotypes into genetic and environmental covariance matrices is considered by means of triangular (or Cholesky) decomposition, including three variance components A, C and E. Based on the estimates of the A, C and E covariance matrices the genetic correlations between the phenotypes can be computed. The genetic correlations provide a measure of the extent to which phenotypes are influenced by the same genes.

RESULTS

At age 5 iq data and executive functioning tasks were available for all 237 twin pairs. The dcb was completed by the mother for 228 twin pairs. The trf ap scale was completed for 212 first-born twins and for 211 second-born twins. Of the original sample 172 twin pairs participated again at age 12. The group of non-responders at this age was not significantly different from the group who did participate for iq, executive functioning, and attention problems (as reported by the teacher or parents) at age 5.

For the 12-year-old sample 5 extra dizygotic female twin pairs were recruited, which made a total of 177 twin pairs at age 12. iq data were available for all but one participating twin. Of the executive functioning tasks the selective attention data of 8 children, the working memory data of 6 children, and the sustained attention data of 7 children were not recorded. Of the original sample at age 5 cbcl data at age 12 were available for 198 twin pairs and the trf ap scale was completed for 105 first born twins and 104 second born twins.

For the executive functioning tasks only correct responses (i.e., hits and correct rejections) were used for the analyses. In the sample at age 5 the data of children with an error rate >40% (n = 2 for selective attention) or a mean reaction time (RT) that was higher than three times the standard deviation above mean RT of the sample (n = 3 for selective attention, n = 2 for working memory) were excluded. In the sample at age 12 none of the children had >40% errors. For working memory one child was excluded because of a mean RT higher than three times the standard deviation. The left part of Table 1 gives an overview of total numbers of subjects and total number of complete twin pairs for each variable.

Descriptives

The right part of Table 1 shows for both ages the means and standard deviations of the total IQ scores, the executive functioning tasks (in ms.), and the AP scales of the DCB, TRF and CBCL. Longitudinal correlations between phenotypes at age 5 and IQ scores at age 12 are shown in Table 2. Because the operationalization of executive functioning was reaction time (RT) this correlated negatively with IQ (i.e., the higher the RT, the lower the IQ score). To avoid confusion the RT scores were multiplied with minus 1. Hence, positive correlations between selective attention, working memory and sustained attention and IQ, are presented.

As expected IQ performance at age 5 was the best predictor for IQ performance at age 12 (r = 0.52). Working memory, selective and sustained attention only correlated weakly (r = 0.13, 0.16 and 0.10 respectively). Notable was the correlation between AP as rated by the mother and the teacher with IQ performance at age 12 (r = -0.28 and -0.36 respectively). To test whether the correlations between AP and IQ at age 12 were influenced by IQ at age 5 we performed additional analyses in which we corrected for IQ scores at age 5. The phenotypic correlations decreased slightly but stayed significant with -0.23 and -0.28 respectively. As a comparison the correlation patterns of the same phenotypes, but measured at age 12, are also shown in Table 2. Noteworthy is that the phenotypic correlations between AP at age 12 and IQ performance at age 12 were almost similar to the longitudinal correlations (-0.30). The phenotypic correlations between working memory, selective and sustained attention at age 12 and IQ were higher than the longitudinal correlations (0.25-0.38 vs. 0.10-0.16).

Table 1:
Means and standard deviations (in ms.) for processing speed of selective attention, working memory, and sustained attention at age 5 and at age 12, and means and standard deviations for IQ scores at age 5 and age 12, and the syndrome scores on the AP scale of the behavior checklists DCB and TRF at age 5, and CBCL and TRF at age 12.

	N complete twin pairs	N subjects	Mean	SD
Total IQ score age 5	237	474	115.50	12.51
Selective Attention age 5	233	469	1911.38	420.42
Working Memory age 5	235	472	1900.07	329.60
Sustained Attention age 5	237	474	1716.91	254.10
DCB AP scale age 5	228	457	11.86	3.43
TRF AP scale age 5	209	423	5.03	6.22
Total IQ score age 12	176	353	99.45	14.91
Selective Attention age 12	171	346	930.96	209.85
Working Memory age 12	171	347	1074.86	239.16
Sustained Attention age 12	172	347	1090.08	259.04
CBCL AP scale age 12	198	386	2.47	2.59
TRF AP scale age 12	94	209	4.73	5.80

Note: DCB AP = Devereux Child Behavior Rating Scale, Attention Problems scale
TRF AP = Teacher Report Form, Attention Problems scale
CBCL AP = Child Behavior Checklist, Attention Problems scale

Table 2:
Phenotypic longitudinal correlations between IQ performance, executive functioning and attention problems at age 5, and IQ performance at age 12, and phenotypic correlations between executive functioning and attention problems at age 12, and IQ performance at age 12.

Phenotypic correlations	Phenotypes age 5 with IQ age 12	Phenotypes age 12 with IQ age 12
IQ performance	0.52	---
Selective Attention	0.16	0.25
Working Memory	0.13	0.38
Sustained Attention	0.10	0.35
DCB/CBCL AP	-0.28	-0.31
TRF AP	-0.36	-0.30

Note 1: DCB AP at age 5; CBCL AP at age 12
Note 2: DCB AP = Devereux Child Behavior Rating Scale, Attention Problems scale
TRF AP = Teacher Report Form, Attention Problems scale
CBCL AP = Child Behavior Checklist, Attention Problems scale

Genetic Modeling

Twin Correlations and Heritability Estimates

Bivariate, longitudinal genetic analyses were performed for phenotypes assessed at age 5 and their corresponding phenotypes at age 12 (for example selective attention at age 5 with selective attention at age 12). Twin correlations at each age and 'cross trait-cross twin' correlations were obtained separately for MZ and DZ pairs from a saturated model. Next, heritability was estimated from the best fitting bivariate longitudinal models. Table 3 shows the twin correlations and parameter estimates of the relative contribution of genetic and environmental influences, as well as the model fitting results for the best fitting longitudinal models. To obtain the χ^2, the likelihood of the saturated model was subtracted from that of the genetic model and multiplied by 2.

Table 3
Left part: Twin correlations and estimates of genetic, common and unique environmental influences for IQ performance, selective attention, working memory and sustained attention and attention problems at age 5 and 12.
Right part: Model fitting results for the best fitting bivariate model; the χ^2, degrees of freedom (df) and *p*-value reflect whether the A(C)E model fits well compared to the saturated model. A *p*-value < 0.05 indicates that the A(C)E model fits significantly worse.

Twin correlations	MZ	DZ	a^2	c^2	e^2	χ^2	df	*p*
IQ age 5	0.68	0.54	31	37	32	1.87	3	0.60
IQ age 12	0.81	0.43	81	---	19			
Selective Attention age 5	0.50	0.35	52	---	48	6.32	4	0.18
Selective Attention age 12	0.60	0.48	63	---	39			
Working Memory age 5	0.55	0.35	55	---	45	4.05	4	0.40
Working Memory age 12	0.73	0.54	73	---	27			
Sustained Attention age 5	0.60	0.28	59	---	41	5.11	4	0.28
Sustained Attention age 12	0.61	0.49	64	---	36			
DCB AP age 5	0.60	0.04	59	---	41	2.05	3	0.56
CBCL AP age 12	0.68	0.08	67	---	33			
TRF AP age 5	0.80	0.48	81	---	19	3.87	4	0.42
TRF AP age 12	0.72	0.25	71	---	29			

Note 1: a^2, c^2, and e^2 reflect the relative contribution of genetic, and common and unique environmental influences; the a^2 for AP as rated by the mother reflects a broad heritability including additive and non-additive effects
Note 2: DCB AP = Devereux Child Behavior Rating Scale, Attention Problems scale
TRF AP = Teacher Report Form, Attention Problems scale
CBCL AP = Child Behavior Checklist, Attention Problems scale
Note 3: In the saturated model the following parameters were estimated: MZ and DZ twin correlations for both phenotypes, the within person longitudinal correlation between the phenotypes, MZ and DZ 'cross trait-cross twin' correlations, means of both phenotypes, the effect of sex on the means of both phenotypes, and the variance of both phenotypes.
In the A(C)E model the following parameters were estimated: A, (C)and E, means of both phenotypes, and the effect of sex on the means of both phenotypes

DZ correlations for IQ at age 5 were higher than half the MZ correlations, indicating genetic and common environmental influences on individual differences in IQ at this young age. The twin correlation pattern for IQ at age 12 showed that influences of common environment disappear when children enter adolescence. A full model, including additive genetic (A), common (C) and unique environmental (E) factors, was used as a baseline model for the bivariate longitudinal analyses (see Figure 3). Model fitting analyses showed that A (31%), C (37%), and E explained the variance of IQ at age 5 and A (81%) and E explained the variance of IQ at age12. It was tested whether there was an overlap in genetic influences between IQ at age 5 and IQ at age 12 by omitting the covariance due to genetic influences (i.e., factor loading a21) from the model. This was not allowed which indicates that genes contributed significantly to the covariances of IQ at ages 5 and 12, or, in other words, that the same genes are expressed at ages 5 and 12. Variation in working memory, selective and sustained attention showed no significant influences of common environment at either age 5 or age 12. Hence, for all executive functioning tasks a model with A and E described the data best. Heritability estimates were between 52% and 59% at age 5, and between 63% and 73% at age 12. Genes contributed significantly to the longitudinal covariances between executive functioning indices at age 5 and age 12 as it was not allowed to omit the covariance due to genetic influences from the models (i.e., factor loading a21). Also for AP (mother and teacher ratings) no significant influences of C were found and genes contributed significantly to the longitudinal stability over time. AP as rated by the mother showed heritability estimates of 59% (age 5) and 67% (age 12). AP as rated by the teacher showed somewhat higher heritabilities; 81% at age 5 and 71% at age 12.

For all traits it was tested whether the shared variance due to E (i.e., factor loading e21), between the phenotypes assessed at age 5 and at age 12, was significant. The results showed that E only contributed significantly to the covariance of AP as rated by the mother. For IQ, executive functioning and AP as rated by the teacher this factor loading was not significant, so in these cases E did not contribute to the stability over time but had only time specific influences.

Table 4:
Cross trait / cross twin correlations between the phenotypes assessed at age 5 and IQ at age 12.

Cross trait/cross twin correlations with IQ age 12	MZ	DZ
IQ age 5	0.51	0.26
DCB AP age 5	-0.22	-0.03
TRF AP age 5	-0.44	-0.06
Selective Attention age 5	0.15	0.16
Working Memory age 5	0.20	0.13
Sustained Attention age 5	0.12	0.10

Note: DCB AP = Devereux Child Behavior Rating Scale, Attention Problems scale
TRF AP = Teacher Report Form, Attention Problems scale
CBCL AP = Child Behavior Checklist, Attention Problems scale

Genetic Correlations

The longitudinal 'cross trait-cross twin' correlations between IQ at age 12 and the phenotypes assessed at age 5 (for MZ and DZ twins) are summarized in Table 4. For AP at age 5 and IQ at age 12, the cross correlations were higher for MZ twins than for DZ twins. This indicates that longitudinal covariance between AP during childhood and IQ in early adolescence is due to genetic influences, i.e. AP at age 5 predicts IQ at age 12 because the genes that influence AP at age 5 also influence IQ at age 12. For executive functioning at age 5 and IQ at age 12 the pattern of longitudinal 'cross trait-cross twin' correlations was less clear.

We examined the genetic influences on the associations between the phenotypes assessed at age 5 and IQ performance at age 12 in a multivariate analysis. Genetic correlations that indicate to what extent traits are influenced by the same set of genes, were derived from a 7-variate model. Figure 4 shows the 7-

Table 5:
Genetic correlations between the phenotypes assessed at age 5 and IQ at age 12.

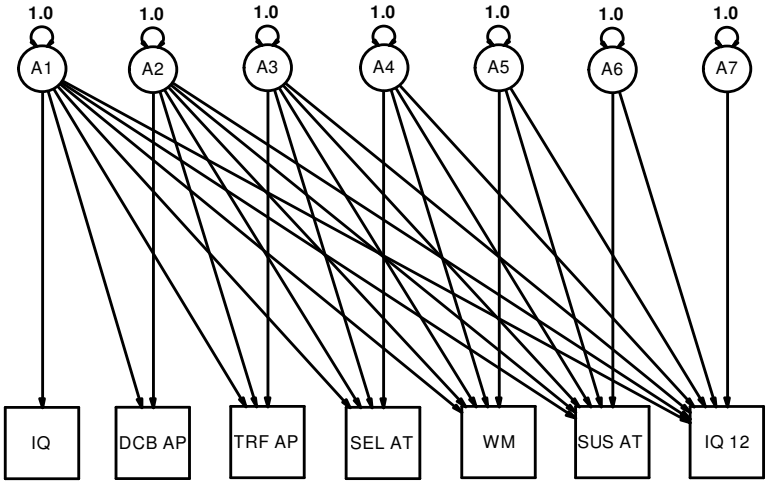
	r_g with IQ age 12
IQ age 5	0.81
DCB AP age 5	-0.42
TRF AP age 5	-0.39
Selective Attention age 5	0.31
Working Memory age 5	0.18
Sustained Attention age 5	0.16

Note: DCB AP = Devereux Child Behavior Rating Scale, Attention Problems scale
TRF AP = Teacher Report Form, Attention Problems scale
CBCL AP = Child Behavior Checklist, Attention Problems sc

variate model that was used to decompose the variances and covariances in and between traits.

In Table 5 the longitudinal genetic correlations between the phenotypes assessed at age 5 and IQ performance at age 12 are presented. The genetic correlations between selective attention, working memory and sustained attention at age 5, and IQ at age 12 were 0.31, 0.18 and 0.16 respectively. Although selective attention at age 5 and IQ at age 12 correlated only weakly on a phenotypic level, there is a shared set of genes influencing both phenotypes. The genetic correlation between IQ at age 5 and IQ at age 12 was 0.81. Notable also was the genetic correlation between AP at age 5 and IQ performance at age 12. For AP as reported by the mother this was -0.42 and for AP as reported by the teacher -0.39.

Underneath Figure 4 the genetic correlations between all traits are shown. The genetic correlations of selective attention, working memory and sustained attention with IQ at age 5 were 0.70, 0.55 and 0.36 respectively which indicates that, contrary to the longitudinal correlations, during childhood a large set of the same genes influence selective attention and IQ, and to a lesser extent working memory and sustained attention and IQ. The genetic correlations between executive functioning and AP as reported by the mother at age 5 were very low



IQ age 5	8.13	***-0.48***	***-0.37***	***0.70***	***0.55***	***0.36***	***0.81***
DCB AP	-1.25	-2.29	***0.27***	***-0.17***	***0.08***	***0.00***	***-0.42***
TRF AP	-2.03	-0.58	-4.99	***-0.38***	***-0.31***	***-0.32***	***-0.39***
SEL AT	13.84	-3.73	3.05	13.40	***0.94***	***0.86***	***0.31***
WM	8.58	-6.11	2.56	10.63	-3.95	***0.80***	***0.18***
SUS AT	6.73	-3.60	4.15	15.17	3.44	6.26	***0.16***
IQ age 12	10.89	0.38	1.15	-5.03	0.81	5.80	0.06

Figure 4:
The multivariate (Cholesky) model with 7 variables represented for one individual

Note 1: First six phenotypes were assessed at age 5, last phenotype (IQ) at age 12
Note 2: Factor loadings of the multivariate analyses are presented on and under the diagonal, genetic correlations are presented above the diagonal
Note 3: DCB AP = Attention Problems as rated with the DCB by the mother
TRF AP = Attention Problems as rated with the TRF by the teacher
SEL AT = selective attention; WM = working memory; SUS AT = sustained attention

(0.00- -0.17). However, AP as reported by the teacher and executive functioning showed substantially higher genetic correlations (-0.31- -0.38). Working memory, selective and sustained attention amongst themselves correlated high (> 0.80) pointing to a large set of overlapping genes for these measures of executive functioning at this age. The genetic correlation between AP and IQ both at age 5 showed genetic correlations that were similar to the longitudinal genetic correlations between AP and IQ, namely -0.48 and -0.37. Overall this is a strong indication for the existence of common genetic factors influencing attention problems during childhood and IQ performance during early adolescence.

DISCUSSION

Variation in human behavior may be caused by differences in genotype and by differences in environment between individuals. In the present longitudinal study the relative contribution of genotype and environment to phenotypic variation in cognitive abilities (as measured with a standardized IQ test), executive functioning and attention problems was examined for children aged 5 and 12 years old. Furthermore the predictability of IQ, executive functioning and attention problems during childhood for IQ performance in early adolescence, and the longitudinal genetic and environmental mediation of the association between these phenotypes were investigated.

Rather surprising was the weak phenotypic correlation between executive functioning at age 5 and IQ performance at age 12. As executive functioning is believed to be a key factor of cognitive development (Davidson et al. 2006) it was expected that selective attention, working memory or sustained attention would be substantial predictors. This longitudinal effect however, was not found. There was though a longitudinal genetic correlation of 0.31 between selective attention and IQ which indicates that the weak phenotypic relation is due to partly overlapping genes.

Less surprising was the strong correlation between IQ performance at age 5 and IQ performance at age 12. Despite the different IQ tests (at age 5 the RAKIT, and at 12 the WISC was used) and the 7 year time interval this correlation was 0.52.

The stability in iq performance was driven by genetic factors while common and unique environmental factors were not transmitted over time (Bartels et al. 2002; Petrill et al. 2004).

Most remarkable was the finding that attention problems (ap) as reported by the mother and teacher at age 5 were strong predictors for iq performance at age 12. Children with severe attention problems are characterized by impaired attention, impulsive and hyperactive behavior and may clinically be diagnosed as having adhd. Research in clinical samples has speculated that prefrontal dysfunctions contribute to impaired cognitive functioning in children with adhd (Pennington & Ozonoff, 1996; Tannock, 1998; Barkley, 1997). Several studies confirmed that adhd is associated with dysfunction in prefrontal striatal neural circuits (Casey & Durston, 2006; Durston et al. 2006), the evidence for impaired cognitive functioning however is not unambigious (Doyle et al. 2005; Jonsdottir et al. 2006; van Mourik et al. 2005; Castellanos et al. 2006). In our study the genetic correlation between executive functioning and ap as reported by the mother during childhood was very low. ap as reported by the teacher however showed genetic correlations with executive functioning between -0.31 and -0.38. This indicates that mothers probably rate the attention problems of their children at this young age in a different way than teachers do, for example because teachers focus on attention problems that involve scholastic performance. Future studies that examine the relation between ap and cognitive performance should take into account that an outcome may depend on the informant of the child's behavior, and that therefore multiple informants are preferable.

A few studies reported significant negative associations between iq performance and ap (Rucklidge & Tannock, 2001; Kuntsi et al. 2004). Kuntsi et al. (2004) investigated the genetic origin of the co-occurrence of ap and low iq scores cross-sectional in a population based sample of 5-year-old twins. As in the current study the phenotypic correlation between ap (as assessed by mother and teacher reports) and iq was -0.30 which was accounted for by genetic influences that were shared by ap and iq. This confirms our results which also showed that partly the same (and partly different) genes accounted for the longitudinal correlation between ap and iq. Kuntsi et al. (2004) speculated that the common genes that are shared between ap and iq performance may involve brain volume

abnormalities that influence both AP and IQ. Castellanos et al. (2002) reported persistent brain abnormalities in children with ADHD while Shaw et al. (2006a) reported an association between intelligence and the trajectory of cortical development, primarily in frontal regions. In an accompanying study Shaw et al. (2006b) showed that children with ADHD have relative cortical thinning in regions important for attentional control (i.e., medial and superior prefrontal and precentral regions). An association between brain volume and intelligence was reported by Posthuma et al. (2002) who showed that IQ and brain volume are influenced by shared genetic factors.

A very useful design to investigate the genetic and environmental influences on brain deficits related to attention problems is combining cognitive and brain imaging methods in MZ twins discordant or concordant for attention problems. Since MZ twins are genetically identical, the presence of attention deficits in one twin but not the co-twin must originate from experiencing different (pre or postnatal) unique environmental risk factors. This might be reflected in structural or functional brain differences which in turn may enlighten the etiology of attention problems. Two studies using this design so far found diverging results. Castellanos et al. (2003b) collected MRI scans of 9 MZ twin pairs that were discordant for ADHD. It was found that the affected twins had smaller caudate volumes than their unaffected co-twins. In a similar study by van 't Ent et al. (in revision) MRI scans of 3 concordant high, 17 concordant low and 5 discordant MZ twin pairs (as measured with the AP scale of the CBCL) were investigated. The findings indicated that inattention and hyperactivity symptoms are associated with volume deficits for several neocortical areas and the cerebellum, but not the striatum. The difference in outcomes may be due to sample differences as the twin pairs in the study of Castellanos et al. (2003b) were clinically diagnosed as having ADHD while van 't Ent et al. (in revision) collected data in the general population. These exploring results however are highly relevant and future research in this area is of great interest.

Summing up the current results, it was shown that variation in IQ, executive functioning and attention problems are influenced by genetic factors throughout childhood. IQ performance and attention problems in the preschool period were significant predictors of IQ performance in early adolescence. Moreover,

the same genes that influence IQ at age 12 also influence attention problems at age 5. These results strongly support the need for the early tracing of attention problems during childhood. The shared set of genes that was found in this study indicates that children who may be vulnerable for attention problems may also have a higher risk for intellectual deficits. Early treatment and counseling may prevent children not only from severe behavioral problems later in childhood but also from deficits in scholastic and intellectual development.

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3

GENETIC ANALYSES OF TEACHER RATINGS AND PROBLEM BEHAVIOR IN 5-YEAR-OLD TWINS

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ABSTRACT

Behavioral problems in young children can be assessed by asking their parents or teachers to rate their behaviors. Genetic analyses of parental ratings show relatively large heritabilities for emotional and behavioral problems in young children, but data from teachers for this age group are scarce. We examined sources of variation in the Teacher's Report Form (TRF) problem scales. The TRF was completed for 211 Dutch 5-year-old twin pairs and 4 single twins. Twins rated by different teachers had higher means and variances than twins rated by the same teacher, in addition twin correlations were lower in this group. In both groups MZ correlations were generally higher than DZ correlations.

We tested a model for twin resemblance that allowed for these effects. For five problem scales (Withdrawn, Social Problems, Aggressive Behavior, Rule Breaking Behavior and Attention Problems) a model with genetic and unique environmental sources of variation fitted best to the data. For three problem scales (Anxious/Depressed, Thought Problems and Somatic Complaints) there were familial influences but it was not possible to distinguish between common environmental influences or genetic influences. Heritability was 63% for Attention problems, around 45% for Withdrawn, Social Problems, Aggressive Behavior and Rule Breaking Behavior, and around 30% for Anxious/Depressed, Thought Problems and Somatic Complaints.

Behavioral and emotional problems such as overactivity, anxiety, lack of attention or aggression are relatively common in young children (Campbell, 1995; van den Oord et al. 1996; Koot et al. 1997; Bartels et al. 2004). High levels of these problem behaviors are stable over time and not limited to clinical groups. Several studies have reported stability from childhood into adulthood (Campbell & Ewing, 1990; Lavigne et al. 1998; Verhulst & Van der Ende, 1992; Roza et al. 2003). For this reason, early detection and knowledge about the etiology of childhood behavior problems is crucial. Keenan and Wakschlag (2000, 2002) assume that in preschool children problem behavior like aggression is less entrenched than later in life, and that behavioral control emerges during this developmental period. Therefore, intervention at this young age is more effective than later in childhood.

Individual differences in parent-reported problem behavior in children aged 2 to 7 years are to a large degree genetically influenced. Studies using Child Behavior Checklist data (CBCL, Achenbach 1991) from the Netherlands Twin Registry (NTR) found genetic influences for both internalizing and externalizing problems in preschool children. Rietveld et al. (2003) and Van den Oord et al. (1996) studied overactive behavior and attention problems in 3-year-old twin pairs. Their results showed heritability estimates around 68%. Derks et al. (2004) investigated aggressive, oppositional, overactive, withdrawn and anxious behavior in 9689 3-year-old twin pairs. They found high genetic contributions for all problem scales (40-70%), except for oppositional behavior where 20% (as rated by the father) to 32% (as rated by the mother) of the variance was explained by genetic influences.

Using the Devereux Child Behavior Rating Scale (DCB, Spivack & Spotts, 1966) in a sample of 8041 5-year-old twin pairs, Van Beijsterveldt et al. (2004) reported heritabilities of 50 to 80% for maternal ratings of aggression, anxiety, dependency, emotional lability and attention problems.

Research from other twin registries also found genetic influences on parental reports of behavioral problems in young children. In a sample of 199 Norwegian 5- and 6-year-old twin pairs, Gjone et al. (1996) reported a heritability of 73% for internalizing problems. Schmitz et al. (1995) reported for 260 2- and 3-year-old twin pairs of the Colorado Twin Registry, heritabilities of between 29 and 52%

for anxious behavior, withdrawn, sleep problems, somatic complaints, aggression and destructive behavior.

Genetic research on young children's problems is often based on parental reports while behavioral data from teachers about preschool children are scarce. Parents are an important source for the assessment of their children's problems (Van der Valk et al. 2001; Bartels et al. 2003; Arseneault et al. 2003). However, situational variation in children's behaviors at home and at school makes teachers another important source of information. For example, teachers may have a unique view on problems that are specific to the classroom or other school situations, such as problems in the social interactions with other children, or task oriented situations. Teachers also have an advantage over parents in their wide exposure to children of the same age, which makes them able to compare the child's behavior with that of many same-aged peers (Verhulst et al. 1997).

Zahn-Waxler et al. (1996) studied internalizing and externalizing problems and related problems of attention and hyperactivity in 5-year-old twins. They used parental data collected with the CBCL, and teacher data collected with the Preschool Behavior Questionnaire (PBQ, Behar & Stringfield, 1974). For teacher and mother reports they found significant genetic influences for all three problem scales. The father reports showed significant genetic influences for externalizing and attention/hyperactivity problems but not for internalizing problems.

Genetic variation in antisocial behavior was investigated in a representative-plus-high-risk sample by Arseneault et al. (2003). For 1116 5-year-old twins they had data from mothers, teachers, examiner-observers and children themselves. They reported high heritabilities ranging from 42% based on children's self-report to 76% for the teacher reports.

From genetic studies using teacher data in older twin samples we know that twin correlations can be much higher for twin pairs who were rated by the same teacher than for twin pairs who were rated by different teachers (Vierikko et al. 2004; Towers et al. 2000; Simonoff et al. 1998; Derks et al. submitted). According to Simonoff et al. (1998) and Derks et al. (submitted) these high twin correlations are not due to twin confusion (i.e., the teacher confuses the members of a twin pair) but are likely to be associated with teacher and classroom characteristics. Teacher ratings of a particular child's behavior may be influenced by the teacher's

expectations about normal and abnormal behavior, by aspects of the relationship between a teacher and a particular child and by influences the teacher imposes on the classroom as a whole, such as a specific educational approach.

The age of 5 corresponds with the developmental transition from preschool to elementary school and marks an important change in daily occupation, and social and cognitive functioning. In the Dutch system, school is obligatory from age 5 onward, but most children start school when they are 4 years old. In two years time, from age 4 to age 6, children are expected to adapt to the social, emotional and cognitive demands which involve their school participation. Genetic studies covering this important developmental time span are rare. Of the four studies that investigated the behavior of 5-year-old twin pairs, only the ones by Zahn-Waxler et al. (1996) and Arseneault et al. (2003) used teacher data. The other studies (i.e., Gjone et al. (1996) and Van Beijsterveldt et al. (2004)) used parental data.

In the present study Teacher's Report Form data (TRF, Achenbach, 1991) of 211 Dutch 5-year-old twin pairs and 4 single twins were analyzed. The first aim of this study was to examine the sources of variation of eight specific problem scales of the TRF (Withdrawn, Anxious/Depressed, Social Problems, Aggressive Behavior, Rule Breaking Behavior, Attention Problems, Thought Problems and Somatic Complaints).

A second aim of the study was to explore whether teacher-specific styles influence the teacher's ratings. In our sample 126 twin pairs shared the same teacher and 89 twin pairs had a different teacher. We evaluated a model in which the non-shared environmental component was allowed to correlate in children who were rated by the same teacher.

Power analyses showed that the power to detect sex differences in heritabilities was low (see appendix). Therefore, male and female twin data for both zygosities were combined. For the analyses we used a four group design: monozygotic (MZ) twins rated by the same teacher, MZ twins rated by different teachers, dizygotic (DZ) twins rated by the same teacher and DZ twins rated by a different teacher.

METHODS

Subjects

The twins were registered at birth with the Netherlands Twin Registry (NTR) kept by the department of Biological Psychology of the Vrije Universiteit in Amsterdam. Of all multiple births in the Netherlands, 40-50% are registered by the NTR (Boomsma, 1998; Boomsma et al. 2002). Parents of the twins receive a behavior questionnaire every two years (Child Behavior Checklist, Achenbach, 1991). A subsample of all twin pairs participated in a study on neuropsychological development and attention (Groot et al. 2004; Stins et al. in press). This sample consisted of 237 twin pairs, mean age: 5.8 years (SD: 0.1). The sample was selected on the basis of age, city of residence, and zygosity which was determined on the basis of DNA polymorphisms. For practical reasons, children had to live within one hundred kilometre radius of the Vrije Universiteit. None of the children suffered from severe physical or mental handicaps. Parents signed an informed consent form.

The TRF was returned for 215 first-born twins and for 213 second-born twins. IQ data and behavioral ratings by the parents were available for all 237 twin pairs. We compared TRF responders and TRF non-responders on these variables. There were no significant differences between responders and non-responders in total IQ score, socio-economic status or the problem scales of the Devereux Child Behavior Rating Scale, as reported by the parents.

Most twin pairs (N=126) shared the same classroom and the same teacher, 89 twin pairs were in parallel classrooms and were assessed by different teachers. There is no official policy about separating twin pairs when they go to school. However, Dutch twin organisations advise parents and schools to do so, which is reflected by the fact that large schools often enforce such policies. The decision to separate a twin pair thus may be based on parental choice, may be enforced by the school or, in the case of smaller schools, is not possible because there is simply only one classroom for a particular age group.

For 4 twin pairs only one TRF was returned (i.e., for the first-born twin or for the second-born twin) of which three twins had a different teacher than the co-twin

and one twin had the same teacher as the co-twin. We excluded two children because of missing items. The final sample of twin pairs consisted of 45 monozygotic twin pairs rated by different teachers (MZ-DT), 44 dizygotic twin pairs rated by different teachers (DZ-DT), 67 monozygotic twin pairs rated by the same teacher (MZ-ST) and 59 dizygotic twin pairs rated by the same teacher (DZ-ST).

Procedure

The children were visited at home to perform a neuropsychological test battery consisting of an intelligence test and several tasks of the Amsterdam Neuropsychological Tasks (ANT, De Sonneville, 1999). Behavioral data were collected with the Devereux Child Behavior Rating Scale (DCB, Spivack & Spotts, 1966) filled in by the parents, and after permission of the parents, the Teacher's Report Form (TRF, Achenbach, 1992; Verhulst et al. 1997) was filled in by the teachers.

The TRF consists of two parts. The first part contains questions about daily functioning and school results of the child, the second part consists of 120 problem items. Teachers are instructed to rate the child's behavior over the last two months with 0 if the behavior is not true, 1 if the behavior is sometimes or somewhat true, and 2 if the behavior is very or often true. Items can be scored on eight specific problem scales, two broad band scales (internalizing and externalizing) and a total problem scale. The eight specific problem scales are Withdrawn, Anxious/Depressed, Social Problems, Aggressive Behavior, Rule Breaking Behavior, Attention Problems, Thought Problems and Somatic Complaints. Because the data were not normally distributed, problem scores were square-root transformed.

Analyses

In SPSS (11.5) we performed a MANOVA to test for possible differences in problem behavior between twins who shared the same teacher and twins who had different teachers, as reported by the mother with the CBCL at age 3, and the DCB at age 5. Of the CBCL data the internalizing and externalizing broad band scales were used, and of the DCB data seven specific problem scales were used. The CBCL age 2/3 is described by Derks et al. (2004) and the derived problem scales of the

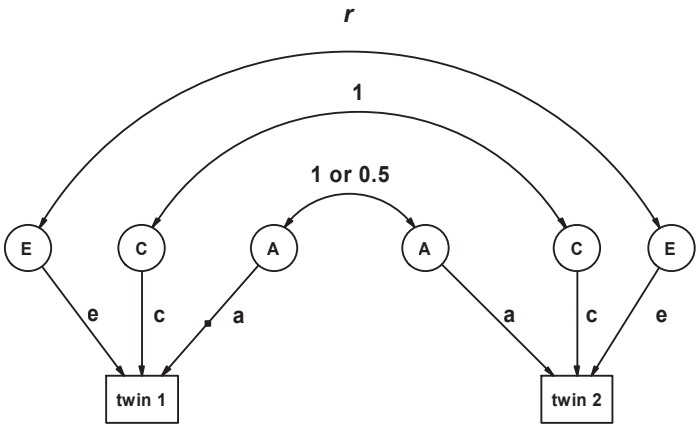

Figure 1a: Path diagram for twins rated by the same teacher. A is the additive genetic variance, correlated 1 for MZ twins and 0.5 for DZ twins, C is the shared environmental variance, correlated 1 for MZ and DZ twins. E is the unique environmental variance, correlated r for MZ and DZ twins who share the same teacher.

