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Genetic analyses of the stability of executive functioning during childhood

Tinca J.C. Polderman [a,b,*], Danielle Posthuma [a], Leo M.J. De Sonneville [c], John F. Stins [d,1], Frank C. Verhulst [b], Dorret I. Boomsma [a]

[a] Department of Biological Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands
[b] Department of Child and Adolescent Psychiatry, Erasmus University Rotterdam, Postbus 2060, 3000 CB, Rotterdam, The Netherlands
[c] Department of Clinical Child and Adolescent Studies, Leiden University, Postbus 9555, 2300 RB, Leiden, The Netherlands
[d] Faculty of Human Movement Sciences Vrije Universiteit, Room D-631, Amsterdam, The Netherlands

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Abstract

Executive functioning is an umbrella term for several related cognitive functions like selective- and sustained attention, working memory, and inhibition. Little is known about the stability of executive functioning during childhood. In this study the longitudinal stability of executive functioning was examined in young twins. The twin design enables to investigate genetic and environmental contributions to (the stability of) executive functioning.

Computerized reaction time tasks on working memory, selective- and sustained attention were collected in twins at age 5 years ($N = 474$ children) and at age 12 ($N = 346$ children). The longitudinal correlations of processing speed on all tasks were substantial (~0.38). 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 results hinted at genetic factors being an important mediator of stability of executive functioning over time. Also, genetic variation was the most important explanation for individual differences in executive functioning at both ages.

Keywords: Cognitive development; Attention; Children; Twin study; Endophenotypes

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 (i.e., 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, working memory and inhibition are to a certain extent present from early infancy (Davidson et al., 2006). Selective attention, including the ability to suppress distracting information, as in a conflict task, improves significantly during childhood (Ridderinkhof and Van der Stelt, 2000; Rueda et al., 2004b). 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; McCardle et al., 2002; Weissberg et al., 1990), depending on methods, age ranges, and test–retest intervals. For example, Weissberg et al. (1990) found a correlation of 0.79 for simple reaction time tasks, with a test–retest interval of 6 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 8–14 years old, was about 2 years.

* Corresponding author at: Department of Biological Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands. Tel.: +31 20 598 69 51; fax: +31 20 598 88 32.
E-mail addresses: jc.polderman@psy.vu.nl (T.J.C. Polderman), j.stins@fbw.vu.nl (J.F. Stins).
[1] Tel.: +31 20 598 85 43.

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They measured speed of naming words, numbers and geometrical figures and reported correlations between 0.28 and 0.47.

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 environmental variation. In other words, do children differ from each other because they have different genes or because they grow up in different environments? The classical twin design is often used to unravel genetic, common environmental (i.e., environment that is shared among siblings who grow up in the same family) and unique environmental (i.e., environment that is not shared among siblings who grow up in the same family) sources of variance (Boomsma et al., 2002). For example, Stins et al. (2005) investigated processing speed of selective attention and working memory in 5-year-old mono- and dizygotic twin pairs. It was shown that there were familial influences on task performance but no clear distinction could be made between genetic and common environmental influences. For inhibition, as measured with a go-no-go task, and sustained attention in the same 5-year-old twin pairs, Groot et al. (2004) found genetic influences on both tasks while no significant common environmental influences were present. Polderman et al. (2006b) investigated individual differences in working memory in the same twins as Groot et al. (2004) and Stins et al. (2005) when they were 12 years old. Variation in indices of working memory was for 43–56% explained by genetic variance. Ando et al. (2001) reported comparable findings in young adults where genetic variance contributed for 43–48% to the variance in WM performance.

The heritability of executive functioning (or cognitive traits) is of interest 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 and 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 was tested on executive functioning when they were 5 years old. Approximately 75% of these twins were tested 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 years (Schmitz et al., 1998), and that the causes of longitudinal stability can be investigated.

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. The third aim is to investigate if estimates of variance components for executive functioning at age 5 years differ from estimates of variance components at age 12 years. Is the contribution of genetic influences, for example higher in young adolescents than in preschool children?

