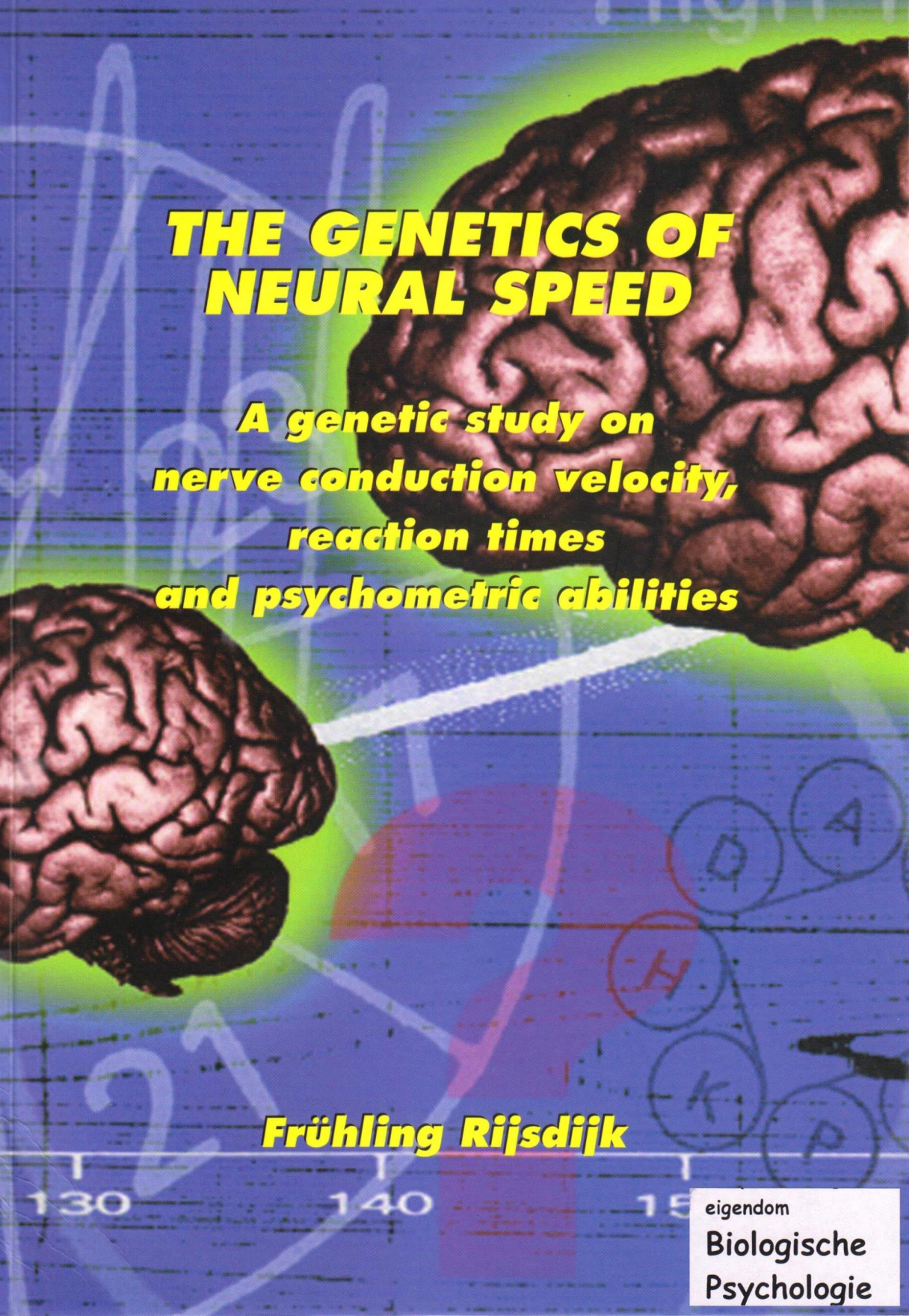
THE GENETICS OF NEURAL SPEED
A genetic study on nerve conduction velocity, reaction times and psychometric abilities
Frühling Rijsdijk
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Biologische Psychologie

The genetics of neural speed

A genetic study on nerve conduction velocity, reaction times and psychometric abilities

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The genetics of neural speed

A genetic study on nerve conduction velocity, reaction times and psychometric abilities

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door

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geboren te Paramaribo

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Inhoudsopgave

1

General introduction

For decades the structure of human mental abilities has been the main subject of discussion among psychologists. Contemporary theories of intelligence can be generalized in a hierarchical structure with general intellectual ability, Spearman's *g* at its apex, derivable from the relationships that exist among group (second order) factors and more specific abilities represented at a lower level of abstraction in the hierarchy (Gustafsson, 1988). However, information about underlying reasoning processes, measured by different tests, is not provided by such a taxonomy. Psychometric studies provide little insight into the causes of individual differences in performance on mental abilities (Brody, 1992). Understanding the nature of psychometric intelligence may benefit from knowledge of the underlying neurophysiological processes that contribute to this trait and to its variation. The search for biological determinants of individual differences in intelligence, has long been a subject of experimental psychology, and in the last 15 years many psychologists have developed theories of individual differences in intellectual processes based on experimental research (Brody, 1992; Deary & Stough, 1996).