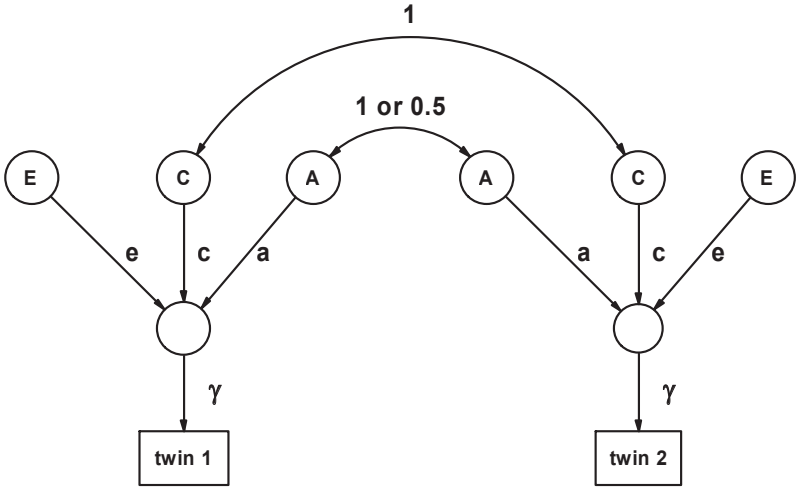

Figure 1b: Path diagram for twins rated by different teachers. The variances of twins who were rated by different teachers were modeled as scalar (γ) times the total variance of twins rated by the same teacher. Path coefficients a, c and e are equal for both groups.

DCB are described by Van Beijsterveldt et al. (2004).
Genetic analyses were carried out using the statistical software package Mx (Neale, 1999). The total variation in problem scores was decomposed into sources of additive genetic variance (A), common environmental variance (C) and unique environmental variance (E). A is due to additive effects of different alleles, C is due to environmental influences shared by members of a twin pair, and E is due to environmental influences not shared by members of a twin pair. E also includes measurement error and is therefore always included in the models.
We fitted full ACE models to the data of each problem scale. To obtain the most parsimonious model for each problem scale, we compared AE and CE models to the full ACE model using the likelihood ratio test which is computed by taking twice the difference between the log-likelihood of the full model and the log-likelihood of a reduced model. The associated degrees of freedom are computed as the difference in degrees of freedom between the two nested models.
The possibility that teachers bring in their own influences when rating the children was tested with the model as proposed by Simonoff et al. (1998), where the increase in correlations for twins rated by the same teachers is reflected as a correlation different from zero between the latent unique environmental influences (E) of the two members of the twin pairs who share the same teacher (see Figure 1a).

RESULTS

Descriptives

The results of the MANOVA showed that there were no significant differences in problem behavior between twins who shared the same teacher and children who were in separate classrooms, as rated by the mother at age 3 and age 5 (p = 0.24). When examining the univariate results only the aggression scale of the DCB showed a significant difference (p = 0.087 for the first-born twin and p = 0.009 for the second-born twin). No significant differences were found at age 3 (p > 0.7).

Table 1:
Means and standard deviations (based on untransformed data), and twin correlations with confidence intervals (based on transformed data) for each problem scale, for MZ and DZ twin pairs rated by the same teacher (ST) and for MZ and DZ twin pairs rated by different teachers (DT)

	Means DT (means girls/ boys)	SD	Twin correlations MZ-DT (n = 45)	Twin correlations DZ-DT (n = 44)	Means ST (means girls/ boys)	SD	Twin correlations MZ-ST (n = 67)	Twin correlations DZ-ST (n = 59)
Withdrawn	2.14/2.53	2.83	0.48 (0.25-0.66)	0.05 (-0.29-0.36)	1.29/1.42	1.80	0.74 (0.62-0.82)	0.42 (0.15-0.61)
Anxious/ Depressed	3.07/3.72	4.01	0.19 (-0.10-0.44)	0.41 (0.11-0.62)	1.57/2.72	2.88	0.71 (0.57-0.80)	0.45 (0.22-0.62)
Social Problems	1.70/2.35	2.72	0.39 (0.14-0.59)	0.31 (-0.03-0.56)	0.77/1.78	1.95	0.71 (0.58-0.80)	0.49 (0.26-0.646
Aggressive Behavior	3.33/7.18	6.75	0.40 (0.16-0.59)	0.21 (-0.16-0.50)	2.97/4.90	6.07	0.84 (0.76-0.89)	0.43 (0.16-0.62)
Rule Breaking Behavior	0.43/0.93	1.22	0.34 (0.09-0.54)	0.41 (0.09-0.63)	0.28/0.47	0.84	0.82 (0.73-0.88)	0.48 (0.24-0.65)
Attention Problems	5.22/7.77	6.69	0.67 (0.48-0.78)	0.31 (-0.03-0.56)	2.79/5.43	5.35	0.81 (0.71-0.87)	0.58 (0.39-0.71)
Thought Problems	0.27/0.60	0.97	0.28 (0.04-0.49)	0.28 (-0.17-0.57)	0.20/0.31	0.69	0.62 (0.47-0.73)	0.40 (0.09-0.61)
Somatic Complaints	0.61/0.92	1.02	0.23 (-0.003-0.44)	0.39 (-0.22-0.66)	0.26/0.30	0.66	0.55 (0.37-0.68)	0.34 (0.05-0.56)

Using Mx, we established in a saturated model that means and variances of the TRF problem scales were equal for both members of a twin pair, and for MZ and DZ twins. We then tested if there were teacher differences (i.e., if the ratings by different teachers differed from the ratings by the same teacher) in means and variances. The means and variances of twins who were rated by the same teacher

Table 2:
Model fitting results

	Model	χ^2	df	*p*	AIC	A or C	E	r	γ
Withdrawn	ACE*r*	1.88	1	0.17	-0.12				
	ACE	6.67	1	0.01	4.66				
	AE*r*	0.00	1	-	-2.00	0.49	0.51	0.47	1.63
	CE*r*	13.26	1	0.00	11.26				
	E*r*	21.49	2	0.00	17.49				
Anxious/Depressed	ACE*r*	4.48	1	0.03	2.48				
	ACE	9.56	1	0.00	7.57				
	AE*r*	0.02	1	0.90	-1.98	0.34	0.66	0.52	1.36
	CE*r*	3.16	1	0.08	1.16	0.29	0.71	0.42	1.35
	E*r*	10.47	2	0.01	6.47				
Social Problems	ACE*r*	0.36	1	0.55	-1.64				
	ACE	7.32	1	0.01	5.32				
	AE*r*	0.08	1	0.77	-1.92	0.42	0.58	0.49	1.42
	CE*r*	4.97	1	0.03	2.97				
	E*r*	16.98	2	0.00	12.98				
Aggressive Behavior	ACE*r*	3.19	1	0.07	1.19				
	ACE	18.84	1	0.00	16.84				
	AE*r*	0.00	1	-	-2.00	0.49	0.51	0.66	1.01
	CE*r*	20.88	1	0.00	18.88				
	E*r*	30.96	2	0.00	26.96				
Rule Breaking Behavior	ACE*r*	4.11	1	0.04	2.11				
	ACE	17.91	1	0.00	15.91				
	AE*r*	0.00	1	-	-2.00	0.45	0.55	0.65	1.55
	CE*r*	13.04	1	0.00	11.04				
	E*r*	25.21	2	0.00	21.21				
Attention Problems	ACE*r*	0.51	1	0.48	-1.85				
	ACE	4.62	1	0.03	2.62				
	AE*r*	0.67	1	0.41	-1.33	0.63	0.37	0.49	1.56
	CE*r*	14.76	1	0.00	12.76				
	E*r*	40.50	2	0.00	36.50				
Thought Problems	ACE*r*	0.67	1	0.41	-1.33				
	ACE	6.64	1	0.01	4.64				
	AE*r*	0.00	1	-	-2.00	0.32	0.68	0.43	1.49
	CE*r*	2.56	1	0.11	0.56	0.28	0.72	0.37	1.47
	E*r*	9.75	2	0.00	5.75				
Somatic Complaints	ACE*r*	1.33	1	0.25	-0.67				
	ACE	4.03	1	0.05	2.03				
	AE*r*	0.00	1	-	-2.00	0.27	0.73	0.35	1.52
	CE*r*	1.27	1	0.26	-0.73	0.26	0.74	0.29	1.52
	E*r*	6.74	2	0.03	2.74				

Note: Submodels ACE, AE*r*, CE*r* and E*r* are compared with ACE*r* model, which in turn is compared with the fully saturated model.

were significantly lower than the means and variances of twins rated by different teachers for all problem scales, except for aggressive behavior. We then tested if twin correlations were equal for both groups. Twin correlations of twin pairs who were rated by the same teacher were significantly higher than twin correlations of children who were rated by different teachers. Table 1 shows means and standard deviations (based on untransformed data), and twin correlations (based on transformed data) according to zygosity and same versus different teacher.

Genetic Modeling

As the variances of twin pairs who were rated by different teachers were higher than the variances of twin pairs rated by the same teacher, a scalar model was fitted in which the variances of twins who were rated by different teachers were modeled as scalar times the total variance of twins rated by the same teacher (see Figure 1b). Table 2 shows the genetic modeling analyses for each problem scale. The correlation (*r*) of the unique environmental influences in MZ and DZ twin pairs who shared the same teacher was substantial (0.35 to 0.66) and could not be left out of the model without significantly reducing the fit of the model to the data.

Reduced models were compared to the full ACE*r* model. Analyses showed that for all problem scales we could drop C from the full model. However, for the problem scales Anxious/Depressed, Thought Problems and Somatic Complaints it was possible to drop A or C from the full model, indicating that the variance was explained by familial influences, however, we could not distinguish between genetic or common environmental influences. Unique environmental influences (E) contributed most to the total variance (around 0.60) except for Attention Problems (0.39).

DISCUSSION

The age of 5 is a vital period of progress in which children change from dependent, needy toddlers to self-assured, independent school children. The development of social competence and emotion regulation in preschool children

is crucial as it can predict both emotional disorders and academic outcomes such as school readiness, and positive attitudes toward school (Blair et al. 2004). Therefore, it is important to examine possible underlying sources of variation in this stage of development. However, genetic research involving the behavior of 5-year-old children is scarce. Genetic studies containing teacher ratings about the behavior of children at this young age are especially limited. In the current study teacher reports were assessed in 211 5-year-old twin pairs and 4 single twins. For individual differences in eight specific problem scales of the Teacher's Report Form (TRF, Achenbach, 1991) we estimated the relative contribution of genetic and environmental influences. Furthermore we tested whether or not teachers bring in specific influences to their ratings.

We found that for Withdrawn, Social Problems, Aggressive Behavior and Rule Breaking Behavior, genetic influences explained around 40% of the total variance, and unique environmental influences around 60%. For Attention Problems the genetic component explained around 60% of the variation and the unique environmental component about 40%. For Anxious/Depressed, Thought Problems and Somatic Complaints, familial influences were found but no distinction could be made between common environmental influences and genetic influences.

It is known that in addition to information from parents about a child's behavior, teacher information is valuable as well (Van der Ende & Verhulst, 2005). The school situation enables teachers to compare the behavior of one child with the behavior of many other same-aged, older or younger children through which they can judge whether the behavior of the child is appropriate for his or her age. However, as parents may have a possible rater bias by lacking internal standards to determine 'normal' levels of behavior, teachers too may have their own kinds of 'bias'.

In our results the means and variances for all problem scales were higher in twins rated by different teachers compared to twins rated by the same teacher. This was not due to the fact that more boys than girls were in parallel classrooms (as boys generally tend to have higher means than girls) nor to the fact that children were in different schools, for example specific schools for learning or behavioral problems. The question arises, why do twins who were rated by different teachers appear to have more behavioral and emotional problems? A first explanation

may be that twins who were rated by different teachers were probably separated from each other for the first time in their lives. Their increased level of problems may be a reaction to this separation. The reverse may also be true. It may be that problematic twins were separated in school because parents or teachers expected that these twins would be easier to handle apart from each other, in separate classrooms. The differences in teacher ratings may also reflect differences related to location and size of the school: it is likely that children from larger towns and villages have more opportunities to go to separate classrooms than children from smaller villages, in which only one school for elementary education is available and in which no parallel classes exist. Tully et al. (2004) investigated the effects of classroom separation on the behavior of twins when separated at age 5 or at age 7. Compared to non-separated twins, separated twins showed significantly more internalizing problems at both ages, as rated by the teacher. As some twins were not separated at age 5 but only at age 7, the investigators could test if the internalizing problems were already present at age 5. This was not the case, suggesting that the separation caused the emotional problems of these children. No differences between separated and non-separated twins were found for externalizing problems or ADHD. Our TRF results partly confirmed these findings. We found differences in mean problem scores for Withdrawn and Anxious/Depressed, and Social Problems (see Table 1). However, Tully et al. (2004) did not observe differences for Attention Problems whereas we did.

Van Leeuwen et al. (2005) analysed mother ratings (CBCL at ages 3, 7 and 12) and teacher ratings (TRF at ages 7 and 12) in a much larger group of twins from the NTR. No TRF data at age 5 were available, as the NTR routinely collects TRF data only in children of 7 years and older. Van Leeuwen et al. (2005) found that separating the twins when going to school led to more internalizing problems at age 7, but that these problems were no longer present when the children were 12 years old. Twins who were separated at age 5 already had more externalizing problems at age 3. These externalizing problems persisted in time but when the data were corrected for these problems at age 3, there were no additional effects at older ages. This suggested that the decision to separate the twins when starting school was based in part on existing externalizing problems. However, in the current, much smaller sample, there were no differences in problem behavior

between twins sharing a classroom and twins who were in separate classrooms according to maternal ratings of these twins at age 3, and at age 5.

Twin correlations in twins who were rated by different teachers were lower than twin correlations in twin pairs rated by the same teacher. Twin studies using teacher data in older children (age 12-14 year) showed the same pattern (Vierikko et al. 2004; Towers et al. 2000; Simonoff et al. 1998). An explanation for the high resemblance in twins rated by the same teacher is that these ratings include teacher-specific influences. The results of the current study confirmed that specific teacher styles influenced their ratings. With the unique correlation (*r*) estimated around 50%, it was not possible to drop *r* from the model without worsening the fit significantly.

Specific teacher styles can cover a whole range of domains, including personal values and pedagogic qualities but also school systems and educational approaches. Some teachers for example prefer strict rules in the classroom whereas others have a more lenient style. Some children prosper better under free conditions whereas others need a structured environment. An accurate way to explore this phenomenon is by obtaining ratings of the twins from multiple teachers. This is perhaps not an impossible job, as children change teachers almost every school year.

A final question is how to describe the teacher-specific influences as reflected in our model. 'Correlated error' as proposed by Simonoff et al. (1998), suggests a real bias in the teacher ratings but this is not the case. 'Uniquely correlated' might be a better description in this context.

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APPENDIX

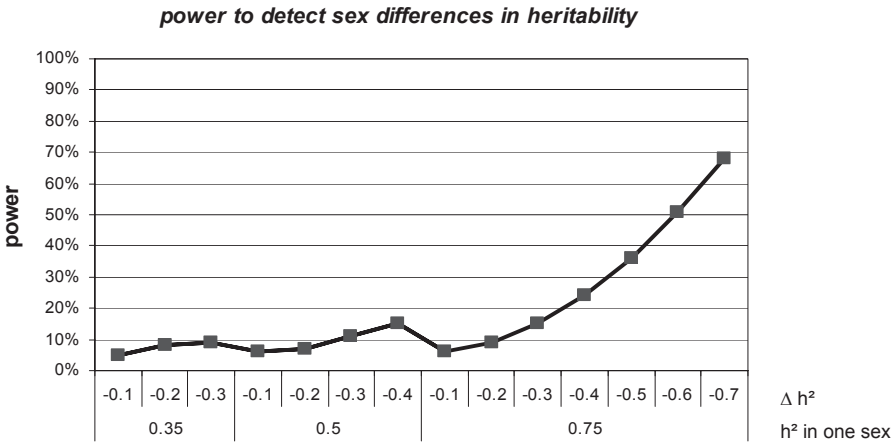

Figure shows the power (y-axis) to detect differences in heritability (x-axis) between boys and girls given a sample size of 215 twin pairs.
For a fixed heritability (h^2) of 0.35, 0.50 and 0.75 in one sex, the power to detect a difference of heritability (Δh^2) between boys and girls of respectively -0.1, -0.2 and -0.3, -0.1, -0.2, -0.3 and -0.4, and -0.1, -0.2, -0.3, -0.4, -0.5, -0.6 and -0.7 is shown.

4

ACROSS THE CONTINUUM OF ATTENTION SKILLS: A TWIN STUDY OF THE SWAN ADHD RATING SCALE

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ABSTRACT

Most behavior checklists for Attention Problems or ADHD such as the Child Behavior Checklist (CBCL) have a narrow range of scores, focusing on the extent to which problems are present. It has been proposed that measuring attention on a continuum, from positive attention skills to attention problems, will add value to our understanding of ADHD and related problems. The Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN) is such a scale. Items of the SWAN are scored on a seven point scale, with in the middle 'average behavior' and on the extremes 'far below average' and 'far above average'.

The SWAN and the CBCL were completed by mothers of respectively 560 and 469 12-year-old twin pairs. The SWAN consists of nine DSM-IV items for Attention Deficit (AD) and nine DSM-IV items for Hyperactivity/Impulsivity (HI). The CBCL Attention Problem (AP) scale consists of 11 items, which are rated on a three point scale.

Children who had a score of zero on the CBCL AP scale can be further differentiated using the SWAN with variation seen between the average behavior and far above average range. In addition, SWAN scores were normally distributed, rather than kurtotic or skewed as is often seen with other behavioral checklists. The CBCL AP scale, and the SWAN-HI and AD scale were strongly influenced by genetic factors (73%, 90% and 82%, respectively). However, there were striking differences in genetic architecture: variation in CBCL AP scores is for a large part explained by non-additive genetic influences. Variation in SWAN scores is explained by additive genetic influences only.

Ratings on the SWAN cover the continuum from positive attention skills to attention and hyperactivity problems that define ADHD. Instruments such as the SWAN offer clinicians and researchers the opportunity to examine variation in both strengths and weaknesses in attention skills.

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by the presence of symptoms of inattention, hyperactivity and impulsivity. It is the most common neuro-developmental disorder of childhood with prevalence's ranging from 4 to 12% in the general population (Brown et al. 2001; Faraone, 2003). The diagnosis is typically made by a trained clinician using information that is collected in several ways, varying from behavior checklists, filled in by for example parents or teachers, to interviews and observations by trained psychiatrists. The overlap in diagnoses among the different measures of attention problems such as the Child Behavior Checklist's (CBCL, Achenbach, 1991) Attention Problem Syndrome (AP) and DSM-IV interviewed based ADHD, is moderate to high (Hudziak et al. 2004; Kasius et al. 1997; Derks et al. 2006b).
A feature of most behavior checklists is the strict and narrow range of ratings on the problem items. Possible scores on the AP scale of the widely used CBCL for example are 0, 1 or 2 indicating that a child shows certain behavior 0) not at all, 1) sometimes, or 2) often. Similarly, the Rutter scale has a scoring range of 0 to 3 (Rutter et al. 1970), and the DuPaul ADHD rating scale of 0 to 2 (DuPaul, 1981). When data are collected with these instruments in the general population the distribution of scores is often skewed. This is due to the fact that only a small percentage of subjects have serious attention problems while the majority of the children score in the very low range or have zero problem symptoms. As a result, there is no possibility of studying variance in the other end of the distribution, e.g., those children who have above average or excellent skills in the attentional, hyperactive/impulsive domains.
The skewness seen in regular measures of ADHD may be avoided through the use of a relatively new ADHD scale named the Strength and Weakness of ADHD symptoms and Normal behavior scale (SWAN, Swanson et al. 2006). The SWAN is based on the 18 ADHD items listed in the DSM-IV. What sets it apart from other checklists is that each item is scored on a seven point scale with 'average behavior' scored in the middle and on the extremes 'far below average' and 'far above average'. Because the SWAN measures both the strength and weakness characteristics of ADHD it is expected that it yields a normal distribution of scores in the general population (Swanson et al. 2006). This broader range of scores might provide additional information about the nature of attention problems.

Genetic studies showed that variation in ADHD is strongly influenced by genetic factors with heritability estimates ranging from 70 to 90% (Rietveld et al. 2004; Hudziak et al. 2000; Faraone & Doyle, 2002; Nadder et al. 1998) for both attention deficit and hyperactivity/impulsivity. The prevalence of ADHD tends to be higher in boys than in girls, but there is no evidence for substantial sex differences in the relative importance of genetic or environmental influences (Derks et al. 2006a). The heritability of ADHD appears to be the same for extreme cases of ADHD as for individual differences in the normal population, suggesting that attention problems are normally distributed with ADHD being on the tail of the distribution (Levy et al. 1997). Most genetic studies on ADHD found no significant influences of common environment (i.e., the environment that is shared by members of a family) but suggested, based on a pattern of DZ twin correlations being lower than half the MZ twin correlations, the influence of contrast effects or genetic non-additivity (i.e., dominance or epistasis effects). Contrast effects may arise because of competitive social interaction among siblings, or because parents compare the behavior of their twins and stress differences between them (Eaves et al. 1997; Simonoff et al. 1998; Nadder et al. 1998; Van den Oord et al.1996; Van Beijsterveldt et al. 2004; Eaves, 1976). Low DZ correlations can also indicate the influence of genetic dominance (i.e., non additive genetic effects) as is reported by for example Rietveld et al. (2003), Martin et al. (2002), Derks et al. (2004) and Thapar et al. (2000). Interestingly, teacher ratings do not indicate the presence of dominance or contrast effects suggesting that only in parental data these phenomena play a role. In parental ratings, however, the results are inconclusive and seem to vary across instruments, age (of the twins) and methods (Derks et al. 2006a). For example Rietveld et al. (2004) reported in a longitudinal study contrast effects at age 3 and effects of dominance at ages 7, 10 and 12. Thapar et al. (2000) found significant contrast effects on the Rutter scale (Rutter et al. 1970) and in addition significant dominance effects on the DuPaul ADHD rating scale (DuPaul, 1981). To our knowledge there has been only one published genetic study on parental ratings using the SWAN. In this study Hay et al. (2006) investigated in a twin sample of young children (N = 528 pairs, aged 6 to 9 years old) and a sample of older children (N = 488 pairs, aged 12 to 20 years old) the genetic influences on the SWAN. They showed, in contrast to the

studies discussed above, moderate contributions of common environment (28%) for Attention Deficit, and substantial contributions of common environment (66%) for Hyperactivity/Impulsivity. Heritability estimates were much lower than usually reported for ADHD and attention problems.

For the present study maternal SWAN ratings were collected in 560 12-year-old twin pairs. Of this sample CBCL data were available for 469 twin pairs. As the wider range of SWAN scores allows reporting not only the severity of attention problems, but also the extent to which children do better on certain items, we expect the distribution of SWAN scores to approach a normal distribution. Second, we aimed to investigate the relation between the SWAN and the CBCL AP scale. It was determined if children who score in the very low distribution of the CBCL AP scale could be further differentiated using the SWAN average or far above average range. The third aim is to compare the genetic architecture of the CBCL and the Attention Deficit and Hyperactivity/Impulsivity scale of the SWAN. Of the latter instrument the impact of the 'above average' tail of the distribution, that are children who have no attention problems and score very low on the CBCL (i.e., score zero), and hence do not contribute to the variance, may provide additional information. It could be that this 'strength part' (which reflects for example children's ability to sustain attention, to sit still, and to wait their turn) is due to parental style, or for example school systems or educational approaches, and that by including this variance, common environmental influences come into play (as reported in the study of Hay et al. 2006). It may also be that previous results are confirmed, namely that additive and non-additive genetic effects explain the variance in ADHD scores as assessed by SWAN ratings. Our findings will be discussed in the context of how these data may affect assessment and treatment as well as scientific investigation of the ADHD symptom domains.

METHODS

Subjects and Procedure

The subjects are Dutch twins whose parents voluntarily registered with the Netherlands Twin Registry (NTR) when the twins were born (Boomsma, 1998; Boomsma et al. 2002b). All twin pairs are participating in a longitudinal study in which surveys are sent to their parents and teachers (Bartels et al. 2007). Parents are asked to fill in the CBCL for their twins at ages 3, 7, 10 and 12.

Of the total NTR population data on the SWAN were collected in two samples of approximately 12-year-old children. Twin mothers were asked to complete the SWAN (N= 681 pairs). The first sample consisted of 177 Dutch twin pairs who were born between 1990 and 1992 and who participated in a longitudinal study on Cognition, Attention and Attention Problems (Polderman et al. 2006). Data on the SWAN were collected when the twins were 12 years old (mean age= 12.42, SD= 0.16). The sample is unselected with respect to attention problems. Invitation to participate in this study was based on age and a sample equally distributed across sex and zygosity. Zygosity was determined on the basis of DNA polymorphisms. None of the children suffered from severe physical or mental handicaps. Parents signed an informed consent form.

The second sample consisted of 504 Dutch twin pairs, aged between 10 and 13 years old (mean age = 11.71; SD = 0.77) who were born between 1989 and 1994 and participated in a study on Attention Problems (Derks et al. 2006b). For this sample subjects were selected from an initial sample of 6191 twin pairs on the basis of their maternal CBCL ratings (T-scores; Mean=50, SD=10) at the ages 7, 10, and 12 years. Subjects were excluded if maternal ratings were available only at one time-point, or if they suffered from a severe handicap, which disrupts daily functioning. Twin pairs were selected if at least one of the twins scored high on AP (affected pairs) or if both twins scored low on AP (control pairs). A high score was defined as a T-score above 60 at all available time-points (age 7, 10, and 12 years) and a T-score above 65 at least once. A low score was defined as a T-score below 55 at all available time-points. The control pairs were matched with the affected pairs on the basis of sex, cohort, maternal age, and Social Economic

Status. T-scores were computed in boys and girls separately. In other words, girls were selected if they scored low or high compared to other girls, and boys were selected if they scored low or high compared to other boys. This procedure resulted in the selection of an equal number of boys and girls. Zygosity for 403 twin pairs was determined on the basis of dna polymorphisms. In the remaining twin pairs zygosity was based on a 10-item questionnaire. Zygosity determination using this questionnaire is almost 95% accurate (Rietveld et al. 2000). Parents signed an informed consent form.

Mothers of children of the first sample completed the swan when their children performed a neuropsychological test battery at the Vrije Universiteit. Mothers of children of the second sample received and returned the swan by mail. Of the first sample data of 9 twin pairs were missing, and of the second sample the data of 99 twin pairs were missing. Twelve twin pairs participated in both studies. Of these 12 twin pairs, the questionnaires of one of both studies were selected at random. The combination of both samples then resulted in a sample of 224 mz twin pairs and 337 dz twin pairs (N = 561 pairs).

Maternal cbcl data (age 12) were collected as part of the parental surveys by the ntr every two years (total N = 6191 twin pairs for cohorts 1989-1994). For the current sample cbcl data were available for 469 twin pairs.

Instruments

The cbcl (Achenbach, 1991) is a behavioral checklist for parents to report the frequency and intensity of behavioral and emotional problems of their children. Parents are instructed to rate the child's behavior over the last six months with 0 if the behavior is not true, 1 if the behavior is sometimes or somewhat true, and 2 if the behavior is very or often true. The Attention Problem scale of the cbcl consists of 11 items so the maximum score on this scale is 22. The more attention problems a child has, the higher his or her score on the Attention Problem scale.

The swan (Swanson et al. 2006) employs 18 items on a 7 point scale ranging from 'far below average' (1) to 'far above average' (7) to allow for ratings of relative strengths (above average) as well as weaknesses (below average). The first nine items correspond to the Attention Deficit (ad)scale and the last nine items to

the Hyperactivity/Impulsivity (HI) scale. The maximum score on a SWAN scale is 63. The more attention problems a child has, the lower his or her score on the SWAN rating scales.

Analyses

Of the total sample (N = 561 pairs) one part was unselected with respect to attention problems and one part was selected based on longitudinal scores on the CBCL-Attention Problem (AP) scale. The selection procedure which was described above resulted in an under representation of twins with moderate CBCL scores. Data-weighting was used to take account of the fact that the sample was not a random sample (Heath et al. 1998). With this method, the CBCL scores at age 12 and the SWAN scores of the sample were reweighted so that the distribution of the problem behavior scores was the same as the distribution in the original sample. Using logistic regression analyses, the probability of being included in the selected sample was predicted for each twin pair based on their longitudinal CBCL AP scores. As a result of our selection procedure, this probability was higher for twin-pairs with high or low CBCL-AP scores than for twin-pairs with moderate CBCL scores. Therefore, in the selected sample, twin-pairs with a low probability of participation were underrepresented. To correct for this underrepresentation, these pairs received a higher weight than twin-pairs with a high probability of participation. The logistic regression analyses and the calculation of weights were performed in SPSS (11.5). The weights were then used for the ensuing analyses in the statistical software package Mx (Neale et al. 2003). The weights were entered as fixed variable in the model and twin pair scores were reweighted by this variable.

Structural equation modeling, as implemented in Mx (Neale et al. 2003), was used for the genetic analyses. Mx provides parameter estimates by maximizing the raw data likelihood. The goodness of fit of nested models is evaluated by hierarchic likelihood ratio (χ^2) tests. Specifically, the χ^2 statistic is computed by taking twice the difference between the log-likelihood of the full model and the log-likelihood of a reduced model ($\chi^2 = -2(LL_0 - LL_1)$). The associated degrees of freedom are computed as the difference in degrees of freedom between the

two hierarchic models (Neale & Cardon, 1992). In a saturated model means and standard deviations and phenotypic twin correlations were estimated.
The total variation of each variable can be decomposed into sources of additive genetic variance (A), non additive genetic variance (dominance, D), common environmental variance (C) and unique environmental variance (E). A is due to additive effects of different alleles, D is due to non additive genetic effects reflecting interaction effects between alleles of the same gene locus, C is due to environmental influences shared by members of a family, and E is due to environmental influences not shared by members of a family. E also includes measurement error and is therefore always included in the models. The effects of C and D in the classical twin design are confounded; C will decrease differences between MZ and DZ covariances while D will increase the differences. Therefore C and D can not be estimated simultaneously.
A first impression of the relative importance of each component is obtained by inspecting the within twin pair correlations. MZ correlations as high as DZ correlations indicate only common and unique environmental influences and no genetic sources of variance. MZ correlations twice as high as DZ correlations indicate additive genetic influences. DZ correlations higher than half the MZ correlations designate common environmental influences while DZ correlations lower than half the MZ correlations point to dominance or contrast effects (Boomsma et al. 2002). Contrast and dominance effects can theoretically be distinguished by making use of the fact that contrast effects lead to differences in variances in MZ and DZ twins while non-additive genetic effects do not (Carey, 1986).

RESULTS

Descriptives

Because there is no evidence for sex differences in heritability for ADHD (Derks et al. 2006a), data from male and female twins for both zygosities were combined in the analyses. There were no significant differences in means and variances between MZ and DZ twins for the CBCL (χ^2 (4) = 7.73, p = 0.102) or for the SWAN/HI

Table 1:
Means (including the effects of sex on the means), SD and twin correlations of scores on the Attention Problem scale of the CBCL, and Hyperactivity/Impulsivity and Attention Deficit scale of the SWAN

	CBCL AP		SWAN Hyperactivity/ Impulsivity		SWAN Attention Deficit	
Means boys/ girls (SD)	3.09 / 2.33 (2.97)		43.9 / 45.6 (8.63)		44.0 / 45.7 (8.08)	
Twin correlations		N pairs		N pairs		N pairs
MZ	0.67	190	0.91	221	0.85	218
DZ	0.25	269	0.43	335	0.38	331

(χ^2 (4) = 3.24, p = 0.518) and SWAN/AD scale (χ^2 (4) = 6.71, p = 0.152). Means and standard deviations of the CBCL AP scale and the HI and AD scale of the SWAN are shown in the upper part of Table 1. SWAN scores were normally distributed for both scales covering the continuum across the strengths and weaknesses of ADHD characteristics whilde CBCL AP scores were skewed. In Figure 1 the histograms for the CBCL AP scale, the SWAN/HI scale and SWAN/AD scale are shown. Skewness and kurtosis of the CBCL were 1.76 and 4.50, of the SWAN/HI scale these were 0.10 and 0.06 respectively and of SWAN/AD these were -0.13 and 0.06.
Figure 2 shows a scatter plot of SWAN scores on the y-axis and CBCL AP scores (at age 12) on the x-axis. Children who score high on the CBCL AP scale also show many HI or AD problems on the SWAN. Notable is the fact that children who show no variation (i.e., score zero) on the CBCL AP scale, show variation on the SWAN. This pattern was similar for the HI and AD scale of the SWAN. The correlation between the CBCL and the SWAN/HI scale and the SWAN/AD scale were -0.38 and -0.42 respectively.