1. Methods

1.1. Subjects

The sample at age 5 years consisted of 237 Dutch twin pairs born between 1990 and 1992 with a mean age of 5.8 years (S.D. 0.1, range 5.67–5.92). All subjects were registered at birth with the Netherlands Twin Registry (NTR). 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 at age 5, 172 twin pairs participated again when they were 12 years old (mean age = 12.42, S.D. = 0.16). To gain power for the analyses in the 12-year-old sample five extra, dizygotic female twin pairs were recruited (Posthuma and Boomsma, 2000). The sample thus consisted of 177 twin pairs. There were 41 MZM twin pairs, 28 DZM twin pairs, 56 MZF twin pairs, 24 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 2 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, S.D. = 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.

1.2. Procedure

Processing speed, as an important index for cognitive development (Fry and Hale, 2000; Gathercole, 1999; Just and Carpenter, 1992) was operationalized as reaction time (RT) on tasks measuring selective attention, working memory and sustained attention, respectively. RT was measured in milliseconds (ms). 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 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 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, Günther et al., 2004; Huijbregts et al., 2002; Serra

et al., 2003; Slaats-Willemse et al., 2005). 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 h 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 years 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 Haasen 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 approximately 4 h, including breaks. After finishing the assessments, the children received a small present.

To measure the reliability of the test battery that was used, 6 months after their first assessment 16 twin children at age 12 years 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.

1.3. Materials

1.3.1. Selective attention age 5 years

In this task a fruit basket was presented with four pieces of fruit. Two pieces of fruit were aligned in a vertical fashion (top and bottom) and two pieces in a horizontal fashion (left and right). Subjects were instructed to give a yes-response if the target fruit was shown at one of the two relevant locations (the top or bottom location of the vertical axis). They were instructed to give a no-response if the target fruit was shown but at an irrelevant location (left or right of the horizontal axis), or if the target fruit was absent altogether. The display with the target fruit on the vertical axis was the target condition; the display with the target fruit on the horizontal axis was the distracting condition, and the display that contains only the four non-target fruits was 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).

1.3.2. Selective attention age 12 years

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 were instructed 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).

1.3.3. Working memory age 5 years

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).

1.3.4. Working memory age 12 years

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 were instructed 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).

1.3.5. Sustained attention age 5 years

During this task a house with three windows was continuously present on the screen. In each trial one animal appeared randomly in one of the windows. Subjects were instructed to press the yes-key when they detected a target animal and the no-key when they detected a non-target animal. The task consisted of 20 series of 12 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.

1.3.6. Sustained attention age 12 years

During this task a square with 3, 4 or 5 dots is presented on the screen. Subjects were instructed to press the yes-key when they detected 4 dots and the no-key when 3 or 5 dots were presented. The task consisted of 50 series of 12 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 RTs for hits, correct rejections, false alarms and misses. RTs at age 5 years and age 12 years had to be generated between 200 and 6000 ms post-stimulus onset. RTs before 200 ms were not considered to be the result of a cognitive evaluation and were automatically replaced by trials of a similar type.

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 years) or part 1 and part 3 (age 12 years) 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 years) or 50 (age 12 years) 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').

1.4. Analyses

1.4.1. 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 years, were willing to participate again at age 12 years. 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

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 years	Selective attention test age 12 years	Selective attention retest age 12 years	Working memory age 5 years	Working memory test age 12 years	Working memory retest age 12 years	Sustained attention age 5 years	Sustained attention test age 12 years	Sustained attention retest age 12 years
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

responders for processing speed, IQ, and attention problems as reported by the teacher or parents at age 5 years.

For all tasks only correct responses (i.e., hits and correct rejections) were used for the analyses. In SPSS Inc. (2002) (11.5) the mean RT and standard deviation of each variable was calculated. At age 5 years the data from children with an error rate >40% ($n = 2$ for selective attention) or a mean 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. At age 12 years the selective attention data from 8 children, and the working memory data 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.

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).

1.4.2. Genetic analyses

Monozygotic (MZ) twins share all their genes while dizygotic (DZ) twins share on average half of their segregating genes. The different degree of genetic relatedness between MZ twins and DZ twins 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 three sources of variance; additive genetic factors (*A*), common environmental factors (*C*) and unique environmental factors (*E*). *A* is due to additive effects of different alleles; as said, MZ twins share all the genetic variance while DZ twins share about 50%. *C* is due to environmental influences shared by members of a family; thus, this applies to MZ and DZ twins. *E* is due to environmental influences not shared by members of a family. Variance of *E* also includes measurement error and is therefore always included in the models.

