Acta neurol. belg., 2006, **106**, 191-207

Original articles

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.

Key words : Children ; heritability ; cognitive development ; ADHD ; intelligence.

THIS STUDY

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 : $r\text{DZ} = {}^1/_2\, a^2 + c^2$. 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 (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 environmental 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 also can increase the statistical power to detect genetic and environmental effects (Schmitz *et al.*, 1998).

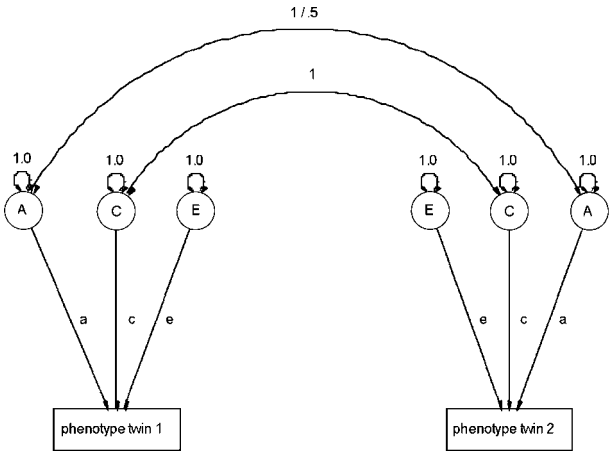


FIG. 1. — The univariate ACE model represented for a twin pair.

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).

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, Bleichordt *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, 2006 ; 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 adolescence 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 problems 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*., submitted ; 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).

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). This 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. 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, and at age 12 this was between 200 and 8000 ms. 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 and 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 equating modelling, as implemented in Mx (Neale *et al*., 2003), was used to perform the analyses. In Mx all available data, also when

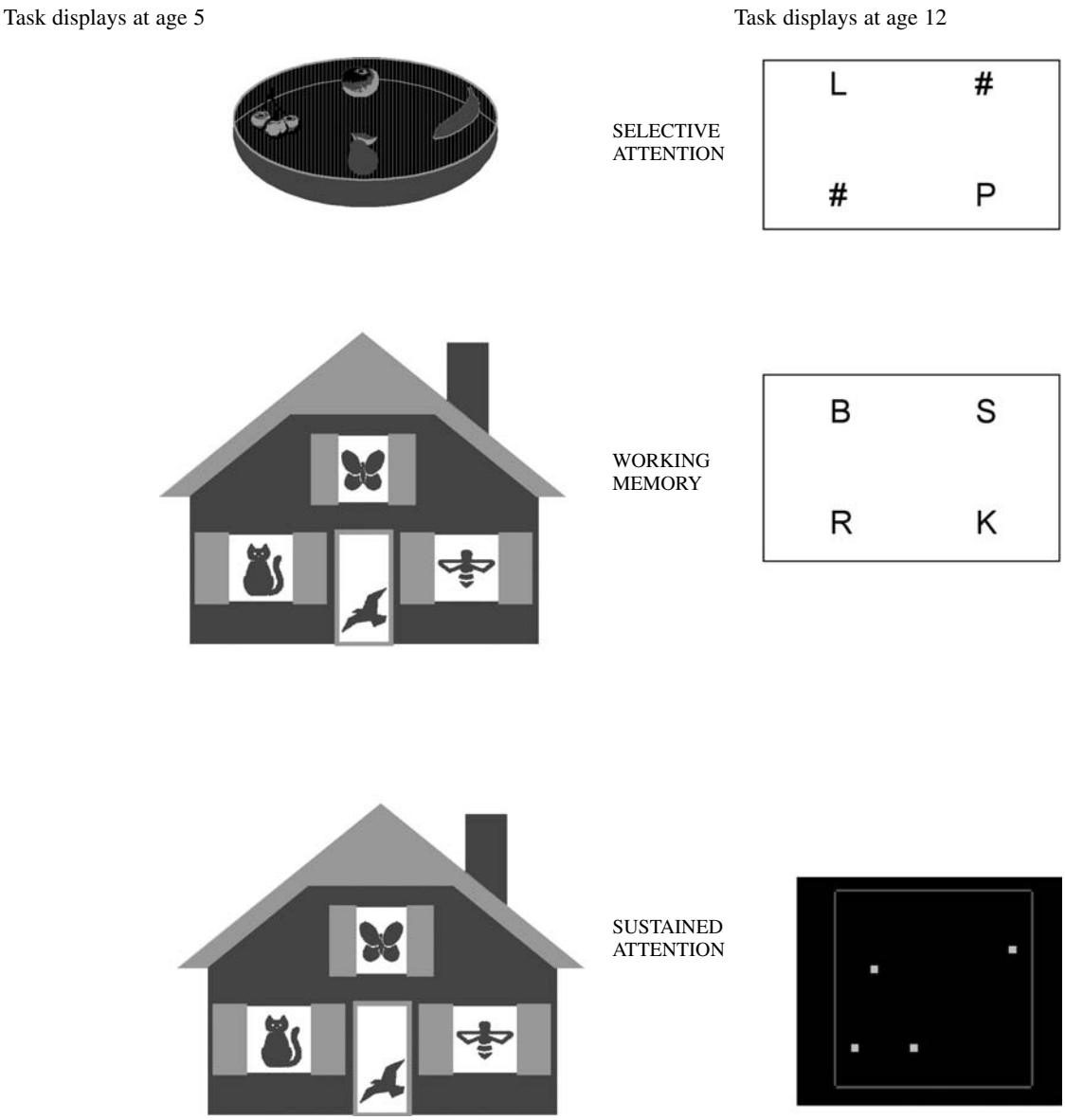


FIG. 2. — An example of stimuli and task displays of respectively the Selective Attention task, the Working Memory task and the Sustained Attention task, at age 5 (left part) and age 12 (right part).