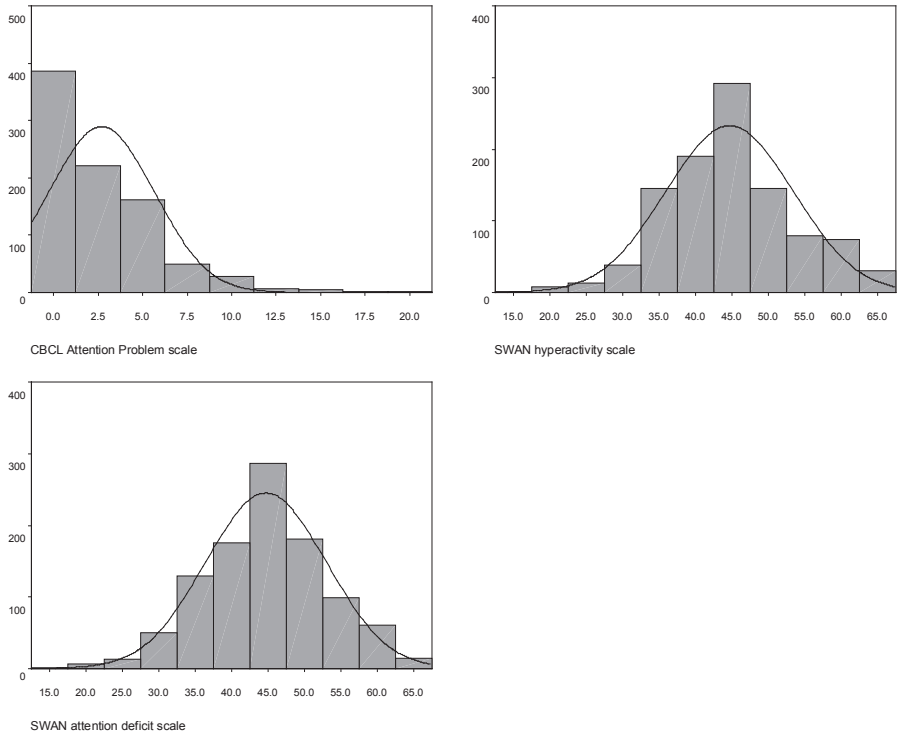
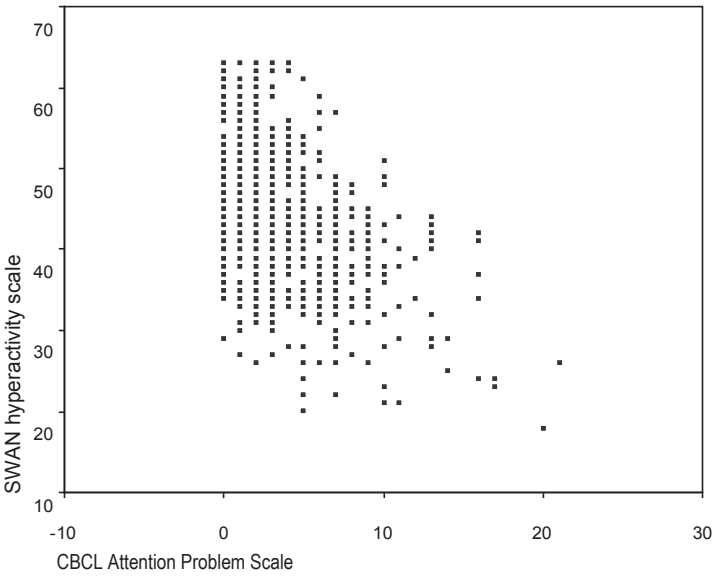


Figure 1:
Distribution of scores of the CBCL AP scale, the SWAN Hyperactivity/ Impulsivity scale and SWAN Attention Deficit scale

Genetic Modeling

Twin correlations of MZ and DZ twin pairs of the CBCL AP scale and of the SWAN scales are shown in the lower part of Table 1. The twin correlation pattern of the CBCL AP scale showed DZ correlations being lower than half the MZ correlations which pointed to dominance or contrast effects. Because contrast effects cause different variances in MZ and DZ twins, and therefore lead to different prevalences of attention problems among these groups, contrast effects were only included if the variances of MZ and DZ twins were different. This was not the case in the present data so a model with dominance effects was tested for the CBCL data. The


SWAN hyperactivity scale
70
60
50
40
30
20
10
-10
0
10
20
30
CBCL Attention Problem Scale

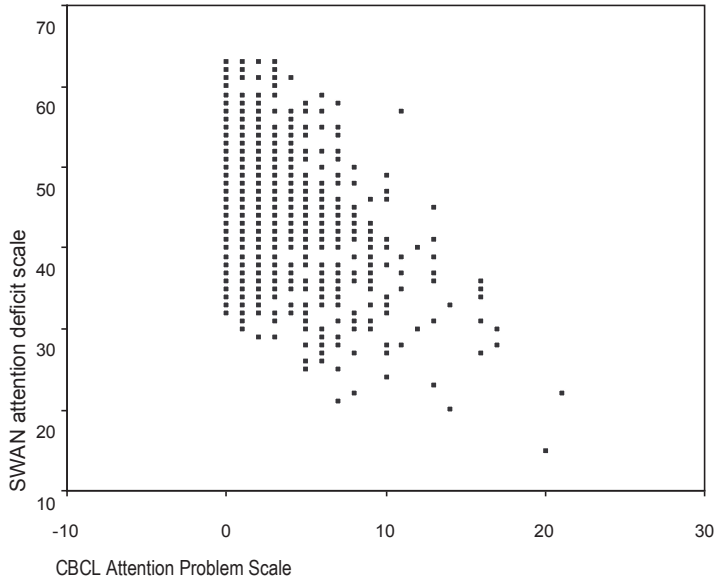

SWAN attention deficit scale
70
60
50
40
30
20
10
-10
0
10
20
30
CBCL Attention Problem Scale

Figure 2:
Scatter plot with CBCL Attention Problem scores on the x-axis and SWAN-Hyperactivity/Impulsivity scores on the y-axis, and scatter plot with CBCL Attention Problem scores on the x-axis and SWAN-Attention Deficit scores on the y-axis

Note:
Maximum score on the CBCL Attention Problem scale is 22. The more Attention Problems a child has, the higher his or her score on the Attention Problem scale. Maximum score on the SWAN is 63. The more Hyperactive/Impulsive or Attention Deficit problems a child has, the lower his or her score on the SWAN.

results showed that a model with additive (A, 21%) and non-additive (D, 52%) genetic effects, and unique environmental influences described the data best. The broad heritability (i.e., A + D) estimate was 73%. To test whether the weighting procedure influenced these estimates we performed the same analyses in all available mother ratings of the cbcl at age 12 from which the swan samples originally were selected (birth cohort 1989-1994; N = 2869 twin pairs). Estimates for A, D and E of the cbcl ap scale were not significantly different in the larger ntr sample and the current sample (χ^2 = 2.94, df = 3, p = 0.40) indicating that the weighting method resulted in the correct parameter estimates in a selected sample. For both swan scales the dz correlations were about half the mz correlations indicating additive genetic influences and unique environmental influences, and no influences of common environment, genetic dominance or contrast effects. Model fitting confirmed that a model with additive genetic and unique environmental sources of variance described the data well for the swan/hi scale and the swan/ad scale (see Table 2).

Heath et al. (1998) pointed out that as a result of data weighting, χ^2 tests are biased. To investigate the direction of this bias we performed simulation analyses. These showed that the statistical test, in which the ae model is compared to the saturated model, is too conservative. When the ae model is the correct model (Ho = true), we would normally expect to reject this model with a probability of 5% (Type-I error rate). In the simulations, it appeared that the probability of rejecting the ae model, given that the ae model is the correct model, is too high (65%). The fact that the ae models for both swan scales were not rejected therefore provides strong evidence that these models fitted well to the data. The

Table 2:
Univariate model fitting results, with heritability estimates for the Attention Problem scale of the CBCL, and the Hyperactivity/Impulsivity and Attention Deficit scale of the SWAN

	-2LL	χ^2	df	p	h^2	e^2
CBCL AP						
Saturated model	4150.220					
ADE model	4158.253	8.033 [1]	5	0.154	73	27
AE model	4164.049	5.796 [2]	1	0.016		
Hyperactivity/Impulsivity						
Saturated model	6844.761					
AE model	6848.941	4.18 [1]	6	0.382	90	10
Attention Deficit						
Saturated model	6789.904					
AE model	6800.005	10.10 [1]	6	0.120	82	18

Note: A = additive genetic factors, D = non-additive genetic factors, E = unique environmental factors
[1] compared to the saturated model; [2] compared to ADE model

heritability estimates were 90% for the Hyperactivity/ Impulsivity scale and 82% for the Attention Problems scale.

DISCUSSION

In this study the distribution and genetic architecture of the Strengths and Weakness of ADHD symptoms and Normal behavior Scale (SWAN, Swanson et al. 2006) was investigated. The SWAN is a questionnaire measuring Hyperactivity/ Impulsivity and Attention Deficit with item scores on a 7 point scale, ranging from 'average behavior' to the extremes 'far below average' and 'far above average'. So in contrast to most other checklists the SWAN scores cover the strengths as well as the weaknesses of a child, ranging from severe hyperactivity to normal activity and from serious attention deficits to a high level of attention. As a result, scores on the SWAN rating scales show a normal distribution in general population samples. The SWAN was compared to a widely used regular checklist, namely the CBCL. Such checklists often have skewed distributions because the range of responses to questions about problems is constrained to only a few possibilities (e.g., 'never', 'sometimes', 'often') and the majority of children in general population samples show no attention problems. The present study demonstrated that especially children who score zero (i.e., 'never'), and hence show no variation on the attention problem scale of the CBCL do show substantial variation on the ratings of the SWAN. The normal distribution of problem scores of the SWAN is particularly an improvement when assessing problems of hyperactivity and attention deficit in general population samples as it offers for example significant potential advantages in gene finding expeditions, and studies of quantitative endophenotypes. The correlation between the CBCL AP scale and the Hyperactivity and Attention Deficit SWAN scale was -0.36 and -0.43 respectively. However, this is probably an underestimation as for the CBCL AP scale the variance of children who score zero is missing.

One of our interests was the contribution of the additional variance of normally 'low scoring' children to the underlying sources of variance of ADHD. We speculated that adding the variance of the 'strength part' of the SWAN might manifest the influences of common environment (C) as it is possible that these abilities are due to parental style, or for example school systems. The only prior genetic study on parental ratings of the SWAN (Hay et al. 2006) showed substantial influences of C. In this study SWAN data of a younger and an older sample, consisting

both of around 500 twin pairs, were analysed. DZ correlations in this study were unusually high (ranging between 0.50 and 0.78), and consequently the heritabilities were unusually low; 31% for hyperactivity in the older sample for example. Their samples however were heterogeneous regarding age, especially in the older sample (i.e., age in the young sample ranged between 6 and 9, and in the older sample between 12 and 20).

The current study did not replicate the findings of Hay et al. (2006) as no evidence for common environmental influences was found. The DZ correlations were about half the MZ correlations and model fitting showed that additive genetic effects and unique environmental effects explained the variance of both SWAN scales. The heritablity estimates were somewhat higher but comparable to the CBCL AP scale (73%) and to many previous studies on attention problems with 90% and 82% respectively (Bartels et al. 2004; Rietveld et al. 2004; Rietveld et al. 2003; Nadder et al. 1998; Nadder et al. 2001; Derks et al. 2006b; Hudziak et al. 2000; Thapar et al.1995; Thapar et al. 2000; Levy et al. 1997; Levy et al. 2001).

The debate has been whether genetic influences in ADHD exist solely of additive genetic effects or whether non-additive genetic (i.e., dominance) effects also play a role. The results for the CBCL AP scale in this sample showed significant effects of dominance but these effects were not found in the SWAN scales; DZ twin correlations were about half the MZ correlations indicating only additive genetic effects. Although the variance of attention skills and attention problems (as obtained with the SWAN) has a broad heritability estimate that is similar to that seen for attention problems only, (as assessed with the CBCL), the genetic architecture underlying these two scales is very different. The variance decomposition of the SWAN showed no effects of genetic dominance, while the variance decomposition of the CBCL AP scale suggests substantial genetic non-additivity.

To summarize, the current results firstly demonstrated that the SWAN rating scale, in contrast to the CBCL, yields a normal distribution of scores covering the strength part as well as the weakness part of attention problems. This makes it a very useful instrument to examine variation of (hyper) activity and attention (problems) in the general population. In addition it might be an attractive option for clinicians to offer parents, because they can score not only the weaknesses of their child but also report on their strengths. Hay et al. (2006) also

concluded that the swan might provide a more 'realistic description of the adhd phenotype' than the ratings of problems do. Secondly, this study found a very high heritability estimate, but did not find any evidence of genetic dominance, or contrast effects.

In the search for more highly refined phenotypes, it appears that the swan offers added benefits by also obtaining ratings on positive attentional skills. These include the added statistical power that is gained in genetic, and endophenotypic studies using a full quantitative trait.

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5

ASSOCIATION BETWEEN THE SNAP-25 GENE AND ATTENTION IN A TWIN SAMPLE

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ABSTRACT

The synaptosomal associated protein of 25 kD (SNAP-25) gene, located on chromosome 20p12-20p11.2, has been associated with ADHD and attention problems. SNAP-25 is differentially expressed in the brain and is during development involved in synaptic plasticity, dendrite formation and axonal growth. In a sample of 255 individuals (from 137 families) we genotyped twelve tagging Single Nucleotide Polymorphisms (SNP's), that cover the SNAP-25 gene. From all individuals scores on the Strength and Weakness of ADHD symptoms and Normal behavior scale (SWAN, Swanson et al. 2006) were available. The SWAN contains two scales, Hyperactivity/Impulsivity and Attention Deficit, which can be rated on a continuum, ranging from severe problems to suberb skills. Using a family based association test, one SNP showed a significant association with Attention Deficit scores on the SWAN ($p = 0.017$), and two SNP's showed a trend for association ($p < 0.10$). The results of this study fit in a range of positive associations between the SNAP-25 gene and attention problems that have been reported lately. However, our study was performed in a relatively small sample and the results should therefore be interpreted with caution.

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by the presence of symptoms of inattention, hyperactivity and impulsivity. It is the most common neuro-developmental disorder of childhood with prevalence's ranging from 4 to 12% in the general population (Brown et al. 2001; Faraone, 2003). Twin and adoption studies demonstrated the importance of genetic factors in ADHD and attention problems with heritability estimates between 60 and 90% (Rietveld et al. 2004; Hudziak et al. 2000; Faraone & Doyle, 2002; Nadder et al. 2001). Several candidate genes have been investigated (Cornish et al. 2005; Faraone et al. 2005; Mill et al. 2005; Thapar et al. 2005; Bobb et al. 2005; Brookes et al. 2006). One of them is the synaptosomal-associated protein of 25kDa gene (SNAP-25) that is located on chromosome 20 p11-p12. SNAP-25 is differentially expressed throughout the brain and is during development involved in synaptic plasticity, dendrite formation and axonal growth (Osen-Sand et al. 1993; Grosse et al. 1999). It is a protein that is part of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex which enhances calcium (CA2+) triggered catecholamine release (Weber et al. 1998; Nagy et al. 2005).

Mechanisms underlying the dopaminergic neurotransmission systems have been the focus of previous studies on ADHD as brain imaging studies of affected children suggested that brain regions with rich dopamine content were involved in ADHD (Tannock et al. 1998). The significant reduction of ADHD symptoms after using pharmacological medication (for example methylphenidate) that primarily act on the dopaminergic system additionally pointed to a significant role of the dopamine system in ADHD pathology (Spencer et al. 1996). The focus on SNAP-25 as a candidate gene for ADHD was based specifically on the mouse mutant strain Coloboma. This strain is hemizygous for a deletion of the SNAP-25 gene, resulting in a 50% reduction in the expression of the gene throughout the central nervous system (Hess et al. 1992). The Coloboma mutation (Cm) in mice evoked spontaneous hyperactivity, delays in achieving complex neonatal motor abilities, deficits in hippocampal physiology, and deficits in CA2+ dependent dopamine release in dorsal striatum (Wilson, 2000).

Studies in humans supported evidence for an association between ADHD and the SNAP-25 gene (Barr et al. 2000; Brophy et al. 2002; Mill et al. 2002; Kustanovich

et al. 2003; Mill et al. 2004). For example Feng et al. (2005) reported a significant association between parent and teacher reported ADHD symptoms and four polymorphisms on intron 3, 4 and 5, and exon 6. Mill et al. (2004) investigated 188 probands who were diagnosed with ADHD and their families, and reported an association with three Single Nucleotide Polymorphisms (SNP's) in the promotor region, a microsatellite in intron 1, and one SNP located in intron 7.

Nearly all studies have been performed in clinical samples with DSM-IV ADHD combined type cases. The phenotype 'attention' however is normally distributed with attention problems being on one tail of the distribution and high levels of attention on the other (Hay et al. 2006, Polderman et al. (in press)), and the heritability of attention appears to be equally high at both the low and high ends of the distribution (Levy et al. 1997; Thapar et al. 2003). Mill et al. (2005) investigated the association between the SNAP-25 gene and attention problems in a normal sample of 329 dizygotic male twin pairs, using ratings on the Strengths and Difficulties Questionnaire (SDQ), and the Revised Rutter Parent Scales for Preschool Children questionnaire (RRPSPC). Mill et al. (2005) found in this study weak evidence that a microsatellite (Intron 1, (TAAA)n) in SNAP-25 may have a role in hyperactivity.

The current study investigated in a similar way the possible role of the SNAP-25 gene in the continuum of attention. We assessed in a general population sample a relatively new questionnaire named the Strength and Weakness of ADHD symptoms and Normal behavior scale (SWAN, Swanson et al. 2006). The SWAN measures the continuum of hyperactivity/impulsivity and attention problems with item scores on a 7 point scale, ranging from 'average behavior' to the extremes 'far below average' and 'far above average'. As the range of SWAN scores allows reporting not only the severity of attention problems, but also the extent to which children do better on certain items, it yields a normal distribution of scores in the general population (Hay et al. 2006, Polderman et al. (in press)). The heritability of symptoms of ADHD as measured with the SWAN is investigated in two twin studies so far. Hay et al. (2006) reported for attention problems heritability estimates of 53% (children, N = 528 pairs) and 89% (adolescents, N = 488 pairs), and for hyperactivity 46% (children) and 31% (adolescents). Polderman et al. (in

press) found in 12-year-old twin pairs (N = 560 pairs) heritability estimates of 90% for hyperactivity and 82% for attention problems.
It has been suggested that a significant proportion of the genetic influences underlying ADHD may be contributing independently to hyperactivity and attention deficit dimensions, implying that there are unique (as well as shared) genetic effects for different subtypes (Faraone et al. 2000; Smalley et al. 2001; Todd et al. 2001; Rasmussen et al. 2004). Consequently, a distinction between ADHD subtypes might be a fruitful approach in association studies. The aim of the current study is to investigate whether associations between SNAP-25 and symptoms of ADHD, thus far mainly discovered in clinical samples, can be replicated in a general population sample using continuous ratings of two sub scales of the SWAN, namely Hyperactivity/Impulsivity (HI) and Attention Deficit (AD). Associations that have been reported so far cover all regions of the SNAP-25 gene. Twelve tagging SNP's were used, covering the SNAP-25 gene from the 5' untranslated region (UTR) to the 3'UTR. Selection of the tagging SNP's was based on a correlation of < 0.85 among the tagging SNP's (to avoid redundancy), and a minor allele frequency of > 0.10 (to avoid rare heterozygous genotypes).

METHOD

Subjects

The sample consisted of 177 Dutch twin pairs, born between 1990 and 1992, and 55 of their siblings. The twins were 12 years old (mean age= 12.42, SD= 0.16) and the siblings were between 8 and 15 years old. Twenty seven siblings were younger than their twin brothers or sisters (mean age = 9.60, SD = 0.71) and 28 siblings were older (mean age = 14.69, SD = 0.60). There were 41 monozygotic male twin pairs (MZM), 28 dizygotic male twin pairs (DZM), 56 monozygotic female twin pairs (MZF), 25 dizygotic female twin pairs (DZF) and 27 dizygotic opposite-sex twin pairs (DOS). Zygosity was determined on the basis of DNA polymorphisms. The twins were registered at birth with the Netherlands Twin Registry (Boomsma

1998; Boomsma et al. 2002). None of the children suffered from severe physical or mental handicaps.
The parents of the children were invited for participation of their children in a longitudinal study on Cognition, Attention and Attention Problems (Polderman et al. 2006). In the mailing information about the goals and procedures of the study were included. After two weeks the parents were contacted by phone and asked if they were willing to participate. Participation in this study included a request to provide buccal swabs for DNA extraction. Buccal swabs were obtained from 391 children. Mothers of 382 children completed the SWAN when their children performed a neuropsychological test battery at the Vrije Universiteit. Prior to the assessment parents and children signed an informed consent form.

Instruments

The SWAN (Swanson et al. 2006) is based on the 18 ADHD items listed in the DSM-IV and employs 18 items on a 7 point scale ranging from 'far below average' (1) to 'far above average' (7) to allow for ratings of relative strengths (above average) as well as weaknesses (below average). The first nine items correspond to the Attention Deficit (AD) scale and the last nine items to the Hyperactivity/Impulsivity (HI) scale. The maximum score on a SWAN scale is 63. The more attention problems a child has, the lower his or her score on the SWAN rating scales.

DNA Collection and Genotyping

The DNA isolation from buccal swabs was performed using a cloroform/isopropanol extraction (Meulenbelt et al. 1995; Min et al. 2006). Zygosity was assessed using 11 polymorphic microsatellite markers (Het > 0.80). Tagging single nucleotide polymorphisms (tag-SNP's) selection criteria were defined as SNP's with a minor allele frequency (MAF) above 0.10 and genotypic correlation (ρ) across the genotypes of maximal 0.85 as obtained from a randomly selected population of Western European origin (http://www.celeradiagnostics.com/cdx/applera_genomics). MAF had to be > 0.10 in order to avoid the rare heterozygous genotypes and SNP's with a ρ above 0.85 with any of the other SNP's were not selected to avoid redundancy. Twelve tag-SNP's in the SNAP-25 gene were selected according to these criteria (http://www.appliedbiosystems.com/support/software/snplex/)

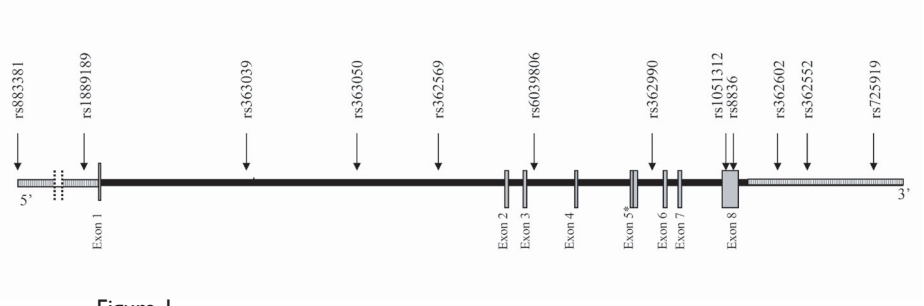

Figure 1

using SNP Browser version 2.0.4, (NCBI build 34) (see Figure 1). Genotyping was performed blind to familial status and phenotypic data. Both MZ twins of a pair were included in genotyping serving as additional controls.

The SNPlex assay was conducted following the manufacturer's recommendations (Applied Biosystems, Foster city, CA, USA). All pre-PCR steps were performed on a cooled block. Reactions were carried out in Gene Amp 9700 Thermocycler (Applied Biosystems, Foster city, CA, USA). PCR products were analyzed with ABI3730 Sequencer (Applied Biosystems, Foster city, CA, USA). Data were analyzed using Genemapper v3.7 (Applied Biosystems, Foster city, CA, USA).

Statistical Analyses

Means and variances were computed in SAS. Linkage disequilibrium (LD) parameters (D' and r^2) were reported in this sample by Gosso et al. (2006). For quantifying and comparing LD in the context of mapping, r^2 is slightly preferred (Ardlie, Kruglyak, & Seielstad, 2002). Values of r^2 ranged from 0.001 to 0.680 in our sample, conforming relatively low LD between the separate tag-SNP's (see Table 2, Gosso et al. 2006).

Genetic association tests were conducted in a model that included the eight SNP's genotypes for which the null hypothesis of HWE was not rejected (i.e., rs363039, rs363050, rs362602, rs362552, rs883381, rs1889189, rs8636, rs725919). For a set of SNP's in LD, such a model need not lose much of the information in the haplotypes and may be as powerful as the use of haplotypes (Clayton et al. 2004). The individual genotypes were decomposed into between and within family components, as

Table 1:
Means (including the effects of sex on the means), and (SD) standard deviation of scores on the Hyperactivity/Impulsivity (HI) and Attention Deficit (AD) scale of the SWAN in the original sample and in the analysed sample.

	N children	SWAN HI	SWAN AD
Mean girls/boys (SD) Original sample	394	40.24/38.49 (7.53)	40.09/38.57 (7.28)
Mean boys/girls (SD) Analysed sample	255	40.56/38.73 (7.34)	40.38/38.97 (7.10)

proposed by Abecasis et al. (2000) and Fulker et al. (1999). The fixed part of the model also included effects for sex and age. In a saturated model the covariances for MZ twins and for DZ twins and siblings were estimated. The variances of all offspring were restricted to be the same. This model was specified separately for males and females. Finally, the model included a separate male-female covariance component. The model was fitted using the Mixed procedure in SAS.

The between-family association component is sensitive to population admixture, whereas the within-family component is significant only in the presence of LD due to close linkage. If population stratification acts to create a false association, the test for association using the within family component is still valid, and provides a conservative test of association. Testing for the equality of the βb and βw effects serves as a test of population stratification. If this test is not significant, the between and within family effects can be replaced by the ordinary genetic effect and a more powerful association test can be conducted, because the within family component can be estimated only from families with genotypic within family variance.

We first tested for all SNP's simultaneously whether the between and within components were equal. This test was based on the empirical or sandwich estimator

of the covariance matrix of the fixed effects, originally proposed by Huber (1967) (see also Freedman, 2006). If the hypothesis was not rejected, the model was fitted using the original genotype scores. If the hypothesis was rejected, the within components of the SNP's were simultaneously tested for deviation form zero.

RESULTS

Because in the Mixed procedure in SAS only subjects are included with a complete set of SNP's, 139 subjects were missing and the final sample thus consisted of 255 subjects. Means and variances of the SWAN scores did not differ between the original sample and the final sample (see Table 1). For HI, the null hypothesis of equality of the between and within effect was not rejected. No evidence of association between HI and any of the SNP's was found. For ad the null hypothesis was rejected ($p < .05$), but the simultaneous test for the within components was not significant ($p = .14$). However, since the number of tested parameters is fairly large for the sample size (N = 255), this may be partly due to lack of power. For two of the SNP's (rs363050 and rs362552) the test for the individual regression weights had p-values of .017 and .071, while a third SNP (rs362602) had a p-value of 0.097, suggesting that for these SNP's an association effect might be present. Tables 2 and 3 show the results of these associated SNP's.

DISCUSSION

In this study the role of the SNAP-25 gene in attention was explored in a relatively small sample of normal population twin children (N = 255). Mothers of the children completed the Strength and Weakness of ADHD symptoms and Normal behavior scale (SWAN, Swanson, 2006), a rating scale that measures the continuum of attention. Of eight tagging SNP's, one SNP showed a significant association with Attention Deficit scores on the SWAN ($p = 0.017$). This SNP (rs363050) is positioned in intron 1 at the 5'UTR. The SNP's rs362602 and rs362552 positioned at the 3'UTR of the SNAP-25 gene showed weak evidence for associa-

Table 2:
Means (SD) per genotype for Hyperactivity (HI) and Attention Deficit (AD) in the eight tagging SNP's within the SNAP-25 gene

tag-SNP position (bp)	Phenotype	Genotype			Total N
		GG	GT	TT	
	Frequency	40%	39.6%	20.4%	255
rs883381	HD	39.70 (6.09)	40.48 (7.54)	38.27 (8.96)	
(10160727)	AD	39.80 (6.76)	39.33 (7.22)	40.37 (7.57)	
		CC	CT	TT	
	Frequency	47.1%	41.2%	11.8%	255
rs1889189	HD	39.65 (7.97)	39.60 (6.82)	40.33 (6.63)	
(10192086)	AD	39.48 (6.81)	39.58 (7.59)	41.23 (6.43)	
		AA	AG	GG	
	Frequency	9%	42.7%	48.2%	255
rs363039	HD	37.26 (8.36)	40.03 (7.23)	39.90 (7.22)	
(10215496)	AD	39.22 (7.83)	39.64 (7.20)	39.90 (6.92)	
		AA	AG	GG	
	Frequency	32.2%	51.4%	16.5%	255
rs363050	HD	40.33 (6.78)	40.14 (7.35)	37.21 (8.01)	
(10229257)	AD	39.92 (6.44)	39.89 (7.35)	38.86 (7.59)	
		CC	CT	TT	
	Frequency	45.5%	42.7%	11.8%	255
rs8636	HD	40.09 (7.88)	39.69 (7.04)	38.37 (6.21)	
(10282742)	AD	40.84 (7.36)	39.04 (6.70)	37.97 (7.02)	
		AA	AG	GG	
	Frequency	34.1%	34.1%	31.8%	255
rs362602	HD	40.52 (7.99)	39.54 (7.18)	39.05 (6.77)	
(10288528)	AD	39.60 (7.54)	40.00 (7.30)	39.58 (6.44)	
		AA	AG	GG	
	Frequency	48.2%	40.8%	11%	255
rs362552	HD	39.65 (7.33)	39.11 (7.01)	42.29 (8.29)	
(10291217)	AD	39.04 (7.05)	40.31 (7.08)	40.61 (7.33)	
		AA	AG	GG	
	Frequency	7.1%	32.2%	60.8%	255
rs725919	HD	42.06 (6.31)	39.35 (7.51)	39.64 (7.36)	
(10298094)	AD	38.78 (5.73)	41.37 (7.43)	38.97 (6.95)	

Table 3:
Results of the within family association analyses between the SNAP-25 gene and the SWAN Attention Deficit (AD) scale

tag-SNP position (bp)	Phenotype	t	*p*-value	Genotypic Effect (increaser allele)
rs883381				
(10160727)	AD	1.28	0.205	2.03 (T)
rs1889189				
(10192086)	AD	0.43	0.671	0.51 (T)
rs363039				
(10215496)	AD	-1.49	0.140	1.88 (G)
rs363050				
(10229257)	AD	-2.45	0.017	2.95 (A)
rs8636				
(10282742)	AD	0.97	0.338	1.30 (T)
rs362602				
(10288528)	AD	1.68	0.097	1.88 (G)
rs362552				
(10291217)	AD	1.83	0.071	3.56 (G)
rs725919				
(10298094)	AD	1.48	0.144	2.85 (G)

tion with attention deficit (p = 0.097 and p = 0.0710 respectively).
The snap-25 gene, located on chromosome 20 p12-12p11.2, encodes a presynaptic terminal protein. During development snap-25 is involved in synaptogenesis, forming presynaptic sites and neuritic outgrowth (Oyler et al. 1989, Osen-Sand et al. 1993). snap-25 is thought to be differentially expressed in the brain, and is primarily present in the neocortex, hippocampus, anterior thalamic nuclei, substantia nigra, and cerebellar granular cells (Oyler et al. 1989).
The evidence of the current study fits in a range of positive associations between the snap-25 and attention problems that have been reported lately. Started a few years ago with the mouse mutant strain Coloboma, which showed symptoms of hyperactivity and attention deficit after a deletion in the snap-25 gene (Hess

et al. 1992, Wilson, 2000), accumulating evidence of an association between the SNAP-25 gene and attention problems in human studies followed (Barr et al. 2000; Brophy et al. 2002; Mill et al. 2002; Kustanovich et al. 2003; Feng et al. 2005; Mill et al. 2004).

Two SNP's in the present study for which a trend was detected (rs362602 and rs362552) are located in the 3'UTR of SNAP-25. In clinical ADHD samples significant effects of haplotypes, that are also located in the 3'UTR region of the SNAP-25 gene, were reported by Brophy et al. (2002), Kustanovich et al. (2003), and Barr et al. (2000).

Recently Gosso et al. (2006) reported an association between three single nucleotide polymorphisms (SNP's) in the SNAP-25 gene and intelligence. They performed association analyses on the same tagging SNP's as the present study in a sample of 667 individuals from 304 families, including the current sample. Strong association was found for SNP rs363050, the same SNP that is in the current sample significantly associated with attention deficit.

A few studies reported significant associations between IQ performance and attention problems (Rucklidge & Tannock, 2001; Kuntsi et al. 2004, Polderman et al. 2006). Kuntsi et al. (2004) investigated the genetic origin of the co-occurrence of attention problems and low IQ scores in a population based sample of 5-year-old twins. The phenotypic correlation between attention problems (as assessed by mother and teacher reports) and IQ was -0.30 which was accounted for by genetic influences that were shared by attention problems and IQ. Similar findings were reported by a recent study of Polderman et al. (2006b) who showed that the longitudinal correlation between attention problems during childhood and intelligence performance in early adolescence was explained by a common set of genes.

In a recent paper Kovas and Plomin (2006) proposed the existence of so called 'generalist genes'. This hypothesis is based on the fact that there is a broad genetic overlap in cognitive functions. Kovas and Plomin (2006) therefore assume that the effects of generalist genes are widespread to the brain and not specifically localized. Consequently, these genes affect multiple brain structures and functions, each of which affects multiple cognitive processes (see also Butcher et al. 2006).

A few studies investigated genetic polymorphisms of the dopamine system that possibly could explain a part of the correlation between ADHD and intelligence. Mill et al. (2006) tested whether the DRD4 seven-repeat allele and the DAT1 ten-repeat allele were associated with variation in intelligence among children with ADHD. They found evidence for this association in two independent cohorts, from New Zealand and Britain. An attempt to replicate these findings in three larger, independent Brazilian samples by Genro et al. (2006) failed. However, given the 'generalist genes' hypothesis, and the important role for the dopaminergic regulation in attention problems and cognitive functioning (Nieoullon, 2002), a further investigation of the moderating role of dopaminergic polymorphisms seems interesting and relevant for future research. The present study was performed in a small sample and the results should therefore be interpreted cautiously. Given the small sample, the results are rather remarkable on the other hand, as effect sizes of genes are assumed to be very little; hence, very large samples are needed to detect genetic effects (Plomin et al. 2006). The current findings however suggest that it is worthwhile to investigate the SNAP-25 gene in larger samples. Currently fine mapping analyses of the SNAP-25 gene are performed, and future research should reveal the robustness of the associations between attention problems and SNAP-25. In addition it is interesting to examine whether the SNAP-25 gene might be one of the genetically connecting factors between intelligence and attention (problems).

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6

THE PHENOTYPIC AND GENOTYPIC RELATION BETWEEN WORKING MEMORY SPEED AND CAPACITY

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ABSTRACT

This study examined the phenotypic and genotypic relationship between working memory speed (WMS) and working memory capacity (WMC) in 12-year-old twins and their siblings (N=409). To asses WMS all children performed a reaction time task with three memory loads from which a basic mental speed measure and the derived slope were used. WMC was measured with two subtests of the WISC-R, namely Arithmetic and Digit Span. The phenotypic correlations among the WMS and WMC indices were around -0.30. Heritabilities for all variables ranged from 43% to 56%. Structural equating modeling revealed that a model with two genetic factors, representing WMS and WMC, which were correlated (-0.54) fitted the data best, indicating that WMS and WMC are partly mediated by the same set of genes and partly by separate sets of genes. When general IQ was simultaneously analysed with the data the correlation between the genetic factors for WMS and WMC decreased (-0.25), but was still significant. This means that ~50% of the genetic correlation between WMS and WMC is explained by IQ.