A first impression of the relative importance of each factor is obtained by inspecting the correlations within MZ and DZ twin pairs. When MZ twins resemble each other more than DZ twins for a certain trait, the only reason can be their genetic resemblance, as the common environmental resemblance is the same for MZ and DZ twins. When 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 'cross age-cross twin' correlations indicate to what extent the performance of twin 1 at age 5 years predicts the performance of twin 2 at age 12 years, 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.

1.4.3. Genetic modelling

Structural equation modelling, 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. This involves that all available data, also when some observations for subjects are missing, can be included. Models were tested by χ^2 tests which were computed by taking twice the difference between the −2log–likelihood (−2LL) of a baseline model and the −2LL of a reduced model ($\chi^2 = -2(LL_0 - LL_1)$). The associated degrees of freedom were computed as the difference in degrees of freedom between the two models (Neale and Cardon, 1992). In addition to the χ^2-statistic, Akaike's Information Criterium (AIC) was computed (AIC = $\chi^2 - (2 \times$ d.f.)). A low AIC indicates a relative good fit of the model (Akaike, 1987).

First means, variances and correlations were computed in a baseline (saturated) model in which means and variances were constrained to be equal for MZ and DZ, and for first born and second born twins. Then it was tested whether a longitudinal genetic model with three sources of variance (i.e., *A*, *C* and *E*, so-called 'full ACE model') described the data well compared to the baseline model. The longitudinal ACE model 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 years) 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 years. The second observation (i.e., performance at age 12 years) loaded on both factors and the variance of this observation consisted of the sum of the respective squared factor loadings (i.e., $(a_{21}^2 + a_{22}^2) + (c_{21}^2 + c_{22}^2) + (e_{21}^2 + e_{22}^2)$). The covariance between both observations was 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 model is shown in Fig. 1.

The full longitudinal model was compared to a simplified and more parsimonious model. To examine whether *A*, *C* or *E* contributed significantly to the *covariance* between ages it was tested whether the path loadings of a_{21}, c_{21}, e_{21} could be omitted from the model. If a_{21} could be omitted this would mean that genes play no role in the stability of executive functioning between age 5 and age 12. If c_{21} or e_{21} would be non-significant this would mean that the

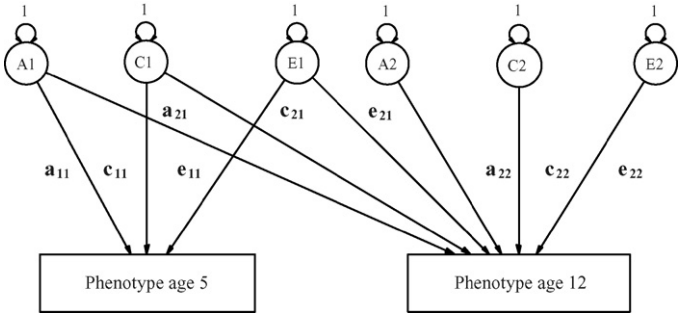

Fig. 1. Phenotype age 5 years: $P = (a_{11}A_1 + c_{11}C_1 + e_{11}E_1)$; $V_P = (a_{11}^2) + (c_{11}^2) + (e_{11}^2)$; h^2 age 5 years is $a_{11}^2/(a_{11}^2 + c_{11}^2 + e_{11}^2)$. Phenotype age 12 years: $P = (a_{21}A_1 + a_{22}A_2 + c_{21}C_1 + c_{22}C_2 + e_{21}E_1 + e_{22}E_2)$; $V_P = (a_{21}^2 + a_{22}^2) + (c_{21}^2 + c_{22}^2) + (e_{21}^2 + e_{22}^2)$; h^2 age 12 years is $(a_{21}^2 + a_{22}^2)/(a_{21}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{21}^2 + e_{22}^2)$. *Note*: *P*, phenotype; V_P, variance of the phenotype; h^2, heritability.

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 years (test and retest assessments)

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

common or unique environment plays no role in the stability of executive functioning. Leaving out the factors for A (i.e., A_1 and A_2), or for C (i.e., (C_1 and C_2) provided a test of whether genes or common environment contributed significantly to the total variance of the longitudinal model.