One approach explores the association between psychometric intelligence and physiological measures. Several physiological variables have been studied as possible biological determinants of individual differences in intelligence. These include averaged brain evoked potentials, regional cerebral bloodflow, cortical glucose metabolic rate as measured by positron emission tomography (see for extensive reviews, Vernon, 1993) and peripheral nerve conduction velocity. Peripheral nerve conduction velocity (PNCV), reflects the speed with which electrical impulses are transmitted along nerve fibers and across synapses. This variable is related to the 'neural efficiency model of intelligence' (Vernon, 1993). In this model individual differences in performance on intelligence tests are attributed to differences in the speed and efficiency with which acquired neurophysiological processes are executed. The greater efficiency of the neural system of individuals with higher IQ might come to expression in the peripheral nerves as well, which makes individual differences in PNCV a promising measure for individual differences in intelligence. In two independent studies of Vernon and Mori

(1992), higher PNCV (measured in the median nerve of the arm) was associated with higher intelligence scores. Vernon and Mori concluded that a general factor of neural efficiency or neural speed is a major aspect and biological determinant of individual differences in psychometric intelligence.

A second approach to studies of individual differences in intellectual abilities is based on the ideas of Galton (1883). This approach relates general intelligence to relatively simple information-processing abilities. Indexes for these basic cognitive processes involve the speed of execution of simple tasks. Psychologists in these traditions share the theoretical assumptions that individual differences in intelligence are determined biologically, and may be influenced by genetic factors. These biological determinants influence the structure and function of the nervous system, and can indirectly be measured by experimental tasks that measure processing speed or accuracy. Individual differences in these basic parameters of information processing influence the complex intellectual skills assessed by intelligence tests (Brody, 1992). Speed-of-information-processing, as measured by Reaction Times on elementary cognitive tasks, can be considered a behavioral manifestation of 'neural efficiency' (Vernon, 1993) and the well established relation between speed of information processing and psychometric intelligence provides additional evidence for the neural efficiency model of intelligence.

Theories, claiming a biological basis for individual differences in intelligence, gain much evidence from the widely observed heritable influences on individual differences in cognitive psychometric abilities as indicated by twin, family and adoption data. If the observed phenotypic association between biological parameters and intelligence is highly determined by genetic rather than environmental factors this parameter may, to some extent, explain the heritable differences in intelligence. Decomposition of the observed (phenotypic) variance of a trait and decomposition of observed covariances between traits into a genetic and environmental component can be accomplished by quantitative genetic methods that require data from relatives such as twin data. Twins are commonly used in quantitative behavior genetic research to examine the contribution of genes and environment to inter-individual variability in traits. Analyses of twin data enables one to distinguish between three classes of influences: heritable influences which have their origin in DNA; environmental influences shared by individuals reared together (often parental and social in origin); and environmental influences which relate more to unique, individual experiences. With twin data the contributions of genetic and environmental influences to individual differences in behaviour can be revealed without intervention in actual genotype and environment. Heritability is an index for the relative contribution of genetic influences to individual

differences of a trait. Environmentality summarizes the relative contribution of environmental factors (Plomin, DeFries & McClearn, 1990).

This dissertation reports the results from a Dutch twin study on the relationship between peripheral nerve conduction velocity (PNCV), reaction times and intelligence. The thesis was inspired by the original findings of the Vernon and Mori (1992) studies, on the association between PNCV, IQ and Reaction Times in which it was concluded that a general factor of neural efficiency is a major aspect of individual differences in intelligence. The present study is the first to investigate to what extent the variation in psychometric intelligence can be attributed to variation in PNCV and Reaction Times and to what extent these variations and covariations are mediated by genetic and/or environmental factors. This is also the first study to investigate the genetic architecture of peripheral nerve conduction velocity in humans. Data were longitudinally collected in a sample of 213 adolescent twin pairs. The first test occasion was at age 16 and the second 1.5 years later.

Psychometric intelligence is the most widely studied trait in human behavior genetics and some genetic studies have examined the IQ-RT association. To summarize the evidence for heritable influences on IQ, the first section of this chapter is devoted to a review of genetic studies on adolescent and adult IQ (the group of interest in this study), followed by a section on the biological basis of individual differences in IQ and peripheral nerve conduction velocity as a potential biological determinant of intelligence. Because, up to now, no studies on the genetics of PNCV in humans were performed, this section also includes some information about the genetic determination of PNCV in animals. Next, a section is provided with a review of IQ-RT studies and studies investigating the genetic basis of this relationship. This is followed by a summary of the few (non-genetic) studies in which the relationship between PNCV, Reaction Times and Intelligence was simultaneously examined. In the final section the twin method and the uni- and multivariate genetic analyses techniques are outlined.