Working memory is conceptualised as a limited capacity system for information processing. It plays an important role in all forms of cognition and is essential in normal daily functioning, for example when reading the paper or watching a football game. It is now widely accepted that WM is not a unitary system, but that it can be divided into subsystems. An influential model was proposed by Baddeley who presented a theoretical WM framework with three distinguishable subcomponents (Baddeley & Hitch, 1974; Baddeley, 1992). First, the visuospatial sketch pad which manipulates visual images. Second, the phonological loop which stores and rehearses acoustic information. And third, the central executive which is an attentional controlling system that coordinates and processes the information of the two other components. Baddeley (2000) extended this model with the episodic buffer. The episodic buffer represents a limited capacity system, controlled by the central executive that is capable of integrating information from various sources into an episodic representation.

Several other authors proposed to partition WM in different components. Miyake and Shah (1999) described working memory as a non-unitary system of processes and mechanisms that allows task-relevant information to be stored temporary in an active state, for further processing or recall. In a similar vein Cowan et al. (2005) stated that WM is a set of mental processes holding limited information in a temporary accessible state in service of cognition. Oberauer et al. (2003) defined WM as a set of limited factors for performance in complex cognitive tasks, organized as a hierarchy of related constructs. Partition of WM in a neuro-anatomical way was for example suggested by Owen (2000) who proposed a process-specific distinction between maintenance and active manipulation of information in WM, which is supported by ventral and dorsal prefrontal cortical regions, respectively. Smith and Jonides (1999) reviewed neuro-imaging studies of the storage and executive components of WM. They concluded that the storage component of WM is activated by different frontal regions like Broca's area and premotor areas while the executive component involves the anterior cingulate and dorsolateral prefrontal cortex.

It is hypothesized that *g* (with '*g*' being the operational definition of 'general intelligence') is largely responsible for better performance on various tasks in which

speed and accuracy are involved (Gray & Thompson, 2004). A large number of studies explored the relationship between WM and *g* (for an overview see Buehner et al. 2005). High correlations between WM and reasoning were found in early studies by Kyllonen and Christal (1990), and recently Colom et al. (2004) found that WM was almost perfectly predicted by '*g*'. Conway et al. (2002) found that among processing speed, short-term memory capacity and WMC the latter was the best predictor for general fluid intelligence. Other studies could not replicate these very strong relationships (for example Ackerman et al. 2005; Conway et al. 2003) but a general finding is that WM and *g* are positively and significantly related. Which specific components of WM play a role in this relation, and how strong these relations are, remains unclear. A small number of adult twin studies addressed the question whether a genetic approach could be used to clarify genetic components underlying WM per se, and of the relationship between WM and intelligence. Ando et al. (2001) studied a twin sample of young adults to investigate the genetic structure of storage and executive functions in the spatial and verbal working memory domain. They also examined the relation between the WM tasks and cognitive ability which was measured with a Japanese intelligence test (Kyodai NX 15, Osaka & Umemoto, 1973). It was found that the phenotypic variances on the spatial and verbal task were significantly due to genetic influences, with heritability estimates between 43 and 48%. The genetic variance was due to modality specific factors (spatial and verbal) and a storage specific factor (7-30%). However, another part of the genetic variance was due to a common genetic factor explaining storage and executive functions in both spatial and verbal functions (11-43%). These findings suggested that multiple, partly overlapping genetic factors influence spatial and verbal working memory. The authors hypothesized that besides the important function of the prefrontal lobes in working memory, modality specific regions of the brain, such as Wernicke's regions (verbal) and the right parietal lobe (spatial) are involved, and that these regions are mediated by separate genetic influences. When they included cognitive ability in the analyses, it was shown that the common genetic factor found for the WM tasks, also explained a substantial part of the phenotypic correlation between the WM tasks and cognition.

Similar findings were presented by Luciano et al. (2001) who measured processing speed, working memory and IQ in 166 monozygotic and 190 dizygotic twin pairs. Subjects were young adults with a mean age of 16.17 (SD = 0.34). Processing speed was measured by a choice reaction task, and working memory was measured by a visual spatial delayed response task. IQ was derived from the Multidimensional Aptitude Battery (MAB, Jackson, 1998). Analysis showed the presence of a common genetic factor influencing all variables. In addition there were specific genetic factors influencing processing speed, working memory and IQ. Based on their findings the authors speculated that the genes common to all variables might actually affect the central executive component of WM, whereas those genes specific to the WM task, relate to the storage component.
Neubauer et al. (2000) pointed out that a distinction should be made between WM capacity and WM speed. In a large sample of adult twins they focused on speed of information processing. The relationship between psychometric IQ and two measures of speed of information processing was investigated. Psychometric intelligence was measured with shortened forms of the Raven's Advanced Progressive Matrices (APM, Raven, 1958) and the Leistung-Prüf-System (LPS, Horn, 1962), which is a well known German intelligence test. Processing speed was measured with two Elementary Cognitive Tasks. The first task was a memory scanning test based on Sternberg's (1969) Short Term Memory paradigm. In this test subjects have to randomly store one, three or five digits. After a warning signal, a target digit is shown and subjects have to indicate as quickly as possible if the target digit was part of the previously shown memory set. The second task was a Posner's letter-matching test (Posner & Mitchell, 1967). In this test subjects have to judge physical identity (i.e., visual discrimination) or name identity (i.e., LTM retrieval) of two characters. The phenotypic correlations between the RT's on the Elementary Cognitive Tasks and IQ were about -0.40 and were largely due to genetic factors. However, there were also specific genes affecting both phenotypes. The phenotypic correlations between the derived slope (i.e., linear increasing RT with increasing memory load) of the memory scanning task and IQ were relatively low (0.00-0.12). In discussing their results Neubauer et al. (2000) suggested that future studies should include both mental speed and WM

capacity to see if this joint contribution yields higher (genetic) correlations with human intelligence.

The present study investigates the genetic covariance between WM speed (WMS) and WM capacity (WMC) in children. In addition the influence of general IQ (*g*) on this genetic covariance is examined. Twelve-year-old twin pairs and their siblings (N=409) performed a choice reaction task with three memory loads from which a basic mental speed measure and the derived slope, as a reflection of delay caused by higher memory load, were used. Two subtests of the Wechsler Intelligence Scale for Children Revised (WISC-R, Van Haasen et al. 1986) that index capacity components of WM, namely Arithmetic and Digit Span (Kaufman, 1975; Engle, 2002) were analysed. General IQ was estimated by two verbal (Vocabulary and Similarities) and two performance (Block Design and Object Assembly) subtests of the WISC-R (Sattler, 1982, 1992).

The first aim is to asses the heritability of WMS and WMC and to examine to what extent individual differences in WMS and WMC performance are due to genetic variation. The second aim is to investigate whether covariance between WMS and WMC is explained by pleiotropic genetic effects. We explore through genetic factor analyses if a common set of genes influences both the WMS and WMC component. Structural equation modeling was used to test whether the genetic influences which are important for WMS are correlated with the genetic influences underlying WMC. This is established by modeling two genetic factors, one for WMS and one for WMC, which are allowed to correlate. If this correlation is one, this means that WMS and WMC are influenced by a common genetic factor (i.e., completely overlapping sets of genes). If this correlation is zero, the two components are influenced by independent sets of genes. If the correlation has a value between zero and (minus) one, WMS and WMC are partly mediated by the same set of genes and partly by separate sets of genes.

The third aim is to investigate whether *g* plays a role in the genetic covariance between WMS and WMC. Therefore the original model with two correlated genetic factors for WMS and WMC is extended to a hierarchical factor model in which genetic influences on *g* are modelled as a latent genetic variable influencing the genetic covariance between WMS and WMC. If, after incorporating *g* in the model, the genetic correlation between WMS and WMC disappears, *g* explains the genetic

covariance. If the correlation does not change significantly from the correlation in the original model, WM itself explains the genetic covariance between WMS and WMC. If the correlation reduces but is significantly different from zero, both *g* and WM explain the genetic correlation between WMS and WMC.

METHODS

Subjects

The sample consisted of 177 Dutch twin pairs, born between 1990 and 1992, and 55 of their siblings. The twins were 12 years old (mean age= 12.42, SD= 0.16) and the siblings were between 8 and 15 years old. Twenty seven siblings were younger than their twin brothers or sisters (mean age = 9.60, SD = 0.71) and 28 siblings were older (mean age = 14.69, SD = 0.60). There were 41 monozygotic male twin pairs (MZM), 28 dizygotic male twin pairs (DZM), 56 monozygotic female twin pairs (MZF), 25 dizygotic female twin pairs (DZF) and 27 dizygotic opposite-sex twin pairs (DOS). Zygosity was determined on the basis of DNA polymorphisms. The twins were registered at birth with the Netherlands Twin Registry (Boomsma, 1998; Boomsma et al. 2002). None of the children suffered from severe physical or mental handicaps. There were 172 twin pairs who had participated in a similar study at the age of 5 (Groot et al. 2004; Stins et al. 2005). The selection at that time was based on age and a sample evenly distributed across zygosity groups. To gain power for the current analyses five extra, dizygotic female twin pairs and 55 siblings of the twins were recruited (Posthuma & Boomsma, 2000).

The parents were invited for participation of their children in the continuing study entitled 'Genetics of Attention'. In the mailing information about the goals and procedures of the study were included. After two weeks the parents were contacted by phone and asked if they were willing to participate. Prior to the assessment parents and children signed an informed consent form.

Procedure

Assessments always started before 11 a.m. Children were tested at the same time but in separate rooms by separate experimenters. All subjects performed the same neuropsychological test battery consisting of 6 subtests of the Wechsler Intelligent Scale for Children Revised (WISC-R, Van Haasen et al. 1986) and computerized reaction time tasks, measuring a diverse range of executive functions such as working memory, divided, sustained, selective and focused attention. The entire test battery took ~4 hours, including breaks. After finishing the assessment, each child received a small present.

WMS was assessed with 'Memory Search' which is one of the tasks of the Amsterdam Neuropsychological Tasks (ANT, De Sonneville, 1999). In this task memory load, operationalized as target set size, increases from one to three target letters. The computer screen shows a fixed display of four consonants arranged in a square from which subjects must detect one or more target letters. For Load I the target signal requiring a yes-response is 'k' (40 trials; 50% target signal). For Load II, target signals are 'k' + 'r' (72 trials; 36 complete target sets, 18 trials one target signal, 18 trials no target signals) and for Load III target signals are 'k' + 'r' + 's' (96 trials; 48 complete target sets, 16 trials one target signal, 16 trials two target signals, 16 trials no target signals). Children were instructed to press the yes button only when a complete set of target letters was present. In all other instances a no-response was required. An example of the stimuli is shown in the bottom part of Figure 1. Responses were made by pressing the left or right mouse button. A yes-response was made with the preferred hand, a no-response with the unpreferred hand. In the instruction, both speed and accuracy were emphasized. Twelve practice trials were provided to ensure instructions were well understood.

WMC was assessed with two subtests of the WISC-R. Factor analyses exploring the structure of the WISC-R showed that a three factor solution fitted the data best (Kaufman, 1975; Kaufman, 1979; Reynolds & Kaufman, 1985; Kroonenberg & Berge, 1987). One of these factors is Working Memory and the accompanying tasks are Arithmetic, Digit Span and Substitution from which the first two tests were assessed. For general IQ (*g*) 4 subtests of the WISC-R were used, namely Similarities, Vocabulary, Block Design and Object Assembly. Standardized

scores of this short form of the WISC correlates 0.94 with standardized IQ scores based on all subtests of the WISC-R (Sattler, 1982, 1992).

Analyses

Descriptives

Only correct WMS responses were used for the analyses. None of the subjects had more than 30% misses or false alarms. The results of children who had a mean reaction time (RT) that was higher than three times the standard deviation above mean RT of the sample (N= 8) and children with a negative slope (i.e., children who had a lower mean RT for Load 3 than for Load 1, N= 3) were excluded. Data of seven children were not recorded. The increase in RT across the loads (i.e., the Slope) was computed as (RT Load III – RT Load I)/2. ANOVA (SPSS, 11.5) was used to test whether there was a significant increase in RT with increasing memory load. To summarize the WMS data the variables Load I, as a basic mental speed measure, and Slope, as a measure of delay caused by higher load, were used for further analyses. WMC was measured as the number of correct responses on Arithmetic, and on Digit Span. Data of 3 children were missing. Standardized IQ scores of Similarities, Vocabulary, Block Design and Object Assembly were used to estimate general IQ (*g*). Table 1 gives an overview of total numbers of subjects and total number of complete twin pairs, and twin-sib pairs for each variable.

Univariate Genetic Analyses

The different degree of genetic relatedness between monozygotic (MZ) twins, dizygotic (DZ) twins, and non-twin siblings (i.e., MZ twins share all their genes while DZ twins and siblings share on average half of their genes) was used to estimate the genetic and environmental contributions to the (co)variance of the variables. The total variation of each variable can be decomposed into sources of additive genetic variance (A), common environmental variance (C) and unique environmental variance (E). A is due to additive effects of different alleles, C is due to environmental influences shared by members of a family, and E is due to environmental influences not shared by members of a family. E also includes

Table 1:
Total numbers of first-born twins, second-born twins, and siblings, and total number of complete twin pairs for each variable

N	Load I	Load II	Load III	Slope	Arithmetic	Digit Span	IQ (g)
First-born twins	172	170	170	168	175	175	176
Second-born twins	175	175	173	171	175	174	177
Siblings	53	52	52	52	53	53	52
Total N	400	397	395	391	403	402	405
Complete twin pairs	171	170	167	166	175	174	176

measurement error and is therefore always included in the models. A first impression of the relative importance of each component is obtained by inspecting the standardized covariances, which are the twin correlations and twin-sib correlations. MZ correlations twice as high as DZ (and twin-sib) correlations indicate additive genetic influences. DZ correlations higher than half the MZ correlations designate common environmental influences. MZ correlations as high as DZ correlations indicate only common and unique environmental influences and no genetic sources of variance (Boomsma, Busjahn, & Peltonen, 2002).
The proportion of phenotypic variance due to genetic influences is known as the heritability (h^2). As power analyses revealed that the power to detect sex differences in heritability was low, male and female data were combined for both zygosities (see appendix). Structural equation modeling, as implemented in the statistical software package Mx (Neale et al. 2003), was used to analyse the data. Mx provides parameter estimates by maximizing the raw data likelihood. The goodness of fit of different models is evaluated by hierarchic likelihood ratio (χ^2) tests. Specifically, the χ^2 statistic is computed by taking twice the difference

between the log-likelihood of the full model and the log-likelihood of a reduced model ($\chi^2 = -2LL_0 - (-2LL_1)$). The associated degrees of freedom are computed as the difference in degrees of freedom between the two hierarchic models (Neale & Cardon, 1992). In addition to the χ^2-statistic, Aikake's Information Criterium (AIC) can be computed (AIC = χ^2 - (2 * df)). A low AIC indicates a relative good fit of the model. In a so called saturated model means and standard deviations and phenotypic twin and twin-sib correlations were estimated. A saturated model is fully parameterized and yields the best possible fit to the data. It is a useful model for evaluating the fit of more restricted models. It was tested whether means and variances of each variable were equal for first-born and second-born members of a twin pair, for MZ and DZ twins, and for siblings. In addition, it was tested whether DZ correlations and twin-sib correlations were equal for all variables. Full ACE models were fitted to the data of each variable to see if the phenotypic twin and twin-sib correlations derived from the saturated models were attributable to A, C or E. In addition, more parsimonious models (i.e., AE, CE and E models) were compared to the ACE model.

Multivariate Genetic Analyses

First, an unconstrained decomposition of the covariance structure of WMS and WMC into genetic and environmental covariance matrices was considered by means of triangular (or Cholesky) decomposition, including three variance components A, C and E. Based on the estimates of the A, C and E covariance matrices the genetic and environmental correlations between the variables were computed. The genetic correlations provide a measure of the extent to which variables are influenced by the same genes. The environmental correlations reflect the extent to which variables are influenced by the same environmental processes. The most parsimonious Cholesky model (i.e., an ACE, AE, CE or E model) was used as a baseline model against which to compare the hypothesized factor model for WMS and WMC.

In the factor model the genetic (A) and environmental components (C and E) were modelled with two latent factors, one for WMS and one for WMC. This was done by deleting four pathways in the original Cholesky model in such a way that the latent WMS factor loaded on the WMS variables and the latent WMC

factor loaded on the WMC variables. To examine whether all the variance could be explained by the latent factors, it was tested whether genetic effects specific for each variable could be deleted from the model without worsening the fit (i.e., all variance is explained by the latent factors). To examine whether the two factor structure fitted to the data it was tested if it was allowed to delete the latent factors for A, C or E (i.e., all variance is explained by specific factors). If the two latent factors for A, C, or E could not be deleted from the model they were allowed to correlate in three different sub models. In the first sub model the correlation between the two latent factors for WMS and WMC was estimated freely. This represented a model with partly independent and partly overlapping factors. In the second sub model the correlation between the two factors was constrained to be 1, reflecting a model with one factor for all variables. In the third sub model the correlation between the two factors was constrained to be zero, indicating two uncorrelated separate factors.

To investigate whether the genetic covariance between WMS and WMC could (partly) be explained by *g*, the factor model was extended with a third latent genetic factor Ag which loaded on general IQ. This factor Ag was modelled as a higher order factor controlling the genetic correlation between WMS and WMC (see Figure 2). It was tested to what extent the correlation between the latent WMS and WMC factors changed in this hierarchical model, compared to the original factor model. This was done in three ways. First, the correlation between WMS and WMC was estimated freely in the hierarchical model. Second, the estimated correlation from the original model was fixed in the hierarchical model to test whether the original correlation changed significantly. If not, the genetic correlation between WMS and WMC would be explained solely by WM. Third, the correlation was fixed to zero to test whether Ag could explain all the covariance between WMS and WMC.

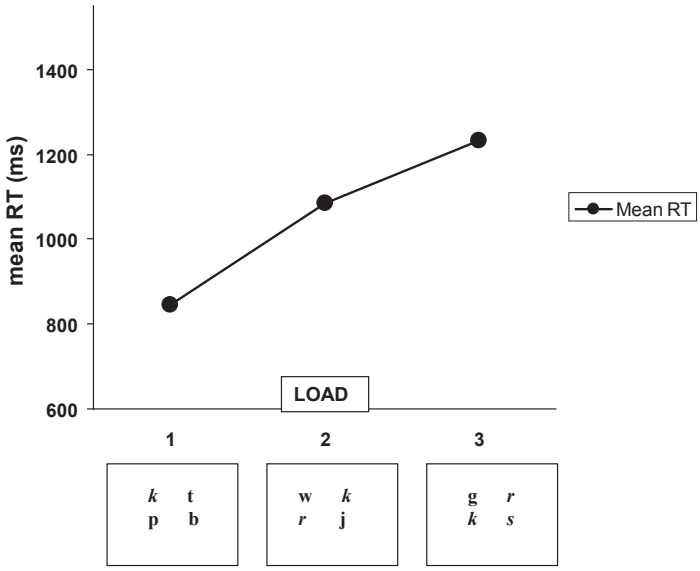

Figure 1:
Pattern of mean RTs over correct responses, including examples of stimuli (requiring a yes-response) of Load I, Load II and Load III of the WMS task.

RESULTS

Descriptives

For WMS, RT's were highest in Load III, lower in Load II and lowest in Load I. These load effects were significant for MZ and DZ twins, and siblings ($p < 0.001$). Figure 1 shows the pattern of mean RT's of the three memory loads, in the entire sample.

Table 2:
Upper part: Means and standard deviations for each variable, with the deviation from the mean for boys, older siblings and younger siblings. Lower part: Phenotypic correlations for MZ, DZ and twin-sibling pairs.

	RT Load I	RT Slope	Arithmetic	Digit Span
Mean (deviation: boy/older sib/younger sib)	811.49 (24.49/ -72.95/ 253.3)	351.08 (23.89/ -81.83/ 288.69)	16.88 (0.92/ 0.89/ -3.75)	11.38 (0.74/ 1.64/-2.14)
SD	144.72	203.20	2.94	2.84
Phenotypic Correlations				
MZ	0.53 (0.37-0.66)	0.40 (0.22-0.55)	0.59 (0.45-0.69)	0.58 (0.43-0.68)
DZ / twin-sib	0.23 (0.08-0.37)	0.28 (0.11-0.42)	0.11 (-0.04-0.27)	0.24 (0.08-0.39)

Univariate Genetic Modeling

Table 2 shows means and standard deviations including the effects of sex and age on the observed data, and phenotypic twin and twin-sib correlations for Load I, Slope, Arithmetic and Digit Span. Means and variances were equal for twins and siblings, and DZ correlations and twin-sib correlations were equal for all variables.

Compared to the saturated models, univariate full ACE models did not worsen the fit significantly. Evaluating more restricted models against the full ACE models showed that for Load I, Arithmetic and Digit Span C could be dropped from the full model. For Slope it was allowed to drop either A or C from the full model but not both. This indicated that the variance was explained by familial influences; however, it was not possible to distinguish between genetic or common environmental influences. A and E contributed equally to the total variance with heritabilities ranging between 43% and 56%. Table 3 shows univariate model fitting results for full ACE models and more restricted models per variable, including parameter estimates.

Table 3:
Univariate model fitting results

	Model	χ^2	df	*p*	AIC	h^2	c^2	e^2
Load 1	ACE	22.86	14	0.06		0.51 (.20-.63)	0.00 (.00-.23)	0.49 (.37-.65)
	AE	0.00	1	---	-2.00	0.51 (.36-.63)		0.49 (.37-.64)
	CE	8.65	1	0.00	6.65		0.32 (.20-.43)	0.68 (.56-.80)
	E	34.51	2	0.00	30.51			
Slope	ACE	23.81	17	0.12		0.26 (.00-.55)	0.14 (.00-.42)	0.60 (.45-.78)
	AE	0.72	1	0.40	-1.28	0.43 (.27-.56)		0.57 (.44-.73)
	CE	1.54	1	0.21	-0.46		0.33 (.19-.45)	0.67 (.55-.81)
	E	25.24	2	0.00	21.24			
Arithmetic	ACE	15.19	17	0.58		0.54 (.36-67)	0.00 (.00-.12)	0.46 (.33-.61)
	AE	0.00	1	---	-2.00	0.54 (.39-.67)		0.46 (.33-61)
	CE	15.97	1	0.00	13.97		0.29 (.17-.41)	0.71 (.59-.83)
	E	39.14	2	0.00	35.14			
Digit Span	ACE	27	17	0.06		0.56 (.28-.68)	0.00 (.00-.22)	0.44 (.32-.58)
	AE	0.00	1	---	-2.00	0.56 (.42-.68)		0.44 (.32-.58)
	CE	11.21	1	0.00	9.21		0.38 (.25-.48)	0.63 (.52-.75)
	E	46.62	2	0.00	42.62			

Note: Submodels AE, CE and E are compared with the full ACE model, which in turn is compared with the saturated model. Confidence intervals of the parameter estimates are put in brackets.

Table 4:
Phenotypic, genetic and unique environmental correlations among measures of WMS, WMC, and IQ

	Slope	Arithmetic	Digit Span	IQ
Load I	0.50/ 0.99/ -0.11	-0.33/ -0.49/ -0.06	-0.30/ -0.46/ 0.00	-0.21/-0.36/-0.06
Slope		-0.26/ -0.57/ 0.15	-0.32/ -0.51/ -0.05	-0.25/-0.42/-0.10
Arithmetic			0.45/ 0.73/ 0.04	0.47/0.75/0.03
Digit Span				0.33/0.48/0.03

Multivariate Genetic Modeling

Multivariate analyses revealed that the most parsimonious Cholesky model, which was used as a baseline model, included an additive genetic component (A) and a unique environmental component (E). Common environmental influences (C) could be dropped from the full Cholesky model without significantly worsening the fit, indicating that common environmental influences played no important role in the covariance between WMS and WMC. Hence, C was not included in the factor analyses.

Table 4 shows phenotypic, genetic and environmental correlations between all variables. Phenotypic correlations between WMS variables (Load I and Slope) and WMC variables (Arithmetic and Digit Span) were 0.50 and 0.45 respectively, and between WMS and WMC variables -0.30 (Load I and Digit Span), -0.32 (Slope and Digit Span), -0.33 (Load I and Arithmetic) and -0.26 (Slope and Arithmetic). Phenotypic correlations with IQ were -0.21 (Load I), -0.25 (Slope), 0.47 (Arithmetic) and 0.33 (Digit Span). Lower mean RT's of WMS were, as expected, negatively correlated with higher WMC and IQ scores. Genetic correla-

tions (i.e., the extent to which variables are influenced by the same genes) were 0.99 between the WMS variables and 0.73 between the WMC variables. Genetic correlations between WMS and WMC variables were lower (~0.50). This suggested for the genetic influences (A) on WM two factors, one for the WMS variables and one for the WMC variables. All unique environmental correlations were low varying between -0.10 and 0.15 and suggested no factor structure but only specific factor loadings for E.

We first tested a model that reflected the genetic (A) and environmental (E) correlation patterns. In the Cholesky decomposition, the pathways between the genetic latent WMS factor (A) and WMC variables were omitted, and in a similar way, pathways from the genetic latent WMC factor (A) to the WMS variables were omitted. For unique environment (E) a specific factor for each variable was specified. The factor model thus contained two latent factors for A (one for the WMS variables and one for the WMC variables), and four specific factors for E. It was tested which of the path loadings were significant. Neither the two factors for A, nor the specific factor loadings for E could be dropped from the model. For A it was allowed to drop specific factor loadings for the variables Load I, Slope and Digit Span. It was then tested whether the two genetic factors were correlated. First, by freely estimating the correlation, second, by constraining the correlation to be one (i.e., a one factor model), and third, by constraining the correlation to be zero. Table 5 shows that a model with two genetic factors, including a freely estimated correlation (-0.54), one specific factor loading for A (Arithmetics), and four specific factor loadings for E, fitted best to the WMS and WMC data. Constraining the correlation to one or zero showed a significantly worse fit of the model.

Secondly, a hierarchical model for WM and IQ with Ag as a third latent genetic factor was tested. The latent factor Ag loaded on general IQ and on the latent genetic factors for WMS and WMC. The correlation between WMS and WMC dropped from -0.54 (as in the first model) to -0.25 in the hierarchical model. Fixing the correlation to -0.54 showed a significantly worse fit of the model indicating that *g* explained a significant part of the genetic WM correlation. However, fixing the correlation between WMS and WMC to zero also showed a significant worsening of the fit, which means that it is not only Ag that explains the genetic covari-

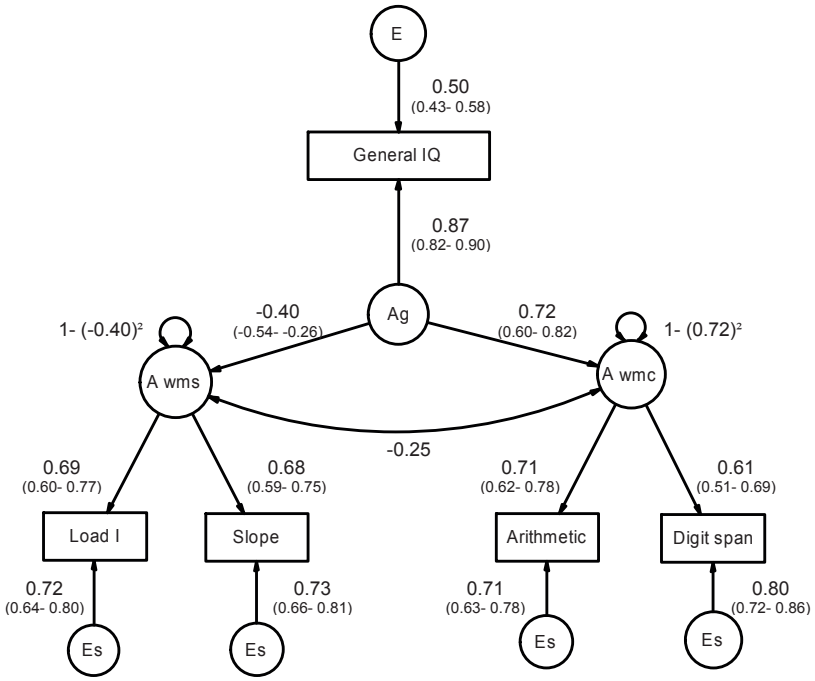

Figure 2:
Factor loadings of the best fitting hierarchical model with three latent factors for additive genetic influences (A-WMS, A-WMC and Ag), for the WM variables specific factors for E, and for the IQ variable a factor for E. Standardized path loadings are shown with confidence intervals in brackets. The correlation between the two latent factors A-WMS and A-WMC, is represented by *r*.

ance between WMS and WMC. Table 6 shows the results of the hierarchical sub models. Comparing the correlation of -0.25 in the hierarchical model to the correlation (-0.54) in the original factor model, we can conclude that WM and *g* contribute both (about 50%) to the genetic correlation between WMS and WMC. In Figure 2 the hierarchical model with three latent factors for A (WMS, WMC

Table 5:
Multivariate model fitting results for WMS and WMC

Correlated factor model (see Figure 2)	-2 LL	χ^2	df	*p*	AIC	*r*A
i. Cholesky ACE	12960.63					
ii. Cholesky AE	12960.97	0.34[1]	10	0.99	-19.66	
2 factor model (see Figure 2)						
correlate A factors free	12970.04	9.07[2]	10	0.53	-10.93	-0.54
correlate A factors 1	13029.42	68.45[2]	11	0.00	46.45	1.00
correlate A factors 0	13009.24	48.27[2]	11	0.00	26.27	0.00

Note: [1] Compared to model i.
[2] Compared to model ii.

Table 6:
Multivariate model fitting results for WMS, WMC, and IQ

	-2 LL	χ^2	df	*p*	AIC	*r*A
Hierarchical factor model (see Figure 3)						
i. genetic covariance WMS-WMC explained by WM and g	16155.32					-0.25
genetic covariance WMS-WMC explained by WM only	16170.73	15.41[1]	1	0.00	13.41	-0.54
genetic covariance WMS-WMC explained by *g* only	16166.99	11.68[1]	1	0.00	9.68	0.00

Note : [1] Compared to model i.

and Ag), the correlation between WMS and WMC, factor loadings and confidence intervals are shown.

DISCUSSION

The present study investigated the phenotypic and genotypic relationship between WM speed and WM capacity in a sample of 12-year-old twins and their siblings. It is the first study that investigated the heritabilities of WM in children of this age, and that examined the genetic structures underlying WM speed (WMS) and WM capacity (WMC). WMS was assessed with a choice reaction task with three memory loads from which a basic mental speed measure and the derived slope were analysed. For WMC we used two subtests of the WISC-R namely Arithmetic and Digit Span. To examine whether the genetic covariance between WMS and WMC could be explained by general IQ (*g*) we performed a hierarchical model that tested this hypothesis. General IQ (*g*) was based on 4 subtests of the WISC-R, Similarities, Vocabulary, Block Design and Object Assembly.

The heritabilities for the WM variables were moderately high, ranging from 43 to 56%, indicating that about half of the phenotypic variance could be explained by genetic variation. These results are comparable to the genetic WM studies in adults (Ando et al. 2001; Luciano et al. 2001). Different heritabilities were reported by Neubauer et al. (2000). For slope they reported a heritability of 11% and for memory scanning set size 1, which is comparable with the basic speed variable of the current study, they found no heritability at all. Other studies did find genetic influences on basal speed measures in adult studies (McGue et al. 1984; Boomsma & Somsen, 1991). However, it is suggested that when the complexity of a task increases, the heritability estimate increases as well (Neubauer et al. 2000; Vernon, 1989). Children might experience a simple WMS task or an increasing load (i.e., the Slope) as more complex than adults do, and therefore use cognitive resources, which adults do not need. The prefrontal lobes play an important role in WM performance and the fact that these brain areas are not completely matured before late adolescence (Kanemura et al. 2003; Anderson, 2002) may explain the extra efforts, and hence higher heritabilities in the cur-

rent age group. The few genetic studies that investigated WM speed in children showed conflicting results. A partly overlapping sample of 5-year-old children performed a similar WM speed task but in a more child friendly version (i.e., this task consisted of two loads and used picture stimuli instead of consonants). Their results were comparable with the present study showing a heritability of 54% for overall RT, and 29% for the derived slope (Stins et al. 2005). Petrill et al. (1995) tested 287 twins between 6 and 13 years old with a set of basic cognitive tasks (Cognitive Abilities Test, CAT; Detterman, 1990). Simple and Choice RT tasks were primarily determined by common environmental factors while a Stimulus Discrimination task appeared to be more influenced by genetic factors. WMC in this study, as measured with a self-paced probe recall task, showed a heritability of 22%.

We tested the hypothesis that WMS and WMC are genetically two different constructs. It was found that our data were best described by two latent factors, one for WMS (Load I and Slope) and one for WMC (Arithmetic and Digit Span). These latent factors were correlated (-0.54) but did not completely overlap. In other words, variation in WMS and WMC is influenced by separate genetic factors but also by a common set of genes. How should the correlated and separate genetic factors be interpreted? Referring to the existing theories about WM one might speculate that these findings hold up the theoretical framework as proposed by Baddeley (1992). The correlated factors (i.e., the same set of genes) influencing both WM constructs possibly represent the general controlling system while the separate factors (i.e., separate sets of genes) involve the two slave systems, responsible for the rehearsal of acoustic information, in this case WMC, and for the manipulation of visual input (WMS). Ando et al. (2001) and Luciano et al. (2001) found a common genetic factor influencing different WM domains (i.e., verbal and spatial) and they also hypothesized that the common set of genes found in their studies involved the central executive. Another suggestion for the common genetic factor is general intelligence (*g*). It is found that on a phenotypic level intelligence and WM performance are strongly related. Kyllonen and Christal (1990) claimed that 'reasoning ability is (little more than) working memory capacity' and Colom et al. (2004) revealed that working memory was 'almost perfectly predicted by *g*'. A recent genetic study of Finkel et al. (2005)

showed that the heritability of cognitive abilities in adulthood results, for the most part, from genetic influences associated with perceptual speed, instead of genes for cognitive functioning specifically.