2. Results

2.1. Descriptives

Table 2a shows means and standard deviations for RT 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 years, and retest assessments at age 12 years.

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 years 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 ($r = 0.12$).

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

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

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.

2.3. 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. Table 5 shows the results of the subsequent tests that were performed for the longitudinal

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

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	−2log–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 (i.e., fix a_{21} to 0)	7388.42	1.48	1	0.22	−0.52
No covariation for C (i.e., fix c_{21} to 0)	7387.46	0.53	1	0.47	−1.47
No covariation for E (i.e., fix e_{21} to 0)	7388.14	1.21	1	0.27	−0.79
No covariation for A and C (i.e., fix a_{21}, c_{21} to 0)	7407.40	20.47	2	0.00	16.47
CE model (i.e., fix a_{11}, a_{21}, a_{22} to 0)	7391.28	4.35	3	0.23	−1.65
AE model (i.e., fix c_{11}, c_{21}, c_{22} to 0)	7391.90	4.97	3	0.17	−1.03
AE model, no covariance for E (1) (i.e., fix c_{11}, c_{21}, c_{22} and e_{21} to 0)	7393.26	1.98	1	0.16	−0.02
CE model, no covariance for E (2) (i.e., fix a_{11}, a_{21}, a_{22} and e_{21} to 0)	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
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

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. 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. The χ^2 (i.e., $-2(LL_0 - LL_1)$), degrees of freedom (df) and p-value reflect whether tested models fit well. A p-value < 0.01 indicates that a model fits significantly worse. A low AIC (i.e., $\chi^2 - (2 \times \text{d.f.})$) indicates a relative good fit of the model.

analyses. First it was tested for each variable whether the full ACE model described the data well by comparing it to the saturated model. As explained above, the χ^2, degrees of freedom (df) and related 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. For all variables the ACE model showed a good fit, therefore in the continuing analyses the full ACE model was used as the baseline model.

It was than 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., a_{21}, c_{21}, e_{21}). Genes (A) contributed significantly to the covariance of sustained attention while common (C) and unique (E) 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, so no clear distinction between the sources of variance was possible. For slope it was allowed to drop the covariance due to A and C simultaneously. The covariance due to E was non-significant for all variables, indicating that this source of variance was not transmitted over time.

As based on the previous tests no clear distinction between genetic or environmental contributions could be made it was tested whether more parsimonious models could describe the longitudinal data. This was done by omitting the total variance due to genetic factors (A) or common environmental factors (C). For all variables a full ACE model could be rejected in favor of a more parsimonious model. For working memory and sustained attention the common environment was non-significant, and a model with genetic and unique environmental factors was the best fitting one. For selective attention, slope and fluctuation a model that included common and unique environmental influences, or a model that included genetic and unique environmental influences was allowed.

It was then tested which reduced model was the best fitting one after omitting the covariance due to unique environmental influences, as this source of covariance was non-significant in the first series of tests. The best fitting model (based on p-value and AIC) for working memory, fluctuation, selective- and sustained attention included genetic and unique environmental factors and covariance due to genetic factors only. For slope, a model with genetic or common environmental influences (and unique environmental influences) fitted equally well.

Based on the estimates of the genetic covariance matrices the genetic correlations between the phenotypes at age 5 and age 12 years were computed. The genetic correlations provide a measure of the extent to which phenotypes are influenced by the same genes. The longitudinal 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.

2.4. Changing of genetic influences over time

To test whether the genetic influences that had an effect at age 5 years were equally important at age 12 years, the factor loading of the genetic variance at age 5 (a_{11}) was equated with the second factor loading (a_{21}). 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 years is due to deamplification (i.e., reduction) of genetic influences over time. In addition it was examined whether new genetic influences emerge at age 12 years by testing whether the factor loading of the second factor of the genetic variance at age 12 years (a_{22}) was different from zero. This was true for all variables, indicating that at age 12 years, besides the genetic effects that are transmitted over time, in addition new genetic influences come into play.