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 envi-

ronmental 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 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., $(a_{11}^2 + a_{22}^2) + (c_{21}^2 + c_{22}^2) + (e_{21}^2 + e_{22}^2)$). 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

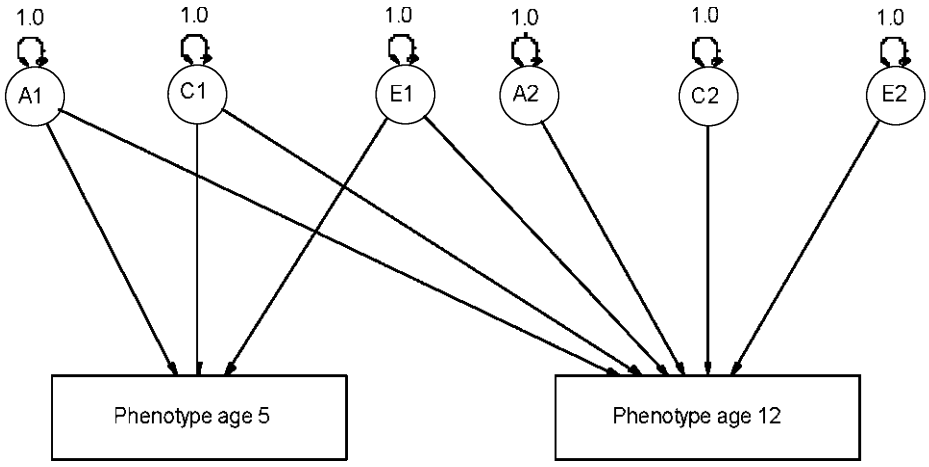


FIG. 3. — The bivariate (longitudinal) model represented for one individual

Note :

Phenotype age 5 :

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

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

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

Phenotype age 12 :

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

$$V_P = (a_{11}^2 + a_{22}^2) + (c_{21}^2 + c_{22}^2) + (e_{21}^2 + e_{22}^2)$$

$$h^2 \text{ age 12 is } \frac{a_{21}^2 + a_{22}^2}{a_{11}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{22}^2 + e_{21}^2}$$

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

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

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 msec.), and the AP scales of the DCB, TRF and CBCL. Means were corrected for sex. 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

Table 1

Means and standard deviations (in msec.) 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 age5	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.

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).

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.

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 a_{21}) 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 a_{21}). Also for AP (mother and teacher ratings) no signficant influences of C were found and genes contribute 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 e_{21}), 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.

Genetic correlations

The longitudinal 'cross trait-cross twin' correlations between IQ at age 12 and the phenotypes

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			

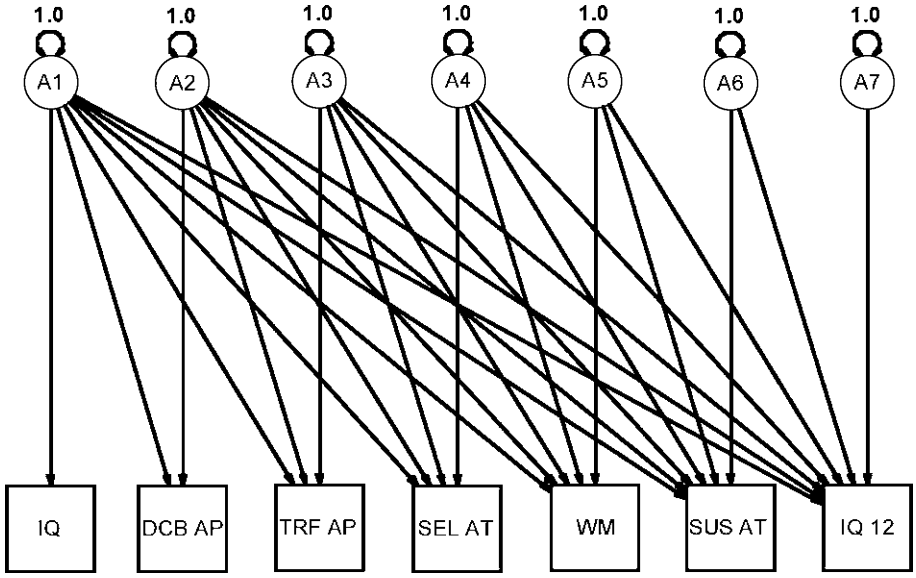
Note$_1$: a^2, c^2, and e^2 reflect the relative contribution of genetic, and common and unique environmental influences ; the a^2 for AP as rated by the mother reflects a broad heritability including additive and non-additive effects.
Note$_2$: DCB AP = Devereux Child Behavior Rating Scale, Attention 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.

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-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 (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



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

FIG. 4. — The multivariate (Cholesky) model with 7 variables represented for one individual

Note$_1$: First six phenotypes (in box) 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.

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.

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 scale.

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.

Acknowledgments

We thank all the participating twin families. This work was supported by NWO grant 904-57-94 and NWO 575-25-006, Zorgonderzoek Nederland (grant 28-2523), The Hague, The Netherlands, and Center for Neuroscience and Cognitive Research (CNCR). D. Posthuma is supported by NWO/MaGW Vernieuwingsimpuls 016-065-318.

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