In the light of these findings the substantial genetic correlation that we found between WMS and WMC might be 'perfectly' explained by *g*, instead of a genetic relation between WMS and WMC per se. This hypothesis was tested with a hierarchical factor model in which a third latent genetic factor (Ag) was allowed to replace the genetic correlation between WMS and WMC and hence could explain the genetic covariance between WMS and WMC. The results of these analyses showed that Ag could not explain the genetic correlation completely, but took out about half of the genetic covariance. This means that both *g* and WM are responsible for the shared genes between WMS and WMC. Looking at the path loadings from the latent WM factors to Ag (0.72 and -0.40 respectively) it is clear that *g* is (genetically) closer related to WMC than WMS. This is in line with previous (phenotypic) research, but it might also have to do with the choice of WMC tasks. As both *g* and WMC were based on subtests of the WISC-R, and WMS tasks were reaction time measures, it is may be not surprising that the former relationship turned out to be stronger. However, Conway et al. (2002) measured WMC with primary verbal tasks and fluid intelligence with nonverbal tasks; still they found a very strong link between both constructs. This suggests that the relation between WMC and fluid *g* is domain-free. The question might be whether WMC in this study was measured in an optimal way. Kyllonen and Christal (1990) already had serious reservations about their battery of WMC tasks, and still there is discussion about the estimation of WM in general and pure estimation of WMC specifically (Cowan et al. 2005; Conway et al. 2003; Oberauer et al. 2003).

Beside a significant genetic correlation between WMS and WMC, our results showed that WMS and WMC are also mediated by different sets of genes. These may be interpreted from a neuro-anatomical point of view. It is reasonable to hypothesize that different WM processes are driven by different parts of the brain which are mediated by separate genetic influences. The existence of distinct neuro-anatomical substrates for different domains, such as spatial, verbal and object WM has been suggested by studies on brain lesions in humans (Müller et al. 2002) and by several studies using brain imaging techniques (Goldman-Rakic,

1996; Courtney et al. 1996; Smith et al. 1996; Postle et al. 2000). Cornette et al. (2001) proposed that for visual stimuli, maintenance of orientations involved a distributed fronto-parietal network, while a more medial superior frontal sulcus region was identified for the manipulative operation of updating orientations retained in the WM. Cowan et al. (2005) emphasized that, especially for WM capacity, parietal lobe mechanisms probably play an important role. They addressed the question whether cortical areas related to WM reflect indeed distinct processes or whether they function as an integrated system. To get a better understanding of cognitive processes resulting from complex mechanisms in the brain, extensive research of different disciplines is required. For future research a joint contribution of genetic and cognitive investigations might be a useful and promising approach to further clarify the mechanisms underlying WM, and in addition illuminate the relation between WM, *g* and other cognitive processes.

Summarizing the current results it is firstly shown that WMS and WMC are heritable traits. Secondly, that the variance in WMS and WMC is explained by both an overlapping set of genes, and a separate set of genes. Thirdly, that the overlap of genes involves not only WM processes but is also explained by general IQ (*g*).

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APPENDIX

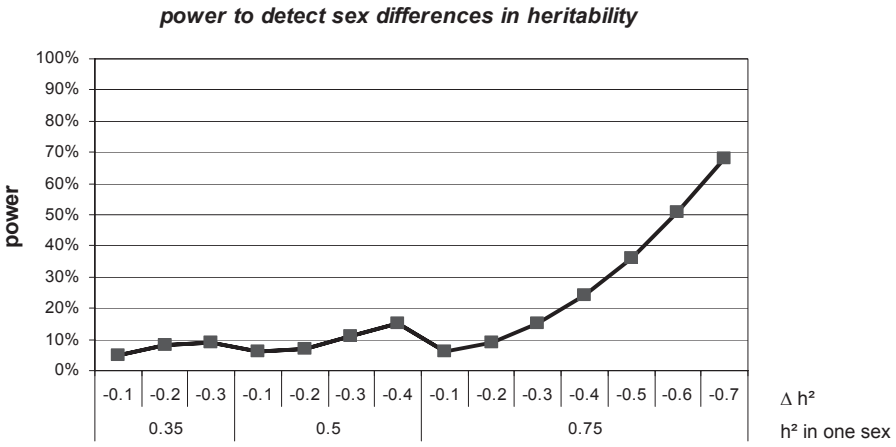

Figure shows the power (y-axis) to detect differences in heritability (x-axis) between boys and girls given a sample size of 177 twin pairs and 55 siblings. For a fixed heritability (h^2) of 0.35, 0.50 and 0.75 in one sex, the power to detect a difference of heritability (Δh^2) between boys and girls of respectively -0.1, -0.2 and -0.3, -0.1, -0.2, -0.3 and -0.4, and -0.1, -0.2, -0.3, -0.4, -0.5, -0.6 and -0.7 is shown.

7

GENETIC ANALYSES OF THE STABILITY OF EXECUTIVE FUNCTIONING DURING CHILDHOOD

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ABSTRACT

The genetic and environmental influences on the longitudinal stability of executive functioning were examined in children. Computerized reaction time tasks on Selective Attention, Working Memory, and Sustained Attention were collected in twin pairs when they were 5 years old (N=474 children) and when they were 12 years old (N=346 children). The longitudinal correlations of processing speed were substantial with 0.37 in the Selective Attention and Working Memory task, and 0.39 in the Sustained Attention task. For Slope (i.e., the delay caused by higher memory load) and Fluctuation in tempo the longitudinal correlations were 0.08 and 0.26 respectively. The stability over time was mediated by genetic factors. In 5 and 12-year-old children genetic variation was the most important explanation for individual differences in executive functioning. At age 12, the genetic influences on variation in executive functioning could be distinguished into genetic effects which were transmitted over time, and new genetic influences which emerged at age 12.

Important features of cognitive development during childhood include the increasing abilities to hold information in mind and to process that information, to select relevant input from the environment and suppress distracting or conflicting information, to inhibit inappropriate reactions, and to maintain alertness over time (Diamond, 1990). Constructs that refer to these abilities are respectively working memory, selective attention, inhibition and alertness (or sustained attention), and are part of abilities that are known as executive functions. Development of executive functioning in childhood occurs at different rates for various functions. For example, temporary storage of information (i.e., working memory) and inhibition are to a certain extent present from early infancy (Davidson et al, 2006). Selective attention, including the ability to supress distracting information, as in a conflict task, improves significantly during childhood (Ridderinkhof & Van der Stelt, 2000; Rueda et al, 2004b). Also when children grow older processing speed becomes faster and storage capacity increases (Kail, 1992; Rueda et al. 2004a).

With respect to the development of executive functioning relatively little is known about the stability over time. Will children who, for example, are slow or error prone at a young age also be slower or less accurate later in childhood? The few studies that investigated the developmental stability of executive functions, reported correlations between 0.28 and 0.79 across time (Demetriou et al, 2002; Weissberg et al, 1990; McCardle et al, 2002), depending on methods, age ranges, and test-retest intervals. Weissberg et al. (1990) found a correlation of 0.79 for simple reaction time tasks, for a test-retest interval of six weeks in a sample of 13 preschool children. The test-retest interval in the study of Demetriou et al. (2002), who tested 113 children aged 8 to 14 years old, was about two years. They measured speed of naming words, numbers and geometrical figures and reported correlations between 0.28 and 0.47. McCardle et al. (2002) collected longitudinal data on psychometric measures of processing speed in a sample of 188 subjects aged between 6 and 10 years old with test-retest intervals varying from less than one year up to four years. The stability for a composite index of processing speed was 0.72.

A small number of studies investigated to what extent individual differences in executive functioning during childhood may be due to genetic variation (i.e.,

heritability) or common environmental variation (i.e., explained by the environment that is shared among siblings who grow up in the same family). The classical twin design is often used to unravel genetic, common environmental and unique environmental sources of variance (Boomsma et al, 2002). Data from genetically related individuals like monozygotic twins and dizygotic twins allow the estimation of genetic, common environmental and unique environmental contributions to the variance of a certain trait. For example Stins et al. (2005) used the classical twin design to investigate processing speed using computerized reaction time tasks, measuring selective attention and working memory. Their sample consisted of 5-year-old mono- and dizygotic twin pairs. Genetic analyses of the data showed that there were familial influences on task performance but no clear distinction could be made between genetic influences and common environmental influences. Groot et al. (2004) investigated inhibition with a go-no-go task, and sustained attention in the same 5-year-old twin pairs and found genetic influences on both tasks. Variation in processing speed on these tasks was for about 50% explained by genetic influences and no significant common environmental influences were present.

Polderman et al. (2006b) investigated working memory in a sub sample of twins who took part in the studies of Stins et al. (2005) and Groot et al. (2004), when the children had reached the age of 12. In the genetic analyses basic processing speed and the difference in RT between two memory loads (i.e., the slope) were examined. The heritability estimates for both indices were around 50%. For working memory capacity, as measured with two subtests (Arithmetic and Digit Span) of the WISC-R (Wechsler Intelligence Scale for Children-Revised, Van Haasen et al., 1986) also 50% of the variation was explained by genetic variance. Ando et al. (2001) examined the phenotypic variances in a spatial and verbal working memory task in 236 young adult twin pairs (mean age 19.9). The heritability of these tasks was between 43 and 48%.

Based on these previous genetic studies it may be concluded that individual differences in executive functioning in preschool children are explained by familial influences, even though some studies could not distinguish between genetic and common environmental factors to explain the familial influences. In older children and young adults genetic variation explained about half of the vari-

ance in working memory performance. The heritability of executive functioning (or cognitive traits) is important to know because impairment of these functions is associated with several cognitive disorders like ADHD (Barkley, 1997). Neurobehavioral phenotypes (or 'endophenotypes') might better characterize the genetic pathways that lead to complex disorders than the behavioral symptoms of pathology. As endophenotypes serve as 'a genetic guide' they should be heritable themselves (Gottesman, 1997; Skuse, 2001; Gottesman & Gould, 2003).

The present study is the first that jointly investigate the phenotypic and genetic stability of three constructs of executive functioning in children, and to investigate the heritability of these traits in a longitudinal genetically informative design. A sample of 237 twin pairs were tested on executive functioning when they were 5 years old, and again when they were 12 years old. An advantage of this longitudinal design is that multiple measures increase the statistical power to detect genetic and environmental effects at ages 5 and 12 (Schmitz et al., 1998), and that the causes of longitudinal stability can be investigated. Processing speed, as an important index for cognitive development (Gathercole, 1999; Fry & Hale, 2000; Just & Carpenter, 1992) was operationalized as reaction time on tasks measuring selective attention, working memory and sustained attention respectively. Faster processing speed may allow more information to be processed before it is lost through decay or interference and is therefore more efficient (Jensen, 1993). Specifically, processing speed in a selective attention task reflects to what extent subjects successfully ignore non relevant information (i.e., they are faster than subjects who are hampered by distracting information) and particularly the distractor trials provide information on the amount of distraction. In working memory reaction times (RT) of information processing increase when more information has to be hold in mind. Subjects who successfully process a certain amount of information are faster than subjects who need more effort to manipulate and process that information (Baddeley, 2003). The increase in effort during higher memory loads is represented specifically by the slope (i.e., the difference in RT between low and high load trials). In a sustained attention task the variation in alertness during the task makes some children slower as the task progresses while others maintain their processing speed and state of alertness. These processes are reflected by overall RT and variation in tempo during the task.

To obtain indices of the reliability of the test battery that was used, six months after their first assessment 16 twin children at age 12 performed all computerized tests again. In addition ten 12-year-old children of a public school were tested and retested with an interval of 2 weeks.
The first aim of this study is to investigate developmental stability in executive functioning during childhood on a phenotypic level. Secondly, we want to examine whether the causes of developmental stability are of genetic or environmental origin. In other words, is the phenotypic stability driven by genes or environment, or both? The third aim is to investigate if estimates of variance components for executive functioning at age 5 differ from estimates of variance components at age 12. Is the contribution of genetic influences for example higher in young adolescents than in preschool children?

METHODS

Subjects

The sample at age 5 consisted of 237 Dutch twin pairs born between 1990 and 1992 with a mean age of 5.8 years (SD. 0.1, range 5.67 – 5.92). All subjects were registered at birth with the Netherlands Twin Registry (NTR), kept by the Department of Biological Psychology at the Vrije Universiteit in Amsterdam. Of all multiple births in the Netherlands, 40-50% is registered by the NTR (Bartels et al., 2007; Boomsma, 1998). The selection was based on age and a sample evenly distributed across sex and zygosity groups. None of the children suffered from severe physical or mental handicaps. There were 52 monozygotic male twin pairs (MZM), 37 dizygotic male twin pairs (DZM), 73 monozygotic female twins pairs (MZF), 36 dizygotic female twin pairs (DZF) and 39 dizygotic opposite-sex twin pairs (DOS) in the sample. In the same sex twin pairs, zygosity was determined on the basis of DNA polymorphisms. Prior to the assessment parents signed an informed consent form.
Of the original sample of 237 twin pairs, 172 twin pairs participated again when they were 12 years old (mean age= 12.42, SD= 0.16). Five extra, 12-year-old dizy-

gotic female twin pairs were recruited. The sample thus consisted of 177 twin pairs. There were 41 MZM twin pairs, 28 DZM twin pairs, 56 MZF twin pairs, 25 DZF twin pairs and 27 DOS twin pairs. The parents were invited by mail for participation of their children in the continuing study entitled 'Genetics of Attention'. After two weeks the parents were contacted by phone and asked if they were willing to participate. Prior to the assessment parents and children signed an informed consent form.

Ten children (4 boys) of 12 years old (mean =12.19, SD =0.36) were recruited at a primary school in Amsterdam to perform five computerized tasks of the ANT (De Sonneville, 1999) for the purpose of test-retest measurements. Children and parents of the children signed an informed consent form prior to the assessments. In addition test-retest data were collected in 8 twin pairs of the 12-year-old sample.

The study was approved by the institutional review board of the VU University Medical Centre.

Procedure

To assess selective attention, working memory and sustained attention the Amsterdam Neuropsychological Tasks (ANT, De Sonneville, 1999) were used. The ANT consists of a series of computerized tasks, designed for measuring a diverse range of executive functions in (young) children, adolescents, adults and elderly. The ANT is an often used test battery in Dutch and international research (see for example Slaats-Willemse et al., 2005; Huijbregts et al., 2002; Serra et al., 2003; Günther et al., 2004). The reliability of several tasks of the ANT was investigated by Günther et al. (2005). They reported test-retest correlations between 0.70 and 0.87.

When the children were 5 years old they were visited at home where trained testers administered the tests on a laptop. In addition to the executive functioning tasks as analysed in this study a go-no-go task, a basic speed task and 6 IQ subtests of the RAKIT (Bleichrodt et al., 1984) were administered. The entire test session took ~2 hours including breaks. When the children were 12 years old they visited the Vrije Universiteit for the assessment where they performed the tasks on a standard computer. Tasks were similar as at age 5 but adjusted for age (for

example consonant stimuli instead of pictures, and more trials per task) and the task battery was expanded with two tasks on motor flexibility, one task on shifting attention, and one task on emotion recognition. In addition six IQ subtests of the WISC-R (Van Haassen et al., 1986) were assessed. Children were tested at the same time but in separate rooms by different test leaders. The entire test session at this time took ~4 hours, including breaks. After finishing the assessments, the children received a small present.

For the test-retest measurements the children of the public school were tested in a quiet room in the school, one by one, by a trained tester. The test-retest interval was 2 weeks. The children of the 12-year-old twin sample were retested with an interval of ~six months. Assessments took place at the children's homes where they were tested one by one, in a quiet room.

Selective Attention, Working Memory, and Sustained Attention Tasks at Age 5

Selective Attention

In this task a fruit basket is presented with four pieces of fruit. Two pieces of fruit are aligned in a vertical fashion (top and bottom) and two pieces in a horizontal fashion (left and right). Subjects have to give a yes-response if the target fruit is shown at one of the two relevant locations (the top or bottom location of the vertical axis). They have to give a no-response if the target fruit is shown but at an irrelevant location (left or right of the horizontal axis), or if the target fruit is absent altogether. The display with the target fruit on the vertical axis is the target condition; the display with the target fruit on the horizontal axis is the distracting condition, and the display that contains only the four non-target fruits is the non-target condition. The three signal types were presented in a random order (28 target signals, 14 distracting signals, and 14 non-target signals). Following a response, the next signal was presented 1200 ms later, preceded the last 500 ms by a warning signal (small fixation cross).

Working Memory

In this task children were presented with an image of a house with four animals presented in the windows and the door opening. Subjects were instructed to

press the yes-key when the signal contained an animal from the memory set, and to press a no-key when this was not the case. On each trial the animals occupied different positions. The task consisted of two parts. In part 1 the memory set contained one animal and in part 2 two animals. In each part 20 target and 20 non-target signals were presented in random order. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation square).

Sustained Attention

During this task a house with three windows is continuously present on the screen. In each trial one animal appears randomly in one of the windows. Subjects are instructed to press the yes-key when they detect a target animal and the no-key when there is a non-target animal. The task consisted of 20 series of 12 trials (i.e., 240 trials). In each series 6 target and 6 non-target signals were presented in random order. To keep the children alert a beep sound was presented in case of an error. Following a response, the next stimulus was presented after 250 ms.

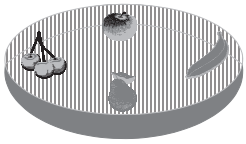
Selective Attention, Working Memory, and Sustained Attention Tasks at Age 12

Selective Attention

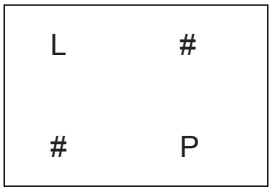
In this task a fixed display with two different consonants was presented on one of two diagonals, the top-left to bottom-right or the top-right to bottom-left diagonal. The task contained three manipulations: 1) location of the consonants: relevant or non-relevant diagonal 2) presence of a target: target or non target letter present, and 3) memory load: in part 1, one target letter, in part 2, three target letters (of which one could appear). Subjects had to give a yes-response when a target appeared on the relevant diagonal (the top-left to bottom-right one). A no-response was required when a target letter appeared on the non-relevant diagonal or when a non-target letter appeared on one of the two diagonals. The task consisted of two parts with each 120 trials. The presentation of stimuli was balanced so that an equal number of yes- and no-responses was required. A stimulus appeared for 300 ms. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation cross).

Task displays at age 5

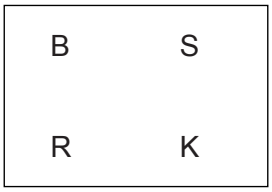
Task displays at age 12



SELECTIVE ATTENTION



WORKING MEMORY



SUSTAINED ATTENTION

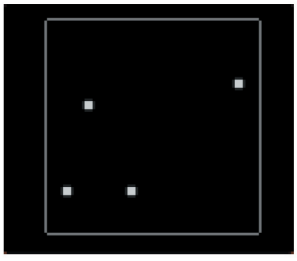


Figure 1:
An example of stimuli and task displays of respectively the Selective Attention task, the Working Memory task and the Sustained Attention task, at age 5 (left part) and age 12 (right part)

Working Memory

In this task memory load, operationalized as target set size, increased from one to three target letters. The computer screen showed a fixed display of four consonants arranged in a square, from which subjects had to detect one or more target letters. For Load 1 the target signal requiring a yes-response was 'k' (40 trials; 50% target signal). For Load 2, target signals were 'k' + 'r' (72 trials; 36 complete target sets, 18 trials one target signal, 18 trials no target signals) and for Load 3 target signals were 'k' + 'r' + 's' (96 trials; 48 complete target sets, 16 trials one target signal, 16 trials two target signals, 16 trials no target signals). Children were instructed to press the yes-button only when a complete set of target letters was present. In all other instances a no-response was required. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation square).

Sustained Attention

During this task a square with 3, 4 or 5 dots is presented on the screen. Subjects are instructed to press the yes-key when they detect 4 dots and the no-key when 3 or 5 dots are presented. The task consisted of 50 series of 12 trials (i.e., 600 trials). In each series 4 target and 8 non-target signals were presented in random order. To keep the children alert a beep sound was presented in case of an error. Following a response, the next stimulus was presented after 250 ms.

In all tasks, at both ages, responses were made by pressing the left or right mouse button. A yes-response was made with the preferred hand, a no-response with the non preferred hand. Prior to the experiments, the children were given verbal instructions in which both speed and accuracy were emphasized. Twelve practice trials were provided for each task to ensure instructions were well understood. Dependent measures were reaction times (RT) for hits, correct rejections, false alarms and misses. Reaction times at age 5 had to be generated between 200 and 6000 ms. post stimulus onset. Reaction times before 200 ms. were not considered to be the result of a cognitive evaluation and were automatically replaced by trials of a similar type. Figure 1 shows an example of each task display, at age 5 and at age 12.

In all tasks processing speed (i.e., overall reaction time, RT) was measured in milliseconds (ms). Additional indices for selective attention, working memory and sustained attention were: a) the difference in RT between trials with the target fruit/letter on the irrelevant location and trials with no target fruit/letter which gives an index of the distractor effect in the selective attention task, b) the difference in RT between part 1 and part 2 (age 5) or part 1 and part 3 (age 12) in the working memory task, which reflects the delay caused by higher memory load, or slope c) the standard deviation of the 20 (age 5) or 50 (age 12) series of 12 trials of the sustained task, which gives an index of fluctuation in tempo.
Thus the variables that were used in the analyses were processing speed (i.e., overall RT) of selective attention, working memory and sustained attention (in this paper referred to as 'selective attention', 'working memory' and 'sustained attention'), and RT of distraction in the selective attention task, RT of the slope in the working memory task and RT of fluctuation in tempo during the sustained attention task (in this paper referred to as the indices 'distraction', 'slope' and 'fluctuation').

Analyses

Descriptives

Longitudinal studies always have the difficulty of subjects dropping out over the years. About 75% of the family's who participated at age 5, were willing to participate again at age 12. The reason for non-responders was half of the time 'no interest without specific reasons', by the children or parents. Other reasons were personal circumstances like divorce, death or illness in the family. A small group was no longer registered in the NTR or not attainable by mail or telephone. There were no differences between the non-responders and responders for processing speed, IQ, and attention problems as reported by the teacher or parents at age 5. For all tasks only correct responses (i.e., hits and correct rejections) were used for the analyses. In SPSS (11.5) the mean response speed (RT) and standard deviation of each variable was calculated. At age 5 the data from children with an error rate >40% (n=2 for selective attention) or a mean reaction time (RT) that was higher than three times the standard deviation above mean RT of the sample

Table 1:
Total numbers of first-born twins, second-born twins, and school children, and total number of complete MZ and DZ twin pairs for the Selective Attention task, the Working Memory task and the Sustained Attention task

N	Selective Attention age 5	Selective Att test age 12	Selective Att retest age 12	Working Memory age 5	Working Mem test age 12	Working Mem re-test age 12	Sustained Attention age 5	Sustained Att test age 12	Sustained Att retest age 12
First-born twins	235	171	8	236	172	8	237	172	8
Second-born twins	234	175	8	236	175	8	237	175	8
School children	0	10	10	0	10	10	0	10	10
Total N	469	346	26	472	347	26	474	347	26
Complete twin pairs MZ/DZ	122/111	95/76	8	123/112	94/77	8	125/112	95/77	8

(n=3 for selective attention, n=2 for working memory) were excluded. At age 12 the selective attention data from 8 children, and the working memory from 6 children, and the sustained attention data from 7 children were not recorded. In none of the tasks children had >40% errors. For working memory 1 child was excluded because of a mean RT higher than three times the standard deviation. Table 1 gives an overview of total numbers of subjects and total number of complete twin pairs for each task.

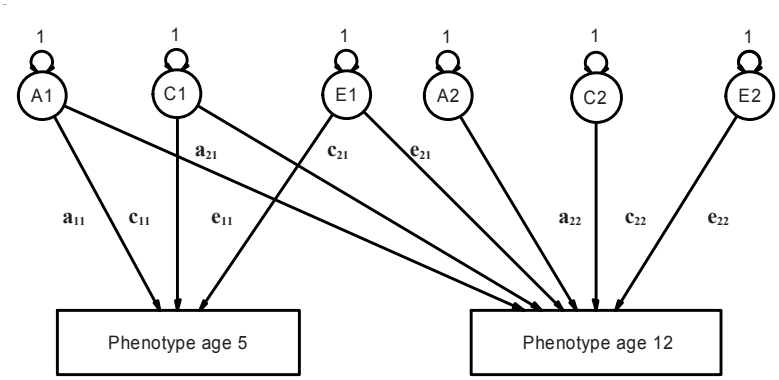
Genetic Analyses

The different degree of genetic relatedness between monozygotic (MZ) twins and dizygotic (DZ) twins (MZ twins share all their genes while DZ twins share on average half of their segregating genes) was used to estimate the genetic and environmental contributions to the (co)variance of the variables. The total variation of a trait can be decomposed into variance due to additive genetic factors (A), common environmental factors (C) and unique environmental factors (E). A is due to additive effects of different alleles, C is due to environmental influences shared by members of a family, and E is due to environmental influences not shared by members of a family. E also includes measurement error and is therefore always included in the models. A first impression of the relative importance of each component is obtained by inspecting the standardized covariances, or the correlations within MZ and DZ twin pairs. If MZ correlations are twice as high as DZ correlations, this indicates the presence of additive genetic influences. If DZ correlations are higher than half the MZ correlations, this suggests the presence of common environmental and genetic influences. If MZ correlations are as high as DZ correlations, this indicates that common environmental influences explain twin resemblance (Boomsma et al., 2002). The relative contribution of genetic influences on individual differences is known as the heritability (h^2). Power analyses revealed that in the current sample the power to detect sex differences in heritability was low. Therefore data from males and females were combined for both zygosities (Polderman et al., 2006a).

Structural equation modeling, as implemented in the statistical software package Mx (Neale et al., 2003), was used to analyse the data. Mx provides parameter estimates by maximizing the raw data likelihood which involves that all avail-

able data, also when some observations for subjects are missing, can be included. Therefore the data of all subjects at age 5 and at age 12, regardless of whether they participated once or twice, were included in the longitudinal analyses. The goodness of fit of different models was evaluated by hierarchic likelihood ratio (χ^2) tests. Specifically, the χ^2 statistic is computed by taking twice the difference between the log-likelihood of the full model and the log-likelihood of a reduced model ($\chi^2 = -2(LL_0 - LL_1)$). The associated degrees of freedom are computed as the difference in degrees of freedom between the two hierarchic models (Neale and Cardon, 1992). In addition to the χ^2-statistic, Akaike's Information Criterium (AIC) was computed ($AIC = \chi^2 - (2 \times df)$). A low AIC indicates a relative good fit of the model (Akaike, 1987). Means, variances, and twin correlations were obtained with maximum likelihood estimation in a saturated model under the assumption that means and variances were the same for first born and second born twins and for MZ and DZ twins. The saturated model is fully parameterized and provided a baseline model against which subsequent, more parsimonious, models were compared.

The 'cross age-cross twin' correlations indicate to what extent the performance of twin 1 at age 5 predicts the performance of twin 2 at age 12, and vice versa. The pattern of 'cross age-cross twin' correlations for MZ twins and DZ twins indicates (in a similar vein as described above) to what extent this correlation is influenced by genetic or environmental variation. A decomposition of the longitudinal covariances of performance data at age 5 and at age 12 into genetic (A) and environmental (C, E) covariance matrices was considered by means of a longitudinal model which contained two latent factors for A, C and E respectively, of which the variances were constrained to be one. The first observation (i.e., performance at age 5) loaded on the first latent factors A, C and E. The sum of squared estimates of factor loadings (i.e., $(a_{11}^2)+(c_{11}^2)+(e_{11}^2)$) represented the phenotypic variance at age 5. The second observation (i.e., performance at age 12) loaded on both factors and the variance of this observation consisted of the sum of the respective squared factor loadings (i.e., $(a_{21}^2+a_{22}^2)+(c_{21}^2+c_{12}^2)+(e_{21}^2+e_{22}^2)$). The covariance between both observations is derived by multiplying the factor loadings of both phenotypes on the first latent factors. The total covariance is the sum of those products (i.e., $(a_{11} \times a_{21})+(c_{11} \times c_{21})+(e_{11} \times e_{21})$). The longitudinal



Phenotype age 5:

$P = (a_{11}A_1 + c_{11}C_1 + e_{11}E_1)$

$V_P = (a_{11}^2) + (c_{11}^2) + (e_{11}^2)$

h^2 age 5 is $\frac{a_{11}^2}{a_{11}^2 + e_{11}^2}$

Phenotype age 12:

$P = (a_{21}A_1 + a_{22}A_2 + c_{21}C_1 + c_{22}C_2 + e_{21}E_1 + e_{22}E_2)$

$V_P = (a_{21}^2 + a_{22}^2) + (c_{21}^2 + c_{22}^2) + (e_{21}^2 + e_{22}^2)$

h^2 age 12 is $\frac{a_{21}^2 + a_{22}^2}{a_{21}^2 + a_{22}^2 + e_{22}^2 + e_{21}^2}$

Genetic covariance is $(a_{11} \times a_{21})$

r_g is $\frac{a_{11} \times a_{21}}{\sqrt{a_{11}^2} \times \sqrt{a_{21}^2 + a_{22}^2}}$

Note: P = Phenotype, V_P = Variance of the phenotype, h^2 = heritability, r_g = genetic correlation

Figure 2:
Example of the longitudinal model with the possible sources of variance and covariance of A, C and E.

model is shown in Figure 2.
The full longitudinal model with all factors was compared to a simplified and more parsimonious model. Leaving out A2 and C2 or A1 and C1 provides a test of whether genes or common environment contributed significantly to the total (co)variance of the longitudinal model. To examine whether A, C or E contributed significantly to the covariance between ages it was tested whether a21, c21, e21 could be omitted from the model. If a21 could be omitted this means that genes play no role in the stability of executive functioning between age 5 and age 12. If c21 or e21 are non-significant this means that common or unique environment plays no role in the stability of executive functioning.

RESULTS

Descriptives

Table 2a shows means and standard deviations for processing speed (RT in ms.) of selective attention, working memory and sustained attention, and the indices distraction, slope and fluctuation in tempo of all children at age 5 and 12, and retest assessments at age 12.
The longitudinal correlations for processing speed were, with regard to the time interval of 7 years, substantial with 0.37 for selective attention and for working memory, and 0.39 for sustained attention. The longitudinal correlations for the indices were low with -0.02 for distraction, and 0.08 for the slope but reasonable (r = 0.26) for fluctuation.
The test-retest correlations that were obtained by the repeated test assessments at age 12 were high for both the twins and the children of the public school. For selective attention, working memory, sustained attention, slope and fluctuation in tempo the correlations were between 0.70 and 0.93. Only the test-retest correlation for distraction in the selective attention task was low (r = 0.12). This indicates that the executive functioning tasks that were used were reliable at age 12.

Table 2:
Means and standard deviations (in ms.) of processing speed of selective attention, working memory and sustained attention, and distraction, slope and fluctuation in tempo at age 5 and at age 12 (test and retest assessments)

Processing Speed	Mean	SD
Selective attention age 5	1911.38	420.42
Working memory age5	1900.07	329.60
Sustained attention age 5	1716.91	254.10
Selective attention age 12	930.96	209.85
Selective attention retest age 12	764.86	238.00
Working memory age 12	1074.86	239.16
Working memory retest age 12	923.26	196.79
Sustained attention age 12	1090.08	259.04
Sustained attention retest age 12	957.60	244.45
Indices		
Distraction age 5	22.89	363.03
Slope age 5	488.22	314.53
Fluctuation age 5	2.58	0.90
Distraction age 12	50.36	96.89
Slope age 12	180.07	100.56
Fluctuation age 12	1.64	0.95
Distraction retest age 12	85.72	107.50
Slope retest age 12	354.57	197.66
Fluctuation retest age 12	1.13	0.64

Table 3:
Twin correlations of processing speed of selective attention, working memory and sustained attention, and distraction, slope and fluctuation in tempo for MZ and DZ twin pairs

Twin correlations Processing Speed	MZ	DZ
Selective attention age 5	0.50	0.35
Working memory age 5	0.55	0.35
Sustained attention age 5	0.60	0.28
Selective attention age 12	0.60	0.48
Working memory age 12	0.73	0.54
Sustained attention age 12	0.61	0.49
Indices		
Distraction age 5	0.13	0.02
Distraction age 12	0.02	-0.07
Slope age 5	0.35	0.01
Slope age 12	0.46	0.31
Fluctuation age 5	0.30	0.13
Fluctuation age 12	0.63	0.42

Twin Correlations

In Table 3 phenotypic MZ and DZ twin correlations are shown. MZ correlations for all variables were higher than DZ correlations, at age 5 and at age 12. This indicated that genetic variation played a role in explaining individual differences in selective attention, working memory and sustained attention. The MZ correlations for selective attention however were less than twice as high as the DZ correlations (at both ages), indicating that for that task common environmental influences may be important as well. The same applied to working memory, sus-

Table 4:
Cross twin-cross age correlations of processing speed of selective attention, working memory and sustained attention, and distraction, slope and fluctuation in tempo for MZ and DZ twin pairs

Cross age/cross twin correlations	MZ	DZ
Selective attention	0.32	0.22
Working memory	0.37	0.27
Sustained attention	0.42	0.21
Distraction	0.05	-0.12
Slope	0.13	0.10
Fluctuation	0.20	0.19

tained attention, slope and fluctuation at age 12 which showed DZ correlations higher than half the MZ correlations. The twin correlations for distraction were very low at both ages.