Table 6 shows the estimates of the factor loadings of the most parsimonious models, and includes the heritability estimates at both ages, and the longitudinal genetic correlations. The total genetic variance at age 12 years was higher than at age 5 years for all traits except for 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 years than at age 5 years, except for sustained attention and fluctuation in tempo. When including the retest assessments (at age 12 years) in the longitudinal analyses, the unique environmental variance at age 12 years consisted for about 33% of measurement error variance and for about 66% of 'true' unique environmental variance.

The relative genetic contribution to the variance (i.e., the heritability estimates) increased slightly over time. For

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 years which reflects the relative contribution of genetic influences, and the genetic correlation (r_g) between performance at age 5 and age 12 years, for processing speed of selective attention, working memory, and sustained attention, and for slope and fluctuation in tempo

Parameter estimates	a_{11}/c_{11}	a_{21}/c_{21}	a_{22}/c_{22}	e_{11}	e_{22}	h^2/c^2 age 5–12 years	r_g/r_c
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	16.38/13.67	1.69/2.27	6.27/6.07	25.95/27.52	7.64/7.78	0.28–0.42/0.20–0.41	0.26/0.35
Fluctuation	0.49	0.42	0.58	0.74	0.60	0.30/0.59	0.59

The total variance of the most parsimonious model as shown is the sum of $(a_{11}^2) + (a_{21}^2) + (a_{22}^2) + (e_{11}^2) + (e_{22}^2)$. In the most parsimonious model h^2 age 5 years is $a_{11}^2/(a_{11}^2 + e_{11}^2)$ and h^2 age 12 years is $(a_{21}^2 + a_{22}^2)/(a_{21}^2 + a_{22}^2 + e_{22}^2 + e_{21}^2)$. Genetic covariance is $(a_{11} \times a_{21})$. r_g (genetic correlation) is $a_{11} \times a_{21}/(\sqrt{a_{11}^2} \times \sqrt{a_{21}^2 + a_{22}^2})$. For slope the estimates for a model with genetic factors and a model with common environmental factors are shown, for the formulas then **c = a**.

selective attention this was 52% at age 5 years and 61% at age 12 years, of working memory 55% and 71%, and of sustained attention 59% and 63%, respectively. For slope this was 28% at age 5 years and 42% at age 12 years, and for fluctuation in tempo 30% and 59%, respectively.

3. Discussion

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 years. 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 suggested that the longitudinal stability of executive functioning is (partly) 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.

The longitudinal correlations between age 5 and age 12 years 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. 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 years, 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 years. Also between age 11 and 15 years 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 age 16 years were reported by Shaw et al. (2006), while Casey et al. (2000) showed that cognitive ability throughout childhood increases in concert with changes in the prefrontal brain.

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 and 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 5 years, at age 9 and 14 years. 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 years versus 7 years) their longitudinal correlations were similar (∼0.35) to the correlations found in Dutch twins. In this study 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.

Our findings suggested that the longitudinal covariance of executive functions was mediated by genetic factors. When examining the path loadings that represented the stability, it was not possible to distinguish between genetic or common environmental influences. Only for sustained attention the genetic covariance was significant. In the most parsimonious models however it appeared that common environmental factors had no significant contribution to the total variance (which includes the covariance), except for slope. Unique environmental factors played in none of the variables a significant role for the stability over time.

A few studies investigated the genetic stability of related cognitive constructs, like IQ, in children. 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 years. In the current study the genetic covariance was explained by the same genes having an effect at both ages, although at age 12 years 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. Also the transition from preschool to elementary school marks an important change in social and cognitive functioning which may 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 years 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 years 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 years 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 and De Geus, 2007). 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 unique environmental influences.

The substantial heritablity estimates of selective attention, working memory and sustained attention at age 5 and at age 12 years, and the suggestion that stability of these traits is mediated by genetic influences supports the use of these traits as endophenotypes for cognitive disorders like ADHD. Molecular genetic analyses of useful endophenotypes 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 (Castellanos and Tannock, 2002; Goldberg and Weinberger, 2004; Diamond et al., 2004). The results of the current study together hint at the importance of genes in neurocognitive developmental trajectories. A replication of the present results, in different age groups and in larger samples, and the investigation of possible sex differences might be the focus of in the nearby future, while the ultimate goal is the identification of the actual genes that influence typical *and* atypical cognitive developmental trajectories.

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