The genetic basis of individual differences in intelligence

Twin, family and adoption data of psychometric intelligence support the existence of genetic influences upon human cognitive abilities. Approximately 50%-60% of the phenotypic variance in adult IQ is associated with genetic differences among individuals. Bouchard and McGue (1981), have summarized the world literature on IQ correlations obtained in relatives between 1963 and 1980. The authors conclude that the pattern of parent-offspring and twin correlations and

the absence of consistent sex effects strongly suggests polygenic inheritance of intelligence. Average weighted correlations in identical or monozygotic (MZ) twin pairs (N = 4672) and fraternal or dizygotic (DZ) twin pairs (N = 5546) were estimated to be .86 and .60, respectively. By doubling the difference between MZ and DZ correlations a first impression is obtained of the heritability estimate of IQ (see for other reviews Plomin, 1988; Plomin & Rende, 1991; Boomsma, 1993; Bouchard, 1993).

Data on pairs of genetically identical individuals reared in uncorrelated environments directly estimate the contribution of heredity to behavioral variability. Bouchard *et al.* (1990) reported correlations of .78 on the Raven's Progressive Matrices, .69 for the WAIS and .78 for a vocabulary test in 56 reared apart identical or monozygotic (MZ) twins (mean age, 41 years). In contrast to studies in separated MZ twins not many studies have examined reared apart DZ twins. Because fraternal twins are genetically not more related than normal siblings, correlations of separated fraternal twins are a good indication for correlations between first-degree relatives. In a Swedish study of 34 pairs of separated fraternal twins (mean age, 59 years), correlations on three factors extracted from 12 cognitive tests implied substantial genetic influences (Pederson, McClearn, Plomin & Friberg, 1985). A correlation of .52 was observed for the first principal component, a measure of general intelligence.

The few studies on heritability in IQ in older twin pairs have not yielded a very different picture. Pedersen, Plomin and McClearn (1994) reported results of multivariate analysis using data on 13 cognitive ability tests from the Swedish Adoption/Twin Study of Aging (SATSA). The adoption/twin design included 46 pairs MZ reared apart, matched with 67 MZ pairs reared together; 100 DZ pairs reared apart and 89 DZ pairs reared together (mean age, 65.6 years). Pedersen *et al.* reported Specific genetic in addition to General genetic influences. Genetic influences accounted for 32 to 64% of the total variance in these tests.

Another adult IQ twin study of special cognitive abilities was conducted by Tambs, Sundet and Magnus (1986). Results of a multivariate analysis of the WAIS subtests in a Norwegian twin sample of 40 MZ and 40 DZ twin pairs (mean age, 41 years) were reported. The General genetic factor accounted for the predominant part (46%) of the total variance. When subdivided, the General genetic factor accounted for 60% of the Verbal subtests and 47% for the Perceptual Organisation subtests. Common environmental factors specific to each subtest were also shown to be significant and accounted for 11% of the total variance on average and were most pronounced for the Perceptual Organisation subtests.

The biological basis of individual differences in intelligence

The evidence, obtained from twin and family studies, of some genetic determination of individual differences in human cognitive ability is beyond any doubt. As genes code for biological differences, these findings give strong evidence for the existence of biological determinants responsible for individual differences in intelligence. This biological basis of intelligence is influenced by genes which code, via processes of protein synthesis, for neurophysiological and biochemical factors and processes in the brain, but can also be modified by environmental factors, such as education and nutrition.

Biological approaches to the study of human intelligence have attempted to explore the underlying neurophysiological factors and processes that contribute to variance in this trait (e.g. averaged brain evoked potentials, regional cerebral bloodflow, cortical glucose metabolic rate). Peripheral nerve conduction velocity has been investigated as a potential biological marker of intelligence. PNCV is a pure physiological measure involving no cognitive activity. Reed (1984) hypothesized that the heritability of IQ may be a result of genetic variability in the structure and amount of 'transmission proteins' which set limits on impulse speed in peripheral and central nerves and consequently on information processing rates and, thus, on intelligence. Transmission proteins include both enzymes involved in myelin sheathing and neurotransmitters (which are synthesised by specific enzymes). Genetic variability in the structure and amount of transmission proteins may determine information processing rates and neural efficiency. Reed (1988) suggested that PNCV as a quantitative genetic trait may model central nerve conduction velocity. PNCV is a relatively easy obtainable measure of nerve conduction speed.

Peripheral Nerve Conduction Velocity (PNCV)

PNCV is an extensively studied neurological trait in humans for diagnosing neuromuscular and neurological diseases (Desmedt, 1980; Oh, 1993). Three components of nerve action potentials are typically distinguished. Onset PNCV and peak PNCV measure the conduction speed in the fast-conducting (large diameter) nerve axons and the average-conducting (average diameter) nerve axons, respectively, while end PNCV involves slow-conducting (small diameter) axons (Ma & Liveson, 1983; Oh, 1993). Onset PNCV is commonly used in studies examining the relation between IQ and PNCV, because it reflects conduction of the fast nerve fibres. A high IQ is suggested to be a consequence of faster speed of information processing and, hence, of faster and more efficient central