The 'cross age-cross twin' correlations for MZ and DZ twins showed a pattern with cross correlations being slightly higher for MZ twins than for DZ twins, except for sustained attention for which MZ cross correlations were twice as high as DZ cross correlations. Longitudinal stability for this task thus seemed to have genetic influences, while for the other variables the pattern was less clear. The 'cross age-cross twin' correlations for distraction were low ($r < 0.06$). Table 4 shows the 'cross age-cross twin' correlations.

Genetic Modeling

Distraction was excluded from the longitudinal model fitting analyses as the low twin correlations at both ages and the 'cross age-cross twin' correlations indicated that no meaningful genetic analyses could be performed. The full ACE model was used as a baseline model for the longitudinal analyses. For selective attention and sustained attention the covariances due to genetic factors were higher than the covariances due to common environmental factors. For working memory,

the slope and fluctuation the covariance due to common environmental factors was higher than for genetic factors. The covariance due to E was low in all tasks, indicating that this source of variance was not transmitted over time. It was tested whether the contribution of genes, common and unique environment to the longitudinal stability was significant by omitting the second factor loadings of the first factor (i.e., a21, c21, e21). Genes contributed significantly to the covariance of sustained attention while common and unique environment were not significantly present. For selective attention and working memory, and fluctuation in tempo it was allowed to omit the covariance due to A, or C, and E, but not A and C simultaneously. The AIC of these models only slightly differed but indicated that for selective attention and fluctuation in tempo a model without common environmental covariance but with genetic covariance, and for working memory a model without genetic covariance but with common environmental covariance was preferred. For slope it was allowed to drop the covariance due to genetic and common environmental factors simultaneously.

Next it was tested whether more parsimonious models could describe the longitudinal data by omitting the total variance due to genetic factors or common environmental factors. For all variables a full ACE model could be rejected in favor of a more parsimonious model that included genetic and unique environmental factors (working memory and sustained attention) or a model that included common and unique environmental influences (selective attention, slope and fluctuation). After omitting the covariance due to unique environmental influences the best fitting model for all variables (except slope, for which no clear distinction between genetic and common environmental influences could be made) included genetic and unique environmental factors and covariance due to genetic factors only. The common environment thus did not influence the variance or the longitudinal stability of these executive functioning variables.

The longitudinal standardized genetic covariance (i.e., genetic correlation) for sustained attention and fluctuation was 0.59, for selective attention and working memory 0.56 and 0.57 respectively, and for slope 0.26. Table 5 shows the longitudinal model fitting results for all variables. Table 6 shows the estimates of the factor loadings of the most parsimonious models, and includes the heritability estimates at both ages, and the genetic correlations.

Table 5:
Longitudinal model fitting results for processing speed of selective attention, working memory, and sustained attention, and for slope and fluctuation in tempo

Longitudinal model	-2 Log Likelihood	χ^2	df	*p*	AIC
SELECTIVE ATTENTION					
Saturated model	7386.46	---	-	---	---
Full ACE model	7386.93	0.47	3	0.93	-5.53
No covariation for A	7388.42	1.48	1	0.22	-0.52
No covariation for C	7387.46	0.53	1	0.47	-1.47
No covariation for E	7388.14	1.21	1	0.27	-0.79
No covariation for A and C	7407.40	20.47	2	0.00	16.47
CE model	7391.28	4.35	3	0.23	-1.65
AE model	7391.90	4.97	3	0.17	-1.03
AE model, no covariance for E[1]	7393.26	1.98	1	0.16	-0.02
CE model, no covariance for E[2]	7396.50	5.22	1	0.02	3.22
WORKING MEMORY					
Saturated model	7196.21	---	-	---	---
Full ACE model	7201.40	5.19	3	0.16	-0.81
No covariation for A	7202.11	0.71	1	0.40	-1.29
No covariation for C	7205.31	3.91	1	0.05	1.91
No covariation for E	7201.49	0.09	1	0.76	-1.91
No covariation for A and C	7238.56	37.16	2	0.00	33.16
CE model	7211.92	10.52	3	0.02	4.52
AE model	7206.61	5.21	3	0.16	-0.79
AE model, no covariance for E[1]	7206.61	0.00	1	0.99	-2.00
SUSTAINED ATTENTION					
Saturated model	7457.37	---	-	---	---
Full ACE model	7457.84	0.47	3	0.93	-5.53
No covariation for A	7465.15	7.30	1	0.01	5.30
No covariation for C	7457.86	0.01	1	0.93	-1.99
No covariation for E	7458.33	0.48	1	0.49	-1.52
No covariation for A and C	7495.68	37.83	2	0.00	33.83
CE model	7473.93	16.07	3	0.00	10.07
AE model	7462.58	4.72	3	0.19	-1.28
AE model, no covariance for E[1]	7462.91	0.33	1	0.57	-1.67

Longitudinal model	-2 Log Likelihood	χ^2	df	*p*	AIC
SLOPE					
Saturated model	6995.53	---	-	---	---
Full ACE model	6998.59	3.06	3	0.38	-2.94
No covariation for A	6998.62	0.03	1	0.85	-1.97
No covariation for C	6999.23	0.63	1	0.43	-1.37
No covariation for E	6998.94	0.34	1	0.56	-1.66
No covariation for A and C	7002.50	3.91	2	0.14	-0.09
CE model	7002.40	3.80	3	0.28	-2.20
AE model	7001.98	3.39	3	0.34	-2.61
AE model, no covariance for E[1]	7002.47	0.49	1	0.48	-1.51
CE model, no covariance for E[2]	7002.84	0.44	1	0.51	-1.56
FLUCTUATION					
Saturated model	2071.51	---	-	---	---
Full ACE model	2080.32	8.81	3	0.04	2.81
No covariation for A	2082.10	1.78	1	0.18	-0.22
No covariation for C	2080.40	0.08	1	0.78	-1.92
No covariation for E	2080.43	0.11	1	0.74	-1.89
No covariation for A and C	2095.92	15.60	2	0.00	11.60
CE model	2084.14	3.82	3	0.28	-2.18
AE model	2083.62	3.30	3	0.35	-2.70
AE model, no covariance for E[1]	2083.70	0.08	1	0.78	-1.92
CE model, no covariance for E[2]	2085.90	1.76	1	0.18	-0.24

Note 1:
Full ACE models are compared to the saturated models, sub models are compared to ACE models, except [1] which is compared to AE model, and [2] which is compared to CE model. A = additive genetic factors, C = common environmental factors, E = unique environmental factors
Note 2:
The χ^2, degrees of freedom (df) and *p*-value reflect whether tested models fit well. A *p*-value < 0.05 indicates that a model fits significantly worse. A low AIC indicates a relative good fit of the model.

Table 6:
Estimates of the factor loadings of the most parsimonious longitudinal model, the standardized estimates for genetic variances (h^2) at age 5 and age 12 which reflects the relative contribution of genetic influences, and the genetic correlation (r_g) between performance at age 5 and age 12, for processing speed of selective attention, working memory, and sustained attention, and for slope and fluctuation in tempo

Parameter estimates	a_{11}	a_{21}	a_{22}	e_{11}	e_{22}	h^2 age 5/12	r_g
Selective attention	19.93	9.35	13.77	19.05	12.70	0.52/0.63	0.56
Working memory	15.59	11.27	16.31	14.07	12.12	0.55/0.73	0.57
Sustained attention	19.06	12.07	16.48	15.86	15.48	0.59/0.63	0.59
Slope	16.38	1.69	6.27	25.95	7.64	0.28/0.42	0.26
Fluctuation	0.49	0.42	0.58	0.74	0.60	0.30/0.59	0.59

Changing of Genetic Influences over Time

To test whether the genetic influences that had an effect at age 5 were equally important at age 12, the factor loading of the genetic variance at age 5 (a11) was equated with the second factor loading (a21). Except for fluctuation in tempo this resulted for all other variables in a significant worsening of the fit of the model. The change in the impact of genetic influences between age 5 and 12 is due to deamplification of genetic influences over time. In addition it was examined whether new genetic influences emerge at age 12 by testing whether the factor loading of the second factor of the genetic variance at age 12 (a22) was different from zero. This was true for all variables, indicating that at age 12, besides the genetic effects that are transmitted over time, in addition new genetic influences come into play.

The total genetic variance at age 12 was higher than at age 5 for all traits except the slope. This increase in genetic variance was due to newly emerging genetic influences. The other part of the variance was explained by unique environmental variance. The unique environmental variance is lower at age 12 than at age 5, except for sustained attention and fluctuation in tempo. The relative genetic

contribution to the variance (i.e., the heritability estimates) increased slightly over time. For processing speed of selective attention this was 52% at age 5 and 61% at age 12, of working memory 55% and 71%, and of sustained attention 59% and 63% respectively. For slope this was 28% at age 5 and 42% at age 12, and for fluctuation in tempo 30% and 59%. When including the retest assessments (at age 12) in the longitudinal analyses, the unique environmental variance at age 12 consisted for about 33% of measurement error variance and for about 66% of 'true' unique environmental variance.

DISCUSSION

This study examined the longitudinal stability of three important constructs of executive functioning in children. Longitudinal data on selective attention, working memory and sustained attention were collected in a sample of preschool twin children (age 5) and 7 years later when they were young adolescents (age 12). Of the original sample of 237 twin pairs at age 5, 75% participated again at age 12. The age homogeneity of the samples involve that cognitive developmental divergence due to age differences is less likely. This is important as Thompson et al. (2000) showed that, due to dynamic growth processes and tissue loss of children's brains between age 3 and 15, large developmental differences exist between children of different age groups. For example a very fast growth of the frontal networks, that regulate alertness and the planning of actions, was detected between age 3 and age 6. Also between age 11 and 15 substantial changes in parietal regions, which are related to association and language function, occur. Significant changes in cortical thickness throughout several regions of the brain that take place between age 7 and age16 were reported by Shaw et al. (2006), and Casey et al. (2000) showed that cognitive ability throughout childhood increases in concert with changes in the prefrontal brain.

The longitudinal correlations between age 5 and age 12 for processing speed of selective attention, working memory and sustained attention were 0.37, 0.37 and 0.39 respectively. These correlations are quite substantial considering the time interval of 7 years and dramatic brain development throughout this period of

childhood. It is often argued that processing speed indexes operational efficiency and is therefore a crucial and fundamental source of developmental improvement in executive functioning (Bayliss et al., 2005; Dempster, 1981; Kail & Salthouse, 1994). The current results suggest that processing speed is a reliable and stable trait of cognitive development during childhood. In a recent study by Kail and Miller (2006) longitudinal correlations of processing speed were investigated in 116 children with an interval of five years, at age 9 and 14. Like in the current study, all subjects were tested twice on the same tasks. Although compared to the current study the developmental period differed (i.e., a transition from childhood to adolescence versus preschool children to pre adolescence) and also the test interval was somewhat shorter (5 versus 7 years) their longitudinal correlations were similar (~0.35) to the correlations found in Dutch twins. The longitudinal correlations of the indices of selective attention (i.e., distraction) and working memory (i.e., slope) were lower with -0.02 and 0.08 respectively. Fluctuation in alertness, as an index of sustained attention, showed more stability with a longitudinal correlation of 0.26.

An important finding of our study was that the longitudinal covariance of executive functions was mediated by genetic factors. Common and unique environmental factors played no significant role in the stability over time. Genetic studies on the development of related cognitive constructs like IQ, reported similar results. For example Petrill et al. (2004) examined in a group of adoptive siblings and biological siblings the stability of IQ performance from infancy through adolescence over a period of 16 years. They found genetic mechanisms to be primarily responsible for the stability over time, whereas instability appeared to be due to unique environmental influences. Using a longitudinal twin design Bartels et al. (2002) also found that genetic factors contributed significantly to the stability of IQ performance between age 5 and age 12. In the current study the genetic covariance was explained by the same genes having an effect at both ages, although at age 12 the effect of these genetic influences decreased and in addition new genetic influences emerged. The expression of these genes might be related to the altering brain structures and functions during childhood but also the transition from preschool to elementary school marks an important change

in social and cognitive functioning which may as well activate the expression of new genes.

The unique environmental influences played no role of importance in the stability of executive functioning. However, the estimates of the unique environmental variances at age 5 and age 12 were significant indicating the presence of age-specific effects. Even though most genetic studies on executive functioning during childhood found substantial unique environmental influences, the nature of these influences remains unexplored. In this study test-retest measurements were collected at age 12 which allowed to distinguish between true unique environmental variance and variance due to measurement error. About one third of the unique environmental variance at age 12 was due to measurement error. The other part of the variance was explained by certain aspects that differ between children of a family and have an influence on executive functioning. Speculating about aspects of the unique environment which may have an effect on processing speed of executive functioning, one might for example think of one child spending a lot of time playing computer games (which requires alertness and concentration) while his or her sibling prefers to play football in the backyard. However, improved eye-hand (or eye-foot) coordination which is trained in several sports but also for example in playing the piano may enhance in their own way. More obvious unique environmental factors that might influence executive functioning would be (traffic) accidents, or a severe illness, that affect one child and not his or her sibling. As especially processing speed is thought to depend critically on basic brain functions, one might also speculate about influences at a more biological level (Posthuma & De Geus, in press). For example the development of structural aspects of neural wiring like nerve diameter and integrity of myelin-sheating might (due to unique pre- or postnatal environmental influences) differ between siblings. Ideally, one should measure a range of possible environmental and biological factors to gain more insight into the characteristics of these environmental influences.

The relative contribution of genetic influences on executive functioning increased slightly during childhood while influences of the common environment were absent at age 5 and age 12. This is different for IQ performance as several studies reported significant influences of the common environment in young children

(Bartels et al. 2002, Petrill et al. 2004, Boomsma & Van Baal, 1998). In other words, although executive functioning and IQ are both important cognitive indices, their developmental trajectories differ. It might be that performance on an IQ test is more sensitive to the common environment (for example parental style or socio economic status) of a preschool child than executive functioning, as the latter may depend on more basic, biological processes while the former demands some intellectual knowledge. As children go to school they are introduced to this knowledge, hence the influence of the home environment decreases, and genetic variation becomes the most important source of variance for IQ performance.
The substantial heritablity estimates of selective attention, working memory and sustained attention at age 5 and at age 12 and the fact that stability of these traits is mediated by genetic influences supports the use of these traits as endophenotypes for cognitive disorders like ADHD. However, although several studies confirmed that ADHD is associated with dysfunction in prefrontal circuits that are related to executive functioning (Casey and Durston, 2006; Durston et al., 2006), the evidence for impaired cognitive functioning is not unambiguous (Doyle et al., 2005; Jonsdottir et al., 2006; van Mourik et al., 2005; Castellanos et al., 2006). Molecular genetic analyses of useful endophenotypes ultimately may shed light on the neurochemical modulation of cognitive traits which in turn may provide a window on genetic path ways that underlie cognitive deficits (Goldberg & Weinberger, 2004; Diamond et al., 2004; Castellanos & Tannock, 2002). It will be necessary however to define proper endophenotypes first; that is, traits that are heritable themselves, that are grounded in neuroscience and that are really subject to the pathology of interest.
In this longitudinal study the sample was relatively large, and homogeneous with regard to both age of the subjects and time interval between the assessments. The reliabilities of the tasks that were used to measure processing speed of executive functioning were high at age 12. The longitudinal twin design enabled us to examine the genetic and environmental influences on the stability of executive functioning during childhood. This together makes the current results a valuable contribution to the study on developmental profiles of executive functioning during childhood. Summing up the results it is firstly found that the longitudinal phenotypic correlation for processing speed assessed during selective attention,

working memory and sustained attention tasks is substantial between ages 5 and 12 years but that specific indices of executive functions are less stable over time. Secondly, it is shown that the longitudinal stability of executive functioning is principally mediated by genetic factors. Thirdly we found that variation of processing speed in preschool children is for about 55% due to genetic variance while in older children this is about 65%; the increase in genetic variance is mainly due to new emerging genes. These results together thus hint at the importance of genes in neurocognitive developmental trajectories. The next step will be to identify the actual genes that influence typical and atypical cognitive developmental trajectories.

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8

SUMMARY AND DISCUSSION

SUMMARY

The present thesis examined the genetic architecture of attention problems, attention, executive functioning, and intelligence (IQ). In addition, the (longitudinal) genetic relations among attention problems, executive functioning and IQ were investigated. Data were collected twice in a sample of twin children registered at the Netherlands Twin Registry (NTR): when they were 5 years old, and seven years later, when they were 12 years old. In this last chapter the results as presented in this thesis and other publications that have resulted from this project will be summarized and discussed.
First the genetic architecture of attention problems as assessed by different instruments and by different raters at ages 5 and 12 years is summarized. Next, an overview of the genetic studies on executive functioning and IQ, and their relation to attention problems is presented. Finally, the results of this thesis are discussed and put into the perspective of future directions for research into attention and attention problems.

Attention Problems

Attention problems in 5 and 12-year-old children were assessed by asking parents, teachers and children themselves to rate their behaviors. Genetic analyses of teacher ratings in young children are scarce. Chapter 3 presents a study on the sources of variation in the Teacher's Report Form (TRF, Achenbach, 1991a) problem scales in 5-year-old children. In the genetic modeling we accounted for differences in ratings between twin pairs rated by the same teacher and twin pairs rated by different teachers. Means and variances of all problem scales, including the attention problem (AP) scale, were lower and twin correlations were higher, for children who were rated by the same teacher, compared to children who were rated by different teachers. The heritability estimates of the eight problem scales of the TRF (Anxiety, Social problems, Withdrawn, Aggression, Rule breaking, Somatic complaints, Thought problems, and Attention problems) ranged between 30 and 63%.
Chapter 2 presents longitudinal genetic analyses (age 5 and 12) on the AP scale as rated by parents and teachers. Parental ratings on attention problems at age 5

Table 1
Monozygotic (MZ) and dizygotic (DZ) twin correlations for attention problems as assessed with behavior questionnaires at age 5 and at age 12 in the current sample and in larger samples of the NTR.

Age 5	N twin pairs	MZ	DZ
DCB M[1]	228	0.60	0.04
DCB M Van Beijsterveldt et al. (2004)	7679	0.62	0.05
ASH M	234	0.77	0.15
TRF T[1]	209	0.80	0.48
ASH T	209	0.73	0.33
Conners (old version) T	209	0.72	0.39
Age 12			
CBCL M	198	0.68	0.08
CBCL M Rietveld et al. (2004)	1516	0.72	0.26
CBCL M Derks et al. (in revision)	2850	0.75	0.34
Conners M	181	0.79	0.10
Conners M Derks et al. (in revision)	2443	0.84	0.38
SWAN/Hyperactivity M	561[2]	0.91	0.43
SWAN/Attention Deficit M	561[2]	0.85	0.38
TRF T	94	0.72	0.25
Conners T	90	0.63	0.24
YSR C[1]	172	0.51	0.33

Note [1]: M = mothers, T = teachers, C = children
Note [2]: original sample extended with SWAN data of additional 12-year old NTR sample

were collected with a short form of the Devereux Child Behavior Rating Scale (DCB, Spivack & Spotts, 1966; Van Beijsterveldt et al. 2004). At age 12 parental ratings were of AP were obtained with the Child Behavior Checklist (CBCL, Achenbach, 1991b). For teacher and parental ratings longitudinal genetic analyses on the AP scales were performed. For teacher ratings the pattern of twin correlations indicated influences of additive genetic factors at age 5 and at age 12. For parental ratings at both ages DZ correlations were lower than half the MZ correlations, pointing to additive and non-additive genetic factors influencing variation in AP. The heritability estimates for attention problems at age 5 and 12 as rated by their parents were 59% and 67%, and as rated by the teachers 81% and 71% respectively.

Other behavior questionnaires assessing attention problems that were collected at age 5 were the Conner's Rating Scale (Conners, 2001) as rated by teachers, and the Aandachttekort Stoornis met Hyperactiviteit (ASH, Gunning, 1992) as rated by parents and teachers. At age 12 the Youth Self Report (YSR, Achenbach, 1991c) was collected. There are no publications of the current sample on these instruments but Table 1 provides an overview of twin correlations of AP measures on all behavior questionnaires assessed at age 5 and 12 in the current sample. When available, twin correlations for these questionnaire data that were published in larger NTR samples are also included.

At age 12 data on the Strengths and Weakness of ADHD symptoms and Normal behavior Scale (SWAN, Swanson et al. 2006) were collected. These data were also available in an additional NTR sample that was selected for attention problems (Derks et al. 2006a). The SWAN measures Hyperactivity/Impulsivity (HI) and Attention Deficit (AD) with item scores on a 7 point scale, ranging from 'average behavior' to the extremes 'far below average' and 'far above average'. So in contrast to most regular checklists the SWAN scores cover the strengths as well as the weaknesses of a child, ranging from severe hyperactivity to normal activity and from serious attention deficits to a high level of attention. The results of this study, presented in chapter 4, showed that scores on the SWAN rating scales show a normal distribution. Variation on the SWAN/HI and SWAN/AD scale was explained by additive genetic influences (90% and 82% respectively) and unique environmental influences.

Attention (Problems) and the snap-25 Gene

An association study was performed between Single Nucleotide Polymorphisms (snp's) on the snap-25 gene and swan/hi and swan/ad scores. Previous studies have reported significant associations between the snap-25 gene and attention problems (Barr et al. 2000; Brophy et al. 2002; Mill et al. 2002; Kustanovich et al. 2003; Feng et al. 2005; Mill et al. 2004). The snap-25 gene is differentially expressed throughout the brain and is during development involved in synaptic plasticity, dendrite formation and axonal growth. In addition the gene has a regulatory role in the dopamine system (Osen-Sand et al. 1993; Grosse et al. 1999). The results presented in chapter 5 showed that of 8 tagging snp's, covering the snap-25 gene, one snp was significantly associated, and two snp's showed a trend for association, with scores on the swan/ad scale. The significant snp has also been found to be associated with iq in this sample (Gosso et al. 2006).

Executive Functions

The genetic background of three different aspects of executive functioning was investigated, namely of working memory, selective- and sustained attention. Working memory and attention are mainly anchored in the frontal brain regions (Fuster, 1997; Smith & Jonides, 1999; Carpenter et al. 2000; Hampson et al. 2006), and these areas are partially overlapping with neural systems that seem to be affected in neuropsychiatric disorders like adhd (Castellanos & Tannock, 2002; Casey & Durston, 2006; Durston et al. 2006). Previous studies had reported impairment of these functions in children with attention problems (Swaab-Barneveld et al. 2000, Swanson 2003; Joseph 1999, Pennington & Ozonoff, 1996; Tannock, 1998; Barkley, 1997; Manly et al. 2001). A sub sample of the current sample was compared with children diagnosed with adhd on inhibition tasks (Slaats-Willemse et al. 2003) and selective- and sustained attention tasks (Stins et al. 2005). The affected adhd group performed significantly worse on reaction time and accuracy than the normal twin controls.

In chapter 6 the genetic background of working memory was analysed. A distinction was made between working memory speed and capacity and the phenotypic and genotypic relationship between these working memory components was investigated. The phenotypic correlation between working memory speed and

Table 2:
Overview of twin correlations of IQ, working memory, selective attention, and sustained attention at age 5 and at age 12, and the Stroop, Flanker and Simon tasks at age 12

Age 5	N twin pairs	MZ	DZ
IQ	237	0.68	0.54
Working Memory	235	0.55	0.35
Selective attention	233	0.50	0.35
Sustained attention	237	0.60	0.28
Age 12			
IQ	176	0.81	0.43
Working Memory	171	0.73	0.54
Selective attention	171	0.60	0.48
Sustained attention	172	0.61	0.49
Stroop RT	170	0.80	0.39
Stroop effect	170	0.52	0.15
Flanker RT	157	0.43	0.38
Flanker effect	157	0.18	0.26
Simon RT	156	0.51	0.28
Simon effect	156	0.19	0.10

capacity was -0.30, demonstrating that both components involve partly similar working memory processes. The genetic correlation was -0.54 which indicates that working memory speed and capacity are partly mediated by the same set of genes. As on a phenotypic level intelligence and working memory performance

are strongly related (Kyllonen and Christal 1990, Colom et al. 2004) it was tested whether the genetic correlation of -0.54 was not explained by intelligence (*g*), instead of a genetic relation between working memory speed and capacity per se. Adding general IQ to the genetic models revealed that both *g* and working memory itself are responsible for the shared genes between working memory speed and capacity.

In chapter 7 working memory, selective- and sustained attention were analysed in a longitudinal genetic design. These results showed that in young children (age 5) the relative contribution of genes on variation in these executive functions ranged between 28 and 59%, and in older children (age 12) between 42 and 73%. It was also shown that the stability over time of working memory, selective- and sustained attention was due to genetic factors only. At age 12, the genetic influences on variation in executive functioning could be distinguished into stable genetic effects, which were transmitted over time, and new genetic influences which emerged at age 12. The longitudinal genetic correlations of executive functioning were between 26 and 59%. Table 2 presents an overview of twin correlations of IQ and the executive functions as investigated in this thesis.

Attention Problems, Executive Functions and Intelligence

Chapter 2 of this thesis describes genetic influences on variation in IQ during childhood. In young children (age 5) common environmental and genetic factors play an equally important role explaining 37% and 31% of the total variance respectively. At age 12 years the influence of common environment has disappeared and the heritability is estimated as 81%. Also the longitudinal genetic relation between these traits was investigated. The longitudinal phenotypic correlation between IQ at age 5 and IQ at age 12 was 0.51, and the longitudinal genetic correlation was 0.81.

It was examined to what extent IQ performance, executive functions, and attention problems at age 5 predicted IQ performance at age 12. Executive functioning at age 5 was only weakly correlated with IQ scores at age 12 (r = 0.10 - 0.16). The genetic correlations fell in the same range except for selective attention of which the longitudinal genetic correlation with IQ was higher, namely 0.31. Thus, the phenotypic correlation is partly explained by common genes.

Notable was the significant phenotypic correlation between attention problems at age 5, as rated by mothers and teachers, and IQ performance at age 12 (r = -0.28 and -0.36 respectively). This means that attention problems in preschool children are predictors for IQ scores later in childhood. The longitudinal phenotypic correlation was partly explained by a common genetic factor; the genetic correlations were -0.42 and -0.39 respectively. In other words, there is a common set of genes that influences attention problems at age 5 and IQ performance at age 12.
At age 5, executive functions among each other showed very high genetic correlations (r = 0.80, 0.82 and 0.90), and with IQ the genetic correlations were between 0.36 and 0.70. The genetic correlation between executive functioning and attention problems as rated by the teacher ranged between -0.31 and -0.38 (both at age 5). The genetic correlation between executive functioning and maternal ratings of attention problems at this age was low (-0.17 - 0.08).

DISCUSSION

In this final part the findings of this thesis and related publications are interpreted and future directions will be discussed.

Attention Problems Assessed by Behavior Checklists

When multiple raters are used to rate a child's attention problems the situational variation in children's behavior can be taken into account. For example, teachers can report on problems that are specific to the classroom or other school situations, such as problems in the social interactions with other children, or task oriented situations, while parents have unique information about the child's behavior in the family environment. In a similar vein will children themselves have a unique view on their own behavior, at school, at home, with friends or at the sports club (Verhulst et al. 1997; Van der Ende & Verhulst, 2005).
There is only a moderate correlation between parental and teacher assessments of attention problems (Achenbach & Rescorla, 2000; Van der Ende & Verhulst, 2005), while correlations between ratings of parents are generally higher (Derks et al. 2006a). Notable in chapter 3 of this thesis was the fact that also between

teachers there might be differences in their ratings, which may originate from 'specific teacher styles'. These teacher styles can cover a whole range of domains, including personal values and pedagogic qualities but also school systems, social interaction with the children, and educational approaches. Some teachers for example prefer strict rules in the classroom whereas others have a more lenient style. Some children prosper better under free conditions whereas others need a structured environment. One approach to look at this is by obtaining ratings of the twins from multiple teachers. This could be done by asking teachers of specific disciplines, like music or gymnastics, to complete a behavior checklist, or by a regular assessment of the TRF, as children (in the Netherlands) change teachers almost every school year. The longitudinal data collection of the TRF by the NTR may provide the latter opportunity within a few years.

The heritability estimates of attention problems as derived from different raters and different checklists are rather similar and range between 60 and 90%. The SWAN, described in chapter 4, is a questionnaire measuring the continuum of attention. It showed heritability estimates that were slightly higher as those of regular checklists that measure attention problems only. Remarkable was that no influences of dominance (non-additive genetic effects) were detected which is in contrast to previous studies on attention problems. Especially with parental ratings heritability estimates consist often of additive and non-additive genetic effects. One can speculate whether earlier found dominance effects are real or whether they may be an artifact of the format of regular, narrow ranged checklists (i.e., parents have the possibility to rate their child's behavior with ' never', 'sometimes', or ' often'). The pattern of very low DZ correlations that are usually found with parental checklists may therefore point to contrast effects instead of dominance effects. Contrast effects may arise because parents compare the behavior of their twins and stress differences between them (Eaves et al. 1997; Simonoff et al. 1998), and regular checklists may enhance these contrast effects. This is to a lesser extent the case with the SWAN rating scale; instead of the 'all' or 'not' possibility as on regular checklists, parents have on the SWAN scale the opportunity to rate their twins differentially on a much broader range. Due to this broader range, covering the continuum of attention, SWAN scores of both the Hyperactivity and Attention Deficit scale were normally distributed. This

supports the idea that attention problems are not a dichotomous trait (i.e., 'you have attention problems or not'), but indicates that attention and attention problems are normally distributed in the population, with children that have severe problems positioned on the extreme tail of the distribution.

The Search for Genetic Polymorphisms

When a large heritability is found, as was the case for attention and attention problems, it should be possible to localize and identify genes that explain this heritability. Whether or not such undertaking will lead to positive results with the current phenotypes and the current genetic and genomic approaches is still a matter of discussion, as indicated below.

We carried out an association study between the SWAN scores and polymorphisms in the SNAP-25 gene. Two SNP's on this gene showed a trend for association, and one SNP was significantly associated with scores on the AD scale of the SWAN. The latter SNP showed also a significant association with IQ in this sample. In other words, we found evidence for a possible mediating role of the SNAP-25 gene for attention and attention problems, and for IQ. In the last decade several other association studies as well as linkage projects have been conducted to find genes that are related to attention problems and ADHD. The foci of these studies have been mainly on mechanisms underlying the dopaminergic neurotransmission systems. Brain imaging studies of affected children suggested that brain regions with rich dopamine content were involved in ADHD (Tannock et al. 1998). The significant reduction of ADHD symptoms after using pharmacological medication (for example methylphenidate) that primarily act on the dopaminergic system additionally pointed to a significant role of the dopamine system in ADHD pathology (Spencer et al. 1996).

With candidate gene studies several genes in the DA and related path ways have shown a statistically significant association with ADHD in three or more studies. These are Dopamine Receptor D4 (DRD4), Dopamine Receptor D5 (DRD5), Dopamine Transporter (DAT), Dopamine α-Hydroxylase (DBH), Serotonin Transporter (5-HTT), Serotonin receptor (HTRIB), and synaptosomal-associated protein 25 (SNAP-25) (Faraone et al. 2005). However, conflicting results are also reported. For example Hebebrand et al. (2006) could not replicate significant

association for the DAT1 VNTR gene, which is located under the linkage peak they found. Also a meta-analysis by Purper-Ouakil et al. (2005) found no evidence for association of the DAT gene. Of the four genome wide linkage studies that have been conducted so far (Fisher et al. 2002, extended by Smalley et al. 2002, Bakker et al. 2003, Arcos-Burgos et al. 2004, Hebebrand et al. 2006) the overlap in results concerned only chromosome 5p; this region showed nominal evidence of linkage in the first three studies, and strong evidence for linkage in the study by Helebrand et al. (2006). Unfortunately none of the putative candidate genes so far are located under chromosome 5p.

Endophenotypes for Attention Problems

In the past years a lot of effort has been put in the identification of endophenotypes that may elucidate the genetic path ways of disorders like ADHD, and ultimately unravel the causing biological mechanism. The role of endophenotypes is to serve as intermediates between the genes and the manifest disorder itself, as the identification of genes influencing the endophenotype might reveal the (related) genes influencing the phenotype of interest at the same time (Gottesman, 1997; Skuse, 2001; Gottesman & Gould, 2003).

Over time evidence has accumulated that symptoms of ADHD are related to impairment in the frontal cortex and subcortical cortices that project to it (Castellanos & Tannock 2002; Casey & Durston 2006, Shaw et al. 2006b). As the prefrontal cortex is one of the crucial brain regions for executive functioning (Fuster, 1997, Smith & Jonides, 1999, Prabhakaran et al. 2000, Carpenter et al. 2000, Hampson et al. 2006) these functions have been proposed as promising endophenotypes. Executive functions cover interrelated but rather distinct cognitive functions like inhibition, sustained attention, selective attention and working memory. A crucial feature of a useful endophenotype is, logically, that variation on this trait is influenced by genes and that the association of the endophenotype and the clinical disorder is mediated by correlated genetic, rather than correlated environmental influenes.

Working memory, selective- and sustained attention are heritable traits during childhood, and their longitudinal stability is explained by genetic factors. In addition strong genetic correlations ($r > 0.80$) among the executive functions were

found. Two previous studies with the current sample investigated the heritabilities of executive functions in children. Groot et al. (2004) reported a heritability of 54% for reaction time measures of inhibition assessed with a computerised Go-No go task at age 5. In the same sample, at age 12, inhibition was measured with the Stroop Color Word task and the Eriksen Flanker task. Heritability estimates for reaction time on card 1, card 2 and card 3 of the Stroop task were 75%, 70% and 74% respectively, and for the Stroop effect (i.e., the difference in reaction time between card 2 and card 3, which is an index of inhibition) the heritability was estimated as 49%. For performance on the Eriksen Flanker task no genetic influences were found (Stins et al. 2004).
Thus, most endophenotypes that have been proposed as endophenotypes show heritability. They are also reliable as was shown in chapter 7 for the endophenotypes assessed at age 12.

Are Endophenotypes Useful for ADHD?

The use of endophenotypes in the search for genes that influence attention problems and ADHD has been subject of discussion recently. First, despite previous results, some doubts about the phenotypic relation between attention problems and proposed endophenotypes have been postulated. "Deficient attention is hard to find" reported Huang Pollock et al. (2005) when investigating selective attention in a sample of children affected with several forms of ADHD. In a meta-analysis Van Mourik et al. (2005) could not find specific impairments in children with ADHD on Stroop Color Word performance. Other studies also suggested that the evidence for impaired cognitive functioning is not unambiguous (Mason et al. 2003; Jonsdottir et al. 2006; Castellanos et al. 2006). As mentioned before, an important criterion for endophenotypes is a meaningful phenotypic correlation with the trait of interest.
Most important problem in identifying specific (cognitive) impairments in children with attention problems involves the neurocognitive heterogeneity among children with ADHD. Not only variability between ADHD subjects, but also variability within ADHD subjects has been reported. Thus, not every person with ADHD is impaired on every test, and some children with ADHD perform on these tests within the normal range while others perform worse (Pennington &

Ozonoff 1996, Doyle et al. 2000, Pasini et al. 2007). Doyle et al. (2005) summarized the problems in identifying useful endophenotypes on a phenotypic level with the following comments. First they consider the complexity, and probably uselessness of the endophenotypes that have been investigated so far. What is lacking specifically is a) precision of the measures of executive function, b) reliability, sensitivity and validity of these measures and c) results based on large sample sizes. Their second worry involved the neurocognitive heterogeneity of ADHD, and especially the fact that up till now not a single core deficit for ADHD has been acknowledged.

Power Problems

A serious concern about the value of intermediate traits on a genotypic level was raised by Plomin et al. (2006). They argued that complex traits and disorders like ADHD are caused by multiple genes of varying but small effects sizes and that genetic effects of underlying traits (like endophenotypes) perhaps explain less than 1% of the variance. To detect significant associations with 80% power for SNP's that have an effect size of 1% very large sample sizes (> 1000 cases and >500 controls) are needed. Plomin et al. (2006) however assumed that an effect size of 1% is yet too optimistic and that an effect size of 0.1% is maybe more realistic. Hence, to obtain enough power for these kinds of effects even much larger samples are needed and the question is whether this is feasible.

Flint and Munafo (2006) performed a meta-analysis on genetic association studies of endophenotypes to examine whether these intermediate traits exhibit larger genetic effects than the manifest disorders specifically, and to discuss the usefulness of endophenotypes in genetic research in general. They showed that the genetic effect sizes of endophenotypes fall in the same range as those for the behavioral phenotypes of interest. Flint and Munafo (2006) therefore openly doubt about the usefulness of endophenotypes in addition to clinical phenotypes. However, they also argue that especially endophenotypes (that are reliable, robust and quantitative measures) may be suitable to collect the large data sets that are needed for the genetic analyses of complex traits.

Attention Problems and Intelligence

In this study a common set of genes was found for attention problems at age 5 and IQ performance at age 12. Kuntsi et al. (2004) reported similar results in a cross sectional design: they found a set of common genes for attention problems and IQ scores, both measured at age 5. They speculated that the common genes that are shared between attention problems and IQ performance may involve brain volume abnormalities that influence both traits. Castellanos et al. (2002) reported persistent brain abnormalities in children with ADHD while Shaw et al. (2006a) reported an association between intelligence and the trajectory of cortical development, primarily in frontal regions. In an accompanying study Shaw et al. (2006b) showed that children with ADHD have relative cortical thinning in regions important for attentional control (i.e., medial and superior prefrontal and precentral regions). An association between brain volume and intelligence was reported by Posthuma et al. (2002) who showed that IQ and brain volume are influenced by shared genetic factors.

In a recent paper by Kovas and Plomin (2006) they proposed the existence of so called 'generalist genes'. This hypothesis is based on the fact that there is a broad genetic overlap in cognitive functions like language, and general intelligence. Kovas and Plomin (2006) therefore assume that the effects of generalist genes are widespread to the brain and not specifically localized. Consequently, these genes affect multiple brain structures and functions, each of which affects multiple cognitive processes (see also Butcher et al. 2006). In chapter 2 of this thesis it is confirmed that cognitive functions like IQ, working memory, selective- and sustained attention, and cognitive dysfunction, like attention problems, have a genetic correlation. At age 5, executive functions among each other showed genetic correlations of 0.80, 0.82 and 0.90, and with IQ the genetic correlations were between 0.36 and 0.70. Also between IQ and attention problems as rated by mothers and teachers substantial genetic correlations were found, not only at age 5, but also longitudinal.

A few studies investigated genetic polymorphisms of the dopamine system that possibly could explain a part of the correlation between ADHD and intelligence. Mill et al. (2006) tested whether the DRD4 seven-repeat allele and the DAT1 ten-repeat allele were associated with variation in intelligence among children with

ADHD. They found evidence for this association in two independent cohorts, from New Zealand and Britain. An attempt to replicate these findings in three larger, independent Brazilian samples by Genro et al. (2006) failed. However, given the 'generalist genes' hypothesis, and the important role for the dopaminergic regulation in attention problems and cognitive functioning (Nieoullon, 2002), a further investigation of the moderating role of dopaminergic polymorphisms seems interesting and relevant for future research.
In the current sample a significant association was found between IQ and the SNAP-25 gene (Gosso et al. 2006). Moreover, the SNP that was found to associate with IQ did overlap with the SNP that was associated with attention problems. For the moment it remains the question whether the SNAP-25 gene serves as intermediate between attention problems and IQ, as was tested for the DAT1 and DRD4 gene by Mill et al. (2006) and Genro et al. (2006). Future research may enlighten the possible moderating role of SNAP-25 in cognitive and attentional processes.

Conclusions

Attention is normally distributed in the population with superb skills and serious problems on the tails of the distribution. In the general population 4 to 12% of the children have severe problems (Brown et al. 2001; Faraone, 2003), often clinically diagnosed as having Attention Deficit Hyperactivity Disorder (ADHD). Variation in attention, attention problems and ADHD is, independently from informants and questionnaires, sex and age, strongly influenced by genetic factors (Derks et al. 2006b). The results of molecular genetic studies however have not been conclusive yet. Problems for identifying genes include the heterogeneity of the behavioural and neurocognitive phenotype of ADHD, and the fact that many genes with each a small effect mediate the symptoms of hyperactivity, impulsivity and attention deficit (Buitelaar 2005; Doyle 2005; Khan & Faraone 2006).
As a promising approach to unravel the genetic path ways of cognitive disorders like ADHD a decade ago the use of endophenotypes was introduced. It is clear however that the endophenotypic approach has not revealed a short-cut to identifying the genetic factors of ADHD so far and the conclusion after all is that the future role of cognitive endophenotypes is uncertain. The phenotypic relation

with the disorder of interest, in this case ADHD, is unclear (Doyle et al. 2005), endophenotypes do not offer a closer link to the genes than clinical phenotypes do (Flint & Munafo, 2006), and the effect sizes of genes influencing the endophenotypes may even be smaller than those of clinical phenotypes (Plomin et al. 2006). On the other hand, endophenotypic data can be collected relatively easy in large samples, on a reliable and valid way. The use of cognitive endophenotypes may also help to define cognitive homogeneous clusters of ADHD patients (Kuntsi et al. 2006). And, as being cognitive traits, endophenotypes are supposed to be influenced by so called generalist genes, which are wide spread to the brain (Kovas & Plomin, 2006). Hence, multivariate molecular genetic analyses on cognitive functions might provide a window through which we can view brain mechanisms that are functionally related to cognitive (dys) functions.

In this thesis substantial heritability estimates were presented for working memory speed and capacity, and for selective- and sustained attention. It was shown that stability of these traits during childhood is due to genetic factors, and in addition substantial genetic correlations between these cognitive functions were found. Notable also were at age 5 the genetic correlations between the executive functions and IQ, and between executive functions and teacher reported attention problems. Hence, despite the (sometimes) low correlations between attention problems and executive functioning on a phenotypic level, the focus of future research should perhaps be on the genetic correlations among cognitive traits and complex disorders. The executive functioning traits as presented in this thesis can have potential value in identifying genes involved in cognitive disorders as across childhood we found (shared) genes that influence these traits and related cognitive (dys) functions. Multivariate analyses in large samples may identify the actual genes that play a mediating role between cognitive functioning and cognitive disorders. As the NTR has over the years collected large data sets on attention problems and cognitive functioning, and as also the data collection of DNA is growing, these studies may be carried out in the nearby future.

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SAMENVATTING

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In dit proefschrift, getiteld "De genetica van aandacht en executief functioneren", zijn de genetische invloeden op aandachtsproblemen, aandacht, executief functioneren en intelligentie onderzocht. Daarnaast is gekeken naar de mate waarin aandachtsproblemen, executief functioneren en intelligentie (IQ) onderling genetisch correleren. De data voor dit onderzoek zijn verzameld in een groep tweelingen die geregistreerd staan bij het Nederlands Tweelingen Register (NTR). De eerste meting vond plaats toen de kinderen 5 jaar oud waren (N = 237 tweelingparen), de tweede meting vond zeven jaar later plaats, toen ze 12 jaar oud waren (N = 177 tweelingparen). Bij de tweede meting werden ook broertjes en zusjes tussen de 8 en 15 jaar oud uitgenodigd (N = 55 broertjes/zusjes). Het tweelingdesign is een veelgebruikt onderzoeksdesign in gedragsgenetisch onderzoek. Eeneiige, of monozygote tweelingen zijn genetisch identiek terwijl twee-eiige, of dizygote tweelingen en broertjes en zusjes ongeveer de helft van hun genetisch materiaal delen. Door gebruik te maken van dit gegeven kan een onderscheid gemaakt worden tussen genetische en omgevingsgerelateerde invloeden die verschillen en overeenkomsten tussen kinderen (in bepaalde gedragingen of eigenschappen) veroorzaken. Genetische invloeden kunnen additief zijn of dominant (interactief). Omgevingsinvloeden kunnen kinderen van een gezin op elkaar doen lijken (bijvoorbeeld de opvoeding van de ouders) of kinderen van een gezin van elkaar doen verschillen (bijvoorbeeld gebeurtenissen die het ene kind wel heeft ervaren en het andere kind niet). Deze invloeden worden respectievelijk gedeelde- en unieke omgevingsinvloeden genoemd (Boomsma et al. 2002).

Aandachtsproblemen

Aandachtsproblemen werden op 5 en 12 jaar gemeten met vragenlijsten die door ouders, leerkrachten en de kinderen zelf (12 jaar) werden ingevuld. Genetische studies over leerkrachtrapportages zijn vrij zeldzaam bij 5-jarige kinderen. Hoofdstuk 3 van dit proefschrift beschrijft een genetisch onderzoek bij 5-jarige tweelingparen naar acht probleemschalen van de Teacher Report Form (TRF,

Achenbach, 1991a) waaronder een aandachtsproblemenschaal. De resultaten laten zien dat tweelingparen die bij elkaar in de klas zitten minder gedragsproblemen hebben en meer op elkaar lijken dan tweelingparen die niet bij elkaar in de klas zitten. De reden dat tweelingparen die door dezelfde leerkracht beoordeeld zijn meer op elkaar lijken heeft te maken met het feit dat leerkrachten in hun beoordelingen een eigen stijl hanteren. Sommige leerkrachten zijn bijvoorbeeld streng en vinden een kind al snel druk of ongehoorzaam terwijl een andere leerkracht ditzelfde kind als 'normaal' beschouwt. Uit de genetische analyses bleek dat individuele verschillen tussen kinderen voor de diverse probleemschalen verklaard konden worden door genetische invloeden en unieke omgevingsinvloeden. Voor aandachtsproblemen waren deze bijdragen respectievelijk 63% en 27%.

Hoofdstuk 2 gaat over een longitudinaal onderzoek naar aandachtsproblemen, zoals gerapporteerd door ouders en leerkrachten. Ouders vulden de verkorte Devereux Child Behavior Rating Scale (DCB, Spivack & Spotts, 1966) in toen hun kinderen 5 jaar oud waren, en de Child Behavior Checklist (CBCL, Achenbach, 1991b) toen de kinderen 12 jaar oud waren. Op beide meetmomenten werd door de leerkracht van de kinderen een TRF ingevuld. Individuele verschillen in aandachtsproblemen zoals gerapporteerd door de ouders werden voornamelijk veroorzaakt door genetische invloeden. De invloeden verklaarden 59% (5 jaar) en 67% (12 jaar) van de variantie. Wanneer aandachtsproblemen werden gerapporteerd door de leerkracht was de bijdrage van genetische invloeden 81% (5 jaar) en 71% (12 jaar). Unieke omgevingsinvloeden verklaarden op beide leeftijden het andere deel van de variantie.

Toen de kinderen 12 jaar oud waren werd door de ouders ook de Strengths and Weakness of ADHD symptoms and Normal behavior Scale (SWAN, Swanson, 2006) ingevuld. Deze gegevens werden gecombineerd met SWAN data die verzameld waren in een parallel onderzoek bij het NTR naar aandachtsproblemen. De SWAN is een vragenlijst met 18 items die gebaseerd zijn op de DSM-IV criteria voor Attention Deficit Hyperactivity Disorder(ADHD). Negen items gaan over Hyperactiviteit en negen items gaan over Aandachttekort. Elk item kan gescoord worden van 1 (ver beneden gemiddeld) tot 7 (ver boven gemiddeld). De SWAN meet dus het hele spectrum van aandacht, variërend van ernstige aandachtsproblemen tot excellente aandachtsvaardigheden. De resultaten van dit onderzoek

lieten zien dat aandacht als gemeten met de SWAN een normaal verdeelde eigenschap is in de populatie. De erfelijkheidsschattingen (genetische invloeden) waren 90% voor Hyperactiviteit en 82% voor Aandachttekort.
Over de verzamelde gegevens van een aantal andere vragenlijsten die in de groep tweelingen op leeftijd 5 en 12 zijn afgenomen, zijn nog geen publicaties verschenen. Dat zijn op leeftijd 5 de Conner's Rating Scale (Conners, 2001) ingevuld door de leerkrachten, en de Aandachtstekortstoornis met Hyperactiviteitlijst (Gunning, 1992) ingevuld door ouders en leerkrachten. Bij de tweede meting hebben alle tweelingen en broertjes en zusjes die meededen een Youth Self Report (YSR, Achenbach, 1991c) ingevuld. Tabel 1 geeft een overzicht van tweelingcorrelaties van deze vragenlijstgegevens. Wanneer aanwezig worden ook tweelingcorrelaties van al gepubliceerde data over deze vragenlijsten (gemeten in andere NTR cohorten) gerapporteerd.
Er bestaat evidentie dat het SNAP-25 gen is geassocieerd met aandachtsproblemen en de stoornis ADHD. Wij voerden daarom een associatiestudie uit naar dit gen en aandacht zoals gemeten met de SWAN. De resultaten (hoofdstuk 5) lieten zien dat één Single Nucleotide Polymorphisme (SNP) van het SNAP-25 gen een significante relatie vertoonde met de SWAN scores voor Aandachttekort en twee SNP's een bijna significante relatie. De significante SNP was eerder gerelateerd aan IQ in deze groep 12-jarige tweelingen.

Executieve Functies

De cognitieve ontwikkeling van kinderen wordt gekarakteriseerd door een toename van het werkgeheugen en de selectieve aandacht, een afname van impulsieve reacties en een groeiend vermogen om de aandacht te richten op een bepaald doel of bepaalde opdracht (Diamond, 1990). Samen worden deze eigenschappen executieve functies genoemd. Executief functioneren is essentieel in het dagelijkse leven, bijvoorbeeld voor het plannen van activiteiten en het nemen van beslissingen, maar ook voor het volgen van een gesprek. Onderzoek heeft uitgewezen dat het prefrontale deel van de hersenen een belangrijke bijdrage levert aan executief functioneren (Fuster, 1997), en dit deel van de hersenen lijkt ook een rol te spelen bij aandachtsproblemen (Durston et al. 2006). In dit proefschrift zijn de genetische invloeden op drie belangrijke executieve functies on-

Tabel 1:
Overzicht van monozygote (MZ) en dizygote (DZ) tweelingcorrelaties van aandachtsproblemen verzameld met gedragsvragenlijsten in het huidige cohort en in andere cohorten van het NTR.

Leeftijd 5	N tweelingparen	MZ	DZ
DCB M[1]	228	0.60	0.04
DCB M Van Beijsterveldt et al (2004)	7679	0.62	0.05
ASH M	234	0.77	0.15
TRF L[1]	209	0.80	0.48
ASH L	209	0.73	0.33
Conners (oude versie) L	209	0.72	0.39
Leeftijd 12			
CBCL M	198	0.68	0.08
CBCL M Rietveld et al (2004)	1516	0.72	0.26
CBCL M Derks et al (in revision)	2850	0.75	0.34
Conners M	181	0.79	0.10
Conners M Derks et al (in revision)	2443	0.84	0.38
SWAN/Hyperactiviteit M	561[2]	0.91	0.43
SWAN/Aandachttekort M	561[2]	0.85	0.38
TRF L	94	0.72	0.25
Conners L	90	0.63	0.24
YSR K[1]	172	0.51	0.33

Noot [1]: M = moeders, L = leerkrachten, K = kinderen
Noot [2]: data van originele groep tweelingen aangevuld met SWAN data die ook verzameld is door het NTR

derzocht. Dit zijn werkgeheugen, selectieve aandacht, en volgehouden aandacht. Hoofdstuk 6 beschrijft de genetische achtergrond van, en de genetische relatie tussen de snelheid van het werkgeheugen en de capaciteit van het werkgeheugen. De snelheid van het werkgeheugen geeft aan hoe snel informatie opgemerkt en verwerkt wordt, en de capaciteit geeft aan hoe veel informatie opgeslagen en verwerkt kan worden. Genetische invloeden bleken een bijdrage van ongeveer 50% te leveren aan de variantie van de beide componenten van werkgeheugen. De genetische correlatie tussen snelheid en capaciteit van werkgeheugen was 54%; een deel van de genen die een rol speelden bij de snelheid van het werkgeheugen speelden dus ook een rol bij de capaciteit. Omdat IQ en werkgeheugen sterk samenhangen werd onderzocht of de genetische correlatie tussen de snelheid en de capaciteit van het werkgeheugen verklaard kon worden door IQ. Dit bleek voor een deel het geval te zijn.
De genetische invloeden op het werkgeheugen en selectieve- en volgehouden aandacht werden ook geanalyseerd in een longitudinaal design. Bij 5-jarigen bleek de relatieve bijdrage van genetische invloeden te variëren tussen 28 en 59%. Bij 12-jarigen was de genetische bijdrage op variatie in executief functioneren hoger, namelijk tussen de 42 en 73%. De stabiliteit van de executieve functies werd uitsluitend veroorzaakt door genetische factoren. Er kon op leeftijd 12 dan ook een onderscheid gemaakt worden tussen genetische invloeden die al aanwezig waren op leeftijd 5 en dus stabiel bleven over de jaren heen, en genetische invloeden die tot expressie kwamen op leeftijd 12. Tabel 2 geeft een overzicht van tweelingcorrelaties die voor executief functioneren zijn gevonden in de huidige groep tweelingen.

Aandachtsproblemen, Executief Functioneren en Intelligentie

In hoofdstuk 2 van dit proefschrift worden de genetische invloeden op individuele verschillen in IQ tijdens de kindertijd gerapporteerd. Wanneer kinderen 5 jaar oud zijn spelen zowel genetische factoren als gedeelde omgevingsinvloeden een belangrijke rol. Wanneer kinderen 12 jaar oud zijn verdwijnen de invloeden van de gedeelde omgeving en zijn het uitsluitend genetische invloeden, en voor een klein deel unieke omgevingsfactoren, die de variatie in IQ bepalen. Er werd onderzocht welke eigenschappen, die gemeten waren toen de kinderen 5 jaar

Tabel 2:
Overzicht van monozygote (MZ) en dizygote (DZ) tweelingcorrelaties van IQ, en executief functioneren op leeftijd 5 en 12.

Leeftijd 5	N tweelingparen	MZ	DZ
IQ	237	0.68	0.54
Werkgeheugen	235	0.55	0.35
Selectieve aandacht	233	0.50	0.35
Volgehouden aandacht	237	0.60	0.28
Age 12			
IQ	176	0.81	0.43
Werkgeheugen	171	0.73	0.54
Selectieve aandacht	171	0.60	0.48
Volgehouden aandacht	172	0.61	0.49
Stroop RT	170	0.80	0.39
Stroop effect	170	0.52	0.15
Flanker RT	157	0.43	0.38
Flanker effect	157	0.18	0.26
Simon RT	156	0.51	0.28
Simon effect	156	0.19	0.10

Noot: RT = Reactietijd

waren, goede voorspellers waren voor IQ scores wanneer deze kinderen 12 jaar oud waren. Executief functioneren bleek een slechte voorspeller te zijn; de correlaties tussen werkgeheugen, selectief- en volgehouden aandacht op leeftijd 5 en IQ op leeftijd 12 varieerden tussen 0.10 en 0.16. De genetische correlaties tussen executief functioneren op leeftijd 5 en IQ op leeftijd 12 waren ook laag, behalve voor selectieve aandacht (r = 0.31). Aandachtsproblemen (gerapporteerd door

ouders en leerkrachten) correleerden veel sterker met IQ op latere leeftijd (r = -0.28 en -0.36, respectievelijk). Met andere woorden, aandachtsproblemen op jonge leeftijd kunnen voorspellend zijn voor IQ scores zeven jaar later. De genetische correlaties waren ongeveer -0.40; er is dus een genetische factor die zowel aandachtsproblemen op leeftijd 5 als IQ scores op leeftijd 12 beïnvloedt. Zoals verwacht was IQ gemeten op leeftijd 5 de beste voorspeller voor IQ op leeftijd 12. De longitudinale correlatie was 0.51 en de genetische correlatie 0.81.
Executieve functies zoals gemeten op leeftijd 5 hadden onderling zeer hoge genetische correlaties (0.80-0.90), en de genetische correlaties met IQ op deze leeftijd lagen tussen de 0.36 en 0.70. Executief functioneren en aandachtsproblemen zoals gerapporteerd door de leerkracht hadden op deze leeftijd een genetische correlatie tussen de -0.31 en -0.38. De genetische correlaties tussen executief functioneren en aandachtsproblemen gerapporteerd door de moeder waren echter laag (r = -0.17 - 0.08).

Conclusie

Aandacht is een normaal verdeelde eigenschap in de populatie met excellente aandachtsvaardigheden aan de ene kant van de verdeling en ernstige aandachtsproblemen aan de andere kant van de verdeling. Individuele verschillen in aandacht en aandachtsproblemen worden, onafhankelijk van vragenlijst, informant, en leeftijd van de proefpersonen, sterk bepaald door genetische factoren. Executief functioneren bij jonge kinderen wordt voor ongeveer 50% bepaald door genetische invloeden, bij jonge adolescenten is dit ongeveer 60%. De stabiliteit van het executief functioneren tijdens de kindertijd wordt bepaald door genetische factoren. Executief functioneren op leeftijd 5 is een matige voorspeller voor IQ scores op leeftijd 12. Een betere voorspeller blijken aandachtsproblemen op 5-jarige leeftijd te zijn. Tevens is er een gedeelde genetische component die zowel aandachtsproblemen op leeftijd 5 als IQ scores op leeftijd 12 verklaard. In de huidige groep tweelingen is het SNAP-25 gen zowel geassocieerd met IQ (Gosso et al. 2006) als met aandachtsproblemen. Toekomstig onderzoek in een grotere groep kinderen kan mogelijk uitwijzen of het SNAP-25 gen een deel van de correlatie tussen aandachtsproblemen en IQ kan verklaren.

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APPENDICES

APPENDIX I

Sample Characteristics and Data collection

Subjects

This study examined data of twin pairs and their siblings who participated in a longitudinal study on attention, attention problems, cognition, and executive functioning. All twins were registered at birth with the Netherlands Twin Registry (NTR), kept by the Department of Biological Psychology at the Vrije Universiteit in Amsterdam. Of all multiple births in the Netherlands, 40-50% is registered by the NTR (Boomsma et al. 2002; Bartels et al. 2007). The majority of the sample participated twice: the first time at age 5 and the second time at age 12. Selection of the sample was based on age and zygosity, as estimated from questionnaire data, and city of residence; for practical reasons, children had to live within one hundred kilometre radius of the Vrije Universiteit. The twins were born between 1990 and 1992 and were tested when they were 5 years old (mean age 5.8, SD 0.1), and when they were 12 years old (mean age 12.42, SD 0.16). At age 5 there were 237 twin pairs that participated: 52 monozygotic male twin pairs (MZM), 37 dizygotic male twin pairs (DZM), 73 monozygotic female twins pairs (MZF), 36 dizygotic female twin pairs (DZF) and 39 dizygotic opposite-sex twin pairs (DOS). Of the original sample, 172 twin pairs participated again when they were 12 years old. Five extra, 12-year-old dizygotic female twin pairs were recruited. The sample thus consisted of 177 twin pairs, with 41 MZM twin pairs, 28 DZM twin pairs, 56 MZF twin pairs, 25 DZF twin pairs and 27 DOS twin pairs.

Siblings

Siblings of the twins were invited to participate at the second time point when the twins were 12 years old. The siblings were aged between 8 and 15 years old. Twenty seven siblings were younger than their twin brothers or sisters (mean age 9.60, SD 0.71), and 28 siblings were older (mean age 14.69, SD 0.60). At

both time points none of the children suffered from severe physical or mental handicaps. Parents and (at age 12) children signed an informed consent, and the study was approved by the institutional review board of the Vrije Universiteit Medical Centre.

Non-responders

About 75% of the family's who participated at age 5, were willing to participate again at age 12. The reason for non-responders was half of the time 'no interest without specific reasons', by the children or parents. Other reasons were personal circumstances like divorce, death or illness in the family. A small group was no longer registered in the NTR and/or could not be reached by mail or telephone. The group of non-responders was not significantly different from the group who did participate, according to processing speed, IQ, and attention problems at age 5 as reported by the teacher or parents. Because the group of dizygotic female twins was smaller than the other zygosity groups, we recruited 5 extra female, dizygotic twin pairs at age 12.

Data Collection and Procedure

Data collection at age 5 and age 12 consisted of a neuropsychological assessment, which involved computerised executive functioning tasks, IQ tests, and behavioral data assessed by questionnaires. Questionnaires were filled in by the parents, the teachers and (at age 12) the children themselves. DNA samples were collected with buccal swabs. At both ages DNA was used to determine zygosity and at age 12 it was also used for genotyping SNP's at candidate gene loci. At age 12 the hormones cortisol and testosteron were assessed with saliva samples.

When the children were 5 years old they were visited at home where trained testers administered the computerized executive functioning tasks on a laptop. IQ was assessed with the short version of the RAKIT (Bleichrodt, Drenth, Zaal, & Resing, 1984) that includes six subtests (Exclusion, Discs, Hidden Figures, Verbal Meaning, Learning Names, and Idea Production). The entire test session took ~2 hours including breaks. Buccal swabs were collected at home and sent to the university afterwards.

When the children were 12 years old they visited the Vrije Universiteit for the as-

Table 1:
Overview of the data collection at the two time points, questionnaires with an asterisk* are collected every two year in all young twins registered with the NTR. For the siblings the CBCL and TRF data were collected as part of the current study.

Time point 1 (age 5)	Time point 2 (age 12)
Behavior questionnaires:	Behavior questionnaires:
Parents: DCB*, ASH	Parents: CBCL*, Conners*, SWAN
Teachers: TRF, Conners, ASH	Teachers: TRF*, Conners*
	Children: YSR
	Maturation questionnaire:
	Children: Tanner
DNA (buccal): zygosity	DNA (buccal): zygosity, candidate genes
Executive functioning tasks:	Executive functioning tasks:
ANT:	ANT:
Baseline Speed	Baseline Speed
Memory Search	Memory Search
Focused Attention	Focused Attention
Sustained Attention	Sustained Attention
Go-no go task	Go-no go task
	Shifting Set Visual
	Pursuit
	Tracking
	Emotion Identification
	Eriksen Flanker task
	Simon task
	Stroop task
IQ: RAKIT	IQ: WISC-R
Exclusion	Similarities
Hidden Figures	Vocabulary
Discs	Block Design
Verbal Meaning	Object Assembly
Learning Names	Digit Span
Idea Production	Arithmetics
	Hormones:
	Cortisol (2 days/5 samples per day, in saliva)
	Testosteron (1 day/1 sample, in saliva)
	Growth measures:
	Height & Weight

sessment. The executive functioning tasks were performed on a desktop computer. Tasks were similar as at age 5 although adjusted for age (for example consonants instead of pictures, and more trials per task). The ANT task battery was expanded with two tasks on motor flexibility, one task on shifting attention, and one task on emotion recognition. Two additional computerised executive functioning tasks that measure inhibition and selective attention, were performed, namely the Eriksen Flanker task (Eriksen & Eriksen, 1974) and Simon task (Simon & Rudell, 1967), and all children performed the Stroop Color Word Task (Stroop, 1935). Six IQ subtests of the WISC-R (Van Haassen et al. 1986) were assessed at age 12 (Similarities, Vocabulary, Arithmetic, Digit Span, Block Design, and Object Assembly). Children were tested at the same time but in separate rooms by different test leaders. The entire test session at this time took ~4 hours, including breaks. Buccal swabs of the twins and siblings were collected at home and taken to the university. Saliva samples were collected at home (cortisol) and during the visit to the university (testosterone). At both ages children received a small present after finishing the protocol.
For a complete overview of the data collection at both time points see Table 1. A detailed description of the collected questionnaires and neuropsychological tasks is presented below.

Behavioral Questionnaires

Parents of all twin pairs who are registered at the NTR receive a survey about their children every two years (at 0, 2, 3, 5, 7, 10 and 12 years). At ages 3, 7, 10 and 12 years this survey includes the Child Behavior Check List (CBCL; Achenbach, 1991a). At age 5 a behavioral checklist is adapted from the Devereux Child Behavior Rating Scale (DCB; Spivack and Spotts, 1966; Van Beijsterveldt et al. 2004). From age 7 onwards parents are asked permission to send the teacher of the twins a questionnaire as well, the Teacher Report Form (TRF; Achenbach, 1991b). For the twin pairs who participated in this study we collected additional questionnaires at age 5 and at age 12. At age 5 these behavior checklists were the TRF, the 'Aandachttekort Stoornis met Hyperactiviteit' (ASH; Gunning, 1992), and the Conners Rating Scale (CPRS-R; Conners, 2001). At age 12 these behavior checklists were the Strength and Weakness of ADHD symptoms and Normal

behavior scale (SWAN; Swanson, 2006), the Conners Rating Scale, and the Youth Self Report (YSR; Achenbach, 1991c). In addition children at this age were asked to complete a maturation questionnaire, the Tanner (based on Marschall and Tanner, 1969; Van den Berg et al. 2006). For siblings of the twins the same questionnaires were collected as for the twins. The TRF was sent to the teacher of younger siblings only as older siblings were already in secondary school where they are educated by multiple teachers instead of one or two as in primary school. A description of all questionnaires is given below.

Devereux Child Behavior Rating Scale (age 5)

The DCB (Spivack and Spotts, 1966) is a questionnaire on problem behavior for young children. Parents are asked to rate the behavior of their child over the last two months. The original DCB consists of 121 items but for this study 42 items were used. Items were chosen whose scale was associated with intelligence and emotional problem behavior. Items can be scored on a five-points-scale with 1 indicating "never" and 5 indicating "very frequently". Problem scales that were derived from these items were emotional lability, social isolation, aggressive behavior, attention problems, dependency, anxiety problems, and physical coordination (Van Beijsterveldt et al. 2004).

Aandachttekort Stoornis met Hyperactiviteit (age 5)

The ASH (Gunning, 1992) questionnaire is based on the 14 items of Attention Deficit/Hyperactivity Disorder (ADHD) as used in the DSM-III. Parents or teachers rate the child's behavior on a four point scale varying from "not at all" to "very often". Items are related to attention deficit, impulsivity, and hyperactivity.

Teacher Report Form (age 5 and age 12)

The TRF (Achenbach, 1991b) was, after permission of the parents, filled in by the teacher. The TRF consists of 120 problem items. Teachers are instructed to rate the child's behavior over the last two months with 0 if the behavior is "not true", 1 if the behavior is "sometimes or somewhat true", and 2 if the behavior is "very or often true". Items were scored on eight specific problem scales namely Withdrawn, Anxious/Depressed, Social Problems, Aggressive Behavior,

Rule Breaking Behavior, Attention Problems, Thought Problems, and Somatic Complaints.

Conners (age 5 and age 12)

The Conners' Rating Scale-Revised is an instrument to assess behavior problems in children and can be completed by parents and teachers (CPRS-R; Conners, 2001; Conners et al. 1998). The short version contains 28 items. The items are rated on a four-point scale with zero indicating "not true at all" and three indicating "very much true". Problem scales that were derived from the Conners were oppositional behavior, cognitive problems-inattention, hyperactivity, and ADHD.

Child Behavior Check List (age 12)

The CBCL (Achenbach, 1991a) is a standardized questionnaire for parents to report the frequency and intensity of behavioral and emotional problems of their children. The CBCL consists of 120 items. Parents are instructed to rate the child's behavior over the last six months with 0 if the behavior is "not true", 1 if the behavior is "sometimes or somewhat true", and 2 if the behavior is "very or often true". Problem scales that were derived from the CBCL were Withdrawn, Anxious/Depressed, Social Problems, Aggressive Behavior, Rule Breaking Behavior, Attention Problems, Thought Problems, and Somatic Complaints.

Strength and Weakness of ADHD symptoms and Normal behavior scale (age 12)

The SWAN (Swanson, 2006) was filled in by the mothers of the children. The SWAN employs 18 items on a 7 point scale ranging from "far below average" (1) to "far above average" (7) to allow for ratings of relative strengths (above average) as well as weaknesses (below average). The SWAN is based on the 18 items of ADHD in the DSM-IV. The first nine items correspond to the Attention Deficit scale and the last nine items to the Hyperactivity scale.

Youth Self Report (age 12)

The YSR (Achenbach, 1991c) is a questionnaire that is based on the CBCL and is completed by children (between age 11 and 18) themselves. The YSR consists of 120 problem items. Children are instructed to rate their behavior over the last

six months with 0 if the behavior is "not true", 1 if the behavior is "sometimes or somewhat true", and 2 if the behavior is "very or often true". Items can be scored on eight specific problem scales Withdrawn, Anxious/Depressed, Social Problems, Aggressive Behavior, Rule Breaking Behavior, Attention Problems, Thought Problems, and Somatic Complaints.

Tanner (age 12)

At age 12 twins and siblings were asked to fill out an extended Tanner questionnaire (based on Marschall and Tanner, 1969). Girls were asked about their menarche ("no"/"yes", if "yes" the date), breast development (5 categories), and pubic hair development (6 categories). Boys were asked about genital development (5 categories), development of scrotum and testes (4 categories), and pubic hair development (6 categories). The categories were indicated by photographs showing all stages of development.

Neuropsychological Assessment

IQ tests

IQ subtests (age 5)

At age 5 IQ was assessed with the RAKIT, a Dutch intelligence test (Bleichrodt et al. 1984). The following 6 subtests were employed: Exclusion: This measures reasoning by assessing the child's ability to induce a relationship between four figures, and to determine that one of the figures is deviant; Discs: This subtest measures spatial orientation and speed of visualization; Hidden Figures: This subtest relates to transformation of a visual field, and convergence/flexibility of closure; Verbal Meaning: This is a vocabulary index and a measure of passive verbal learning; Learning Names: This subtest measures active learning and remembering meaningful pictures; Idea Production: This subtest measures verbal fluency. Raw scores on these subtests were standardized, and the sum of standardized scores was transformed to a total IQ score. The six subtests represents the shortened version of the RAKIT which has been shown to correlate 0.93 with the full scale IQ score (Bleichrodt et al. 1984).

IQ subtests (age 12)

At age 12 IQ was assessed with the Wechsler Intelligence Scale for Children Revised (WISC-R, Dutch version, Van Haassen et al. 1986). The following 6 subtests were employed: Similarities: This measures verbal abstract reasoning. Subjects describe why two things are similar or alike; Vocabulary: This subtest measures knowledge of word meanings, language development and verbal fluency; Arithmetic: This measures verbal mathematical reasoning skills, concentration and short time memory for meaningful information; Digit Span: This subtest involves a child's ability to remember a sequence of numbers (both backwards and forwards). It measures concentration and short-term auditory memory for non-meaningful information; Block Design: This subtest measures visual abstract ability, spatial analysis and abstract visual problem-solving; Object Assembly: This measures visual analysis and the ability to assemble separate elements into a whole.

Standardized scores of this shortened form of the WISC-R correlate 0.94 with standardized IQ scores based on all subtests of the WISC-R (Sattler, 1982; Sattler, 1992) and the concurrent validity with the RAKIT is 0.86 (Bleichrodt et al. 1984).

Computerised Executive Functioning Tasks of the ANT

All subjects at both ages performed executive functioning tasks of a test battery named the Amsterdam Neuropsychological Tasks (ANT, De Sonneville, 1999). The ANT is especially designed for children as young as five and measures a diverse range of executive functions, like attention, working memory and inhibition. At age 5 tasks were performed on a laptop, and at age 12 on a desktop computer. In all tasks, at both ages, responses were made by pressing the left or right mouse button. A yes-response was made with the preferred hand, a no-response with the non preferred hand. Prior to the experiments, the children were given verbal instructions in which both speed and accuracy were emphasized. Twelve practice trials were provided for each task to ensure instructions were well understood. Dependent measures were reaction times (RT) for hits, correct rejections, false alarms and misses, and accuracy (percentage of misses and false alarms). Reaction times at age 5 had to be generated between 200 and 6000 ms. post stimulus onset, except for the go-no go task in which responses had to be made before 2300 ms.

At age 12 reaction times had to be generated between 200 and 8000 ms with the same exception for the go-no go task. Reaction times before 200 ms. were not considered to be the result of a cognitive evaluation and were automatically replaced by trials of a similar type.

Task descriptions age 5

Baseline Speed

This is a simple reaction time task. Subjects have to concentrate on a fixation cross. When this cross changes in a square they have to respond as quickly as possible. In the first part (32 trials) subjects responded with their preferred hand, in the second part with their unpreferred hand. Both parts consist of 32 trials. Results are mean reaction times for the preferred hand, mean reaction times for the unpreferred hand and a mean reaction time of both hands. Following a response, the next stimulus was presented after 250 ms.

Selective Attention

In this task a fruit basket is presented with four pieces of fruit. Two pieces of fruit are aligned in a vertical fashion (top and bottom) and two pieces in a horizontal fashion (left and right). Subjects have to give a yes-response if the target fruit is shown at one of the two relevant locations (the top or bottom location of the vertical axis). They have to give a no-response if the target fruit is shown but at an irrelevant location (left or right of the horizontal axis), or if the target fruit is absent altogether. The display with the target fruit on the vertical axis is the target signal; the display with the target fruit on the horizontal axis is the distracting signal, and the display that contains only the four non-target fruits is the non-target signal. The three signal types were presented in a random order (28 target signals, 14 distracting signals, and 14 non-target signals). Following a response, the next signal was presented 1200 ms later, preceded the last 500 ms by a warning signal (small fixation cross).

Working Memory

In this task children were presented with an image of a house with four animals presented simultaneously in the windows and the door opening. Subjects were instructed to press the yes-key when the signal contained an animal from the memory set, and to press a no-key when this was not the case. On each trial the animals occupied different positions. The task consisted of two parts. In part 1 the memory set contained one animal and in part 2 two animals. In each part 20 target and 20 non-target signals were presented in random order. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation square).

Sustained Attention

During this task a house with three windows is continuously present on the screen. In each trial one animal is presented randomly in one of the windows. Subjects are instructed to press the yes-key when they detect a target animal and the no-key when a non-target animal is presented. The task consisted of 20 series of 12 trials (i.e., 240 trials). In each serie 6 target and 6 non-target signals were presented in random order. To keep the children alert a beep sound was presented in case of an error. Following a response, the next stimulus was presented after 250 ms.

Go no go

The go-no-go task consists of 24 go-signals (a white arrow on a green square) randomly mixed with 24 no-go signals (a red circle with a horizontal white bar). When a go-signal appears, subjects were instructed to press the yes-button as quickly as possible, when a no-go signal appears, subjects were instructed not to press the button but withhold their response. Results are hits, false alarms and misses whereby false alarms are measurements of impulsivity (disinhibition) and misses are measurements of inattention. Each trial was preceded by a warning signal of 500 ms and the stimulus was presented for 800 ms. (but disappeared when a response was given before this time).

Task descriptions age 12

Baseline Speed

This is a simple reaction time task. Subjects have to concentrate on a fixation cross. When this cross changes in a square they have to respond as quickly as possible. In the first part (32 trials) subjects responded with their preferred hand, in the second part with their unpreferred hand. Both parts consist of 32 trials. Results are mean reaction times for the preferred hand, mean reaction times for the unpreferred hand and a mean reaction time of both hands. Following a response, the next stimulus was presented after 250 ms.

Selective Attention

In this task a fixed display with two different consonants was presented on one of two diagonals, the top-left to bottom-right or the top-right to bottom-left diagonal. The task contained three manipulations: 1) location of the consonants: relevant or non-relevant diagonal 2) presence of a target: target or non target letter present, and 3) memory load: in part 1, one target letter, in part 2, three target letters (of which one could appear). Subjects had to give a yes-response when a target appeared on the relevant diagonal (the top-left to bottom-right one). A no-response was required when a target letter appeared on the non-relevant diagonal or when a non-target letter appeared on one of the two diagonals. The task consisted of two parts with each 120 trials. The presentation of stimuli was balanced so that an equal number of yes- and no-responses was required. A stimulus appeared for 300 ms; after a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation cross).

Working Memory

In this task memory load, operationalized as target set size, increased from one to three target letters. The computer screen showed a fixed display of four consonants arranged in a square, from which subjects had to detect one or more target letters. For Load 1 the target signal requiring a yes-response was 'k' (40 trials; 50% target signal). For Load 2, target signals were 'k' + 'r' (72 trials; 36 complete target sets, 18 trials one target signal, 18 trials no target signals) and for Load 3

target signals were 'k' + 'r' + 's' (96 trials; 48 complete target sets, 16 trials one target signal, 16 trials two target signals, 16 trials no target signals). Children were instructed to press the yes-button only when a complete set of target letters was present. In all other instances a no-response was required. After a response, the next stimulus was presented after 1200 ms, preceded the last 500 ms by a warning signal (small fixation square).

Sustained Attention

During this task a square with 3, 4 or 5 dots is presented on the screen. Subjects are instructed to press the yes-key when they detect 4 dots and the no-key when 3 or 5 dots are presented. The task consisted of 50 series of 12 trials (i.e., 600 trials). In each series 4 target and 8 non-target signals were presented in random order. To keep the children alert a beep sound was presented in case of an error. Following a response, the next stimulus was presented after 250 ms.

Shifting Attentional Set

This task measures the ability to change from a compatible attentional set to an incompatible attentional set. A horizontal bar consisting of ten squares is presented permanently in the centre of the computer screen. From trial to trial a colour square moves across the bar in a random direction, i.e. to the right or to the left. The task has three parts. In part one spatially compatible responses are required: subjects had to copy the movements of a green square, (i.e. right movement-right button, left movement-left button). In part two spatially incompatible responses are required: subjects had to mirror the movements of a red square (i.e. right movement-left button, left movement-right button). In part three the colour of the moving square changes randomly from green to red, subjects had to respond compatible to the green square and incompatible to the red square. Results are mean reaction times of the compatible and incompatible conditions, and number of errors in both conditions. The fixed post-response interval was 250 ms.

Go-no-go task

The go-no-go task is a simple inhibition task. The task consists of 24 go-signals (a closed square) randomly mixed with 24 no-go signals (a square with a little opening). When a go-signal appears, subjects were instructed to press the yes-button as quickly as possible, when a no-go signal appears, subjects were instructed not to press the button but withhold their response. Results are hits, false alarms and misses whereby false alarms are measurements of impulsivity (disinhibition) and misses are measurements of inattention. Each trial was preceded by a warning signal of 500 ms and the stimulus was presented for 800 ms. (but disappeared when a response was given before this time).

Pursuit

This task measures visual-motor fluency. In this task subjects had to follow as closely as possible a randomly moving asterisk with the cursor of the mouse. The task takes 60 seconds with the preferred hand and 60 seconds with the unpreferred hand. The distances between the cursor and the target per second are computed. Results of this task are accuracy of movement and stability of movement.

Tracking

The tracking task is also a visual-motor fluency task. It requires subjects to trace a mouse cursor in between an outer (radius 8.5 cm) and inner circle (radius 7.5 cm). The circle is presented in the screen centre of the computer. Subjects completed the circle first with their preferred hand, and second with their unpreferred hand. Results are completion time, accuracy of movement and stability of movement.

Identification of Facial Emotions

This task measures the ability to recognise facial emotions. The subjects were asked to judge whether a face showed a specific (target) expression ('yes' response) or an expression different from that one ('no' response). The signal consists of a photograph of a face that may show any of the following eight emotions: happy, sad, anger, fear, disgust, surprise, shame and contempt. The task consists of eight parts of 40 trials. In each part half of the trials contain the target emotion

whereas in the other half a random selection of the seven other emotions or a neutral expression is shown. In this study only the first four parts were administered. Target emotions were happy, sad, anger and fear. Results are mean reaction times and number of hits, correct rejections, false alarms and misses.

Reliability of the Executive Functioning Tasks of the ANT at age 12

To examine the reliability of the computerised attention tasks of the ANT in the 12-year-old sample, 20 subjects of the sample (8 twin pairs and 4 siblings) were retested 6 months after their first performance. In addition we recruited 10 12-year-old children from a primary school who also performed the computerised tasks twice, with two weeks in between. To test the reliability we computed correlations between the test and the retest for reaction times (RT) and accuracy (AC). In both groups and on all tasks the correlations for RT and AC between test and retest were moderate to high (0.30 to 0.90). The results are presented in Table 2.

Additional Executive Functioning Tasks at age 12

Two additional computerised executive functioning tasks, measuring inhibition and selective attention, were performed, namely the Eriksen Flanker task (Eriksen & Eriksen, 1974) and Simon task (Simon & Rudell, 1967). Finally all children performed the Stroop Colour Word Task (Stroop, 1935).

Eriksen Flanker task

Children performed the computerised version of the Eriksen Flanker task (Eriksen & Eriksen, 1974). After presentation of a fixation point in the middle of the screen 5 arrows were presented. By pushing a button left or right, subjects had to respond if the centre arrow pointed to the left or the right. The flanking arrows could be either congruent (i.e. pointing in the same direction as the centre arrow) or incongruent (i.e. pointing in the opposite direction as the centre arrow). Children performed in total 80 trials, 50% congruent and 50% incongruent. There is a tendency to respond to the flanking arrows. The mean reaction time difference between congruent and incongruent trials is called the Flanker effect.

Table 2:
test retest correlations for reaction time (RT) and accuracy (AC) of the executive functioning tasks at age 12

	Twins and siblings	School children
Baseline speed RT	0.57	0.58
Selective Attention RT	0.73	0.83
Selective Attention AC	0.45	0.49
Go no go RT	0.85	0.80
Working Memory RT	0.80	0.88
Working Memory AC	0.30	0.57
Sustained Attention RT	0.82	0.83
Sustained Attention AC	0.83	0.90
Emotion Identification RT	0.60	--

Simon task

The Simon task is a selective attention task and was initially developed by Simon & Rudell (1967). In the computerised version of a visual spatial Simon task subjects have to respond to the colour of a stimulus. On the screen a red circle or a green circle appears. In case of a red circle children have to push the right button, in case of a green circle children have to push the left button. By manipulating the position of the stimulus, (i.e. for example position the red circle on the left part of the screen) a response conflict arises. Because there is an initial tendency to react to the location of the stimuli this results in higher RT's and inaccuracy.

Stroop Colour Word Task

The Stroop task is perhaps one of the oldest inhibition tasks (Stroop, 1935). Children have to read aloud 3 Stroop word-colour cards. Each card consists of 10 rows with 10 items. The first card contains words that are all colours (i.e., 'blue', 'red', 'green', 'yellow') printed in black ink. The second card contains squares that are printed in different colours. The third card contains names of colours printed in incongruent colours. Children have to name the colour of the ink in which the word is printed and not the word itself. Each card is scored as the time (in

seconds) to complete one card, also per card corrections and mistakes are counted. The Stroop effect is computed as the difference in time between performance of card 3 and card 2. The Stroop effect is a prototype of inhibition, as subjects have to inhibit the tendency to produce a dominant or automatic response (i.e. the content of the word instead of the colour of the ink).

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MEEDOEN AAN TWEELINGONDERZOEK

ALGEMENE INFORMATIE OVER TWEELINGONDERZOEK

Tweelingonderzoek is een belangrijk wetenschappelijk instrument binnen de geneeskunde en de psychologie. Dankzij onderzoek bij tweelingen kunnen we er achter komen in hoeverre bepaald gedrag, of het krijgen van bepaalde ziektes, word: beïnvloed door iemands gener of door iemands leefomgeving Om goed onderzoek te kunnen doen hebben we gegevens nodig van zeer veel tweelingen. Bovendien willen we graag die tweelingen volgen gedurence hun verdere ontwikkeling. Daarom is in 1987 aan de Vrije Universiteit te Amsterdam het Nederlands Tweelingen Register (NTR) opgericht. Bij het NTR staan momenteel zo'n 33.000 tweelingen ingeschreven. De meeste gegevens van deze tweelingen zijn verkregen door middel van gedragsvragenlijsten die door de tweelingen zelf of door hun familieleden zijn ingevuld. Verschillende wetenschappers maken gebruik van deze gegevens, en onderzoeken zo de invloed van genen en omgeving op onder andere de ontwikkeling van de hersenen, intelligentie, probleemgedrag van kinderen, gezondheid & leefgewoonten, angst & depressie, persoonlijkheid en veroudering. De belangeloze medewerking van tweelingen en hun families is daarbij van onschatbare waarde!

PRIVACY

De gegevens die met dit tweelingonderzoek worden verzameld worden altijd vertrouwelijk behandeld. De gegevens worden geregistreerd en verwerkt onder een nummer en dus niet onder een naam of andere persoonlijke gegevens. Ook in publicaties zijn namen niet terug te vinden. Bij sommige tweelingen wordt bovendien DNA afgenomen voor verder onderzoek. Uiteraard staat ook hier de privacy centraal. Men hoeft dus niet bang te zijn dat DNA aan derden wordt doorgespeeld. Bij elk onderzoek volgen wij de richtlijnen die door de ethische commissie van de Vrije Universiteit zijn opgesteld.

INFORMATIE OVER HET HUIDIGE ONDERZOEK

In dit onderzoek wordt gekeken naar de erfelijkheid van aandacht en aandachtsproblemen. Met dit onderzoek hopen we met name meer te weten te komen over de ontwikkeling van aandacht, maar ook over het ontstaan van aandachtsproblemen, zoals ADHD. We maken gebruik van verschillende tests waarmee we aandacht en intelligentie kunnen meten. Sommige intelligentie- en aandachtstests zijn ongeveer 7 jaar geleden ook al bij tweelingen afgenomen, die toen 5 jaar oud waren. Door diezelfde tweelingen nu op 12-jarige leeftijd weer te testen kunnen we kijken naar de ontwikkeling van deze vaardigheden. Deze testen worden op de Vrije Universiteit bij de tweelingen afgenomen. Naast de testresultaten willen we graag iets te weten komen over de lichamelijke rijping van de tweeling en over zijn/haar DNA. Deze gegevens kunnen thuis worden verzameld en aan ons opgestuurd. Tot slot verzamelen we gegevens uit gedragsvragenlijsten, zoals de CBCL. Meer gedetailleerde informatie over de verschillende tests vindt u hieronder.

Intelligentie

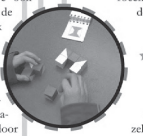
Iemands intelligentie wordt gemeten door middel van een IQ-test. Deze test bestaat uit een groot aantal vragen, waar zo snel mogelijk het juiste antwoord op moet worden gevonden. Sommige vragen testen het taalbegrip, andere testen ruimtelijk inzicht, enz. De totaalscore op de verschillende onderdelen van de test resulteert in een bepaald getal, het zgn. IQ. De officiële naam van deze test is WISC-R en deze wordt op de Vrije Universiteit afgenomen.

Aandacht

We meten aandacht door middel van een aantal computertaakjes. Deze taakjes meten niet alleen aandacht, maar ook concentratie, reactievermogen, geheugen, enz. Deze taakjes zijn leuk om te doen. Veel mensen vinden het een uitdaging om de taakjes zo snel en nauwkeurig mogelijk te volbrengen. De officiële naam van deze test is de ANT (Amsterdamse Neuropsychologische Taken). Ook deze wordt op de Vrie Universiteit afgenomen.

Lichamelijke rijping

Onderzoek naar de lichamelijke rijping is van groot belang omdat de tweelingen, die nu ongeveer 12 jaar oud zijn, zich ongeveer in de puberteit bevinden. Tevens willen we kijken of er verschillen zijn tussen jongens en meisjes. We testen lichamelijke rijping (a) door middel van een vragenlijst die door de tweeling wordt ingevuld, en (b) door het bepalen van de hormoonspiegel. De officiële naam van de rijpingsvragenlijst is de TANNER. De vragenlijst kan gewoon thuis voorafgaand aan het onderzoek door de tweeling worden ingevuld. De hoeveelheid hormonen in het lichaam wordt bepaald aan de hand van speeksel dit in een buisje wordt opgevangen. Ook dit kan gewoon thuis gebeuren.



DNA

Met het oog op mogelijk genetische analyses willen we ook DNA afnemen. DNA is de drager van ons erfelijk materiaal en kan ons in de toekomst helpen om te onderzoeken welke genen betrokken zijn bij aandacht en aandachtsproblemen. Afname van DNA gebeurt door een monduitstrijkje, waarbij een wattenstaafje langs de binnenkant van de wang wordt geschraapt. Dit wattenstaafje moet in een speciaal reageerbuisje worden bewaard en moet worden meegenomen of opgestuurd naar de Vrije Universiteit. Ook deze test kan gewoon thuis worden gedaan. Nogmaals en voor alle duidelijkheid: alle gegevens zijn strikt vertrouwelijk en vallen onder de strenge privacyregels van de Vrije Universiteit.

PRAKTISCHE INFORMATIE

- Proefpersonen zijn geheel vrij in het al dan niet deelnemen aan (een gedeelte van) het onderzoek.
- Er kan altijd zonder opgaaf van redenen worden afgezien van deelname.
- Deelname aan het onderzoek valt onder de verzekering van de Vrije Universteit.
- Er wordt een reiskosten vergoeding uitgekeerd van 18 Eurocent per kilometer, of de kosten die gemaakt zijn met het openbaar vervoer.
- Het is de bedoeling dat de tweeling (plus eventuele broertjes of zusjes) samen op dezelfde dag langskomen om te worden getest.
- Deelnemers krijgen aan het eind van de dag een presentje.
- De belangrijkste resultaten van het onderzoek worden thuisgestuurd.

INFORMATIE

Onderzoek naar erfelijkheid van aandacht

VRIJE UNIVERSITEIT
NEDERLANDS TWEELINGEN REGISTER

NEDERLANDS TWEELINGEN REGISTER

Vrije Universiteit Amsterdam
Biologische Psychologie
Van der Boechorststraat 1
1081 BT Amsterdam

telefoon: 020 4448787
e-mail: ntr@psy.vu.nl
internet: www.psy.vu.nl/ntr

NEDERLANDS TWEELINGEN REGISTER

NTR-INFORMATIEFOLDER

DAGPROGRAMMA

10:00

Ontvangst op de Vrije Universiteit met een drankje en uitleg van het dagprogramma. De buisjes met speeksel en de monduitstrijkjes die thuis zijn afgenomen kunt u nu inleveren, evenals de vragenlijst over lichamelijke rijping die thuis al is ingevuld.

10:15

Aanvang aandachtsonderzoek. Afwisselend worden er taakjes op de computer of met pen en papier gedaan. De taakjes worden van tevoren allemaal duidelijk uitgelegd en elke taak wordt eerst geoefend.

12:15

Er wordt je een eenvoudige lunch aangeboden.

12:45

Vervolg aandachtsonderzoek.

14:45

De deelnemers ontvangen een verrassing en kunnen nog een drankje drinken. Einde van het onderzoek.

MEER INFORMATIE

Het Nederlands Tweelingen Register heeft een website. Surf naar: www.psy.vu.nl/ntr en lees meer over het NTR en het onderzoek dat we doen.

Voor meer informatie kun je bellen of e-mailen:
telefoon: 020-4448731
b.g.g.: 020-4448787
e-mail: jc.polderman@psy.vu.nl

Bedankt voor jullie medewerking!

Tinca Polderman

Nederlands Tweelingen Register (NTR)

Datum	Telefax	Bijlage(n) 2
xxx	xxx	
Ons kenmerk	Telefoon	E-mail
	xxx xxx	jc.polderman@psy.vu.nl

Postadres: Van der Boechorststraat 1, 1081 BT Amsterdam

vrije* Universiteit *amsterdam

Aan de ouders/verzorgers van……

Ongeveer zeven jaar geleden hebben uw kinderen meegedaan aan een onderzoek naar aandacht. De kinderen hebben toen verschillende computertaakjes en een intelligentietest gedaan. Sinds die tijd is er natuurlijk veel veranderd. Kinderen van 5 jaar gedragen zich anders dan kinderen van 12 jaar. Om de ontwikkeling op het gebied van aandacht te meten willen we uw kinderen nogmaals uitnodigen voor een zelfde soort onderzoek. De titel van dit onderzoek luidt "**Erfelijkheid van aandacht**". Wij willen bij deze de tweeling uitnodigen voor een herhaalde deelname aan het onderzoek en we zouden het zeer op prijs stellen als u hiervoor toestemming wilt verlenen. Naast de tweeling willen we deze keer bovendien graag broertjes of zusjes tussen de 8 en 14 jaar uitnodigen om ook mee te doen.

Het huidige onderzoek zal opnieuw bestaan uit diverse computertaken waarin aandacht en concentratie worden gemeten. Ook zullen er weer enkele intelligentietestjes worden afgenomen. Belangrijk verschil met het vorige onderzoek is dat de kinderen deze keer op de Vrije Universiteit zullen worden getest. Daarnaast zouden we het zeer op prijs stellen als de kinderen een beetje genetisch materiaal (DNA), verkregen door middel van een wanguitstrijkje, en wat speeksel af zouden willen staan voor nader onderzoek. **Uiteraard is bij dit onderzoek de privacy van de kinderen gewaarborgd**. Bij deze brief zit een folder met uitgebreide informatie over het onderzoek. Bijgevoegd is ook een brief die u, indien u toestemt in deelname, aan uw kinderen kunt geven. U en uw kinderen zijn vrij in uw keuze wat betreft deelname aan het onderzoek.

Het onderzoek op de Vrije Universiteit zal inclusief pauzes ongeveer vier uur duren en 's ochtends plaatsvinden. De kinderen worden tegelijk getest. Wij zouden het prettig vinden wanneer u op een doordeweekse dag kan komen maar dagen in het weekend zijn ook bespreekbaar. Voor wetenschappelijk onderzoek kan overigens vrij gevraagd worden van school. In april zal ik telefonisch contact met u opnemen om een eventuele afspraak te maken. Mocht u nu al vragen hebben over het onderzoek kunt u natuurlijk telefonisch contact met mij opnemen (tel. onder aan de brief). Het is ook mogelijk dat u een deskundige wilt spreken die niet direct betrokken is bij dit onderzoek om een onafhankelijk advies te krijgen. Professor Dr. J. Sergeant, klinisch neuropsycholoog, is bereid u daarvoor te woord te staan. U kunt via zijn secretaresse een afspraak maken, tel. 020 4448756. Op onze website van het Nederlands Tweelingen Register (www.tweelingenregister.org) kunt u meer algemene informatie vinden over het tweelingonderzoek van de Vrije Universiteit.

Met vriendelijke groet,

Drs. Tinca Polderman (tel. 020-4448731, bgg 020 4448787)

Nederlands Tweelingen Register (NTR)

Datum
xxx

Telefax
xxx

Telefoon
xxx

E-mail
jc.polderman@psy.vu.nl

Postadres: Van der Boechorststraat 1, 1081 BT Amsterdam

vrije* Universiteit *amsterdam

Tweelingonderzoek naar Aandacht op de Vrije Universiteit

Aan …….en…….,

Ongeveer zeven jaar geleden hebben jullie meegedaan aan een onderzoek bij het Nederlands Tweelingen Register. Voor dit onderzoek hebben jullie toen verschillende computertaken gedaan waarbij o.a. aandacht en concentratie werden gemeten. Ook is er toen een intelligentietest afgenomen. Graag willen we jullie op 12-jarige leeftijd uitnodigen om aan een zelfde onderzoek mee te doen. We kunnen de gegevens van toen dan vergelijken met jullie resultaten nu. Naast deelname aan het onderzoek willen we jullie vragen speeksel en wanguitstrijkjes te verzamelen. Hiermee kunnen we jullie DNA (genetisch materiaal) en hormonen onderzoeken. Bij deze brief zit een informatiefolder waarin precies beschreven staat hoe het hele onderzoek er uit zal zien. Het onderzoek op de Vrije Universiteit zal ongeveer 4 uur duren en ‘s ochtends plaatsvinden. Voor meer informatie over tweelingonderzoek op de VU kunnen jullie kijken op www.tweelingenregister.org.

Wij zouden het leuk vinden als jullie samen een dagje naar de Vrije Universiteit in Amsterdam zouden willen komen om aan ons onderzoek mee te doen. Jullie ouders moeten wel toestemming geven voor jullie deelname aan het onderzoek. Voor hen zit een aparte brief in de envelop.

In april zal ik telefonisch contact met jullie opnemen. Als jullie mee willen doen dan kunnen we een dag en tijdstip afspreken waarop jullie naar de Vrije Universiteit komen. Wij zouden het prettig vinden wanneer jullie op een doordeweekse dag kunnen komen. Voor wetenschappelijk onderzoek mogen jullie een dag vrij vragen van school.

Met vriendelijke groet,

Drs. Tinca Polderman (tel. 020 4448731, bgg 020 4448787)

Nederlands Tweelingen Register (NTR)

Datum
xxx

Telefax
xxx

Telefoon
xxx

E-mail
jc.polderman@psy.vu.nl

Postadres: Van der Boechorststraat 1, 1081 BT Amsterdam

vrije* Universiteit *amsterdam

Beste

Hierbij ontvangen jullie een bevestiging van de afspraak voor deelname aan het onderzoek "Erfelijkheid van Aandacht". Fijn dat jullie mee willen doen!

Jullie worden op om verwacht in het Transitorium van de Vrije Universiteit, Van Boechorststraat 1 in Amsterdam (zie routebeschrijving). *Jullie worden in de hal van het Transitorium opgehaald.* Als jullie in het weekend een afspraak hebben kan het zijn dat de deur gesloten is, wij wachten jullie dan voor de deur op.
Mochten jullie op bovenstaande datum onverhoopt toch verhinderd zijn neem dan s.v.p. contact op met Tinca Polderman, tel.nr. 020 4446951, bij geen gehoor 020 4448787 of e-mail jc.polderman@psy.vu.nl.

In deze enveloppe vinden jullie toestemmingsformulieren voor het onderzoek. Hierop kun je voor elk onderdeel aangeven of je wel of niet mee wilt doen. Het is de bedoeling dat elke deelnemer van het onderzoek plus een ouder/verzorger dit formulier ondertekent. Verder is de rijpingsvragenlijst bijgevoegd (zie folder). Vul deze in je eentje op een rustig moment in en neem deze in een gesloten enveloppe mee naar de VU. Tot slot vinden jullie in de enveloppe buisjes, instructiefolders en schema's voor de speekselverzameling. Lees de folders goed door en volg de instructies alsjeblieft zo nauwkeurig mogelijk op. De speekselbuisjes en schema's kun je ook meenemen naar de VU.

Tijdens het onderzoek zorgen wij voor eten en drinken, ook worden alle reiskosten vergoed. Bewaar daarvoor eventuele bonnen en bus of treinkaartjes. Wanneer jullie met de auto komen verzoeken we jullie te parkeren op het parkeerterrein achter de polikliniek (zie plattegrondje). Bij binnenkomst kunnen jullie een parkeerkaartje trekken, bij het weggaan zorgen wij voor een uitrijpas.

Mochten er nog vragen zijn, aarzel niet om mij te bellen!

Tot ziens, met vriendelijke groet,

Tinca Polderman.

FAMILIEONDERZOEK NAAR DE ERFELIJKHEID VAN AANDACHT

VERKLARING VAN TOESTEMMING NA KENNISNEMING

Wilt u hieronder tekenen en daarmee het volgende verklaren:

De onderzoeker heeft mij volledig ingelicht over de aard en het doel van het "familieonderzoek naar aandacht" en ik ben op de hoogte van de onderzoeksmethoden en procedures.
Ik heb de informatie over dit onderzoek, die in de folder en brief worden gegeven, begrepen.
Ik heb de gelegenheid gehad vragen te stellen over dit onderzoek.
Ik begrijp dat ik te allen tijde de medewerking aan dit onderzoek mag afbreken zonder dat dit ongenoegen zal geven.

5) Ik heb toegestemd om deel te nemen aan de volgende onderzoeken:

Toestemming om aan		
* de intelligentietest deel te nemen	0 ja	0 nee
* de aandachtstaken deel te nemen	0 ja	0 nee
* het hormoononderzoek deel te nemen	0 ja	0 nee
* de rijpingsvragenlijst deel te nemen	0 ja	0 nee
* het DNA-onderzoek deel te nemen	0 ja	0 nee
* het gedragsvragenlijstonderzoek deel te nemen (CBCL, TRF, YSR)	0 ja	0 nee

Ik heb toegestemd om de gegevens uit dit onderzoek, voor onderzoeksdoeleinden te koppelen aan mijn informatie uit gerelateerde onderzoeken van de Vrije Universiteit.

Datum:

Naam betrokkene:

Onderzoekers:

Drs. J.C. Polderman

Handtekening betrokkene:

Handtekening onderzoeker:

Handtekening ouder/verzorger

FAMILIEONDERZOEK NAAR DE ERFELIJKHEID VAN AANDACHT

VERKLARING VAN TOESTEMMING NA KENNISNEMING

Wilt u hieronder tekenen en daarmee het volgende verklaren:

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Toestemming om aan		
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* de rijpingsvragenlijst deel te nemen	0 ja	0 nee
* het DNA-onderzoek deel te nemen	0 ja	0 nee
* het gedragsvragenlijstonderzoek deel te nemen (CBCL, TRF, YSR)	0 ja	0 nee

Ik geef toestemming tot het opnemen van mijn gegevens in het Nederlands Tweelingen Register als broer of zus van een tweeling. Inschrijving verplicht mij niet tot deelname aan verdere onderzoeken.
*Wilt u het NTR registratieformulier invullen s.v.p.?

7) Ik heb toegestemd om de gegevens uit dit onderzoek, voor onderzoeksdoeleinden te koppelen aan informatie uit gerelateerde onderzoeken van de Vrije Universiteit.

Datum:

Naam betrokkene:

Onderzoekers:

Drs. J.C. Polderman

Handtekening betrokkene:

Handtekening onderzoeker:

Handtekening ouder/verzorger:

P

LIST OF PUBLICATIONS

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Published

Polderman, T. J. C., Derks, E. M., Hudziak, J. J., Verhulst, F. C., Posthuma, D., & Boomsma, D. I. (2007). Across the continuum of attention skills: a twin study of the SWAN ADHD rating scale. Journal of Child Psychology and Psychiatry (in press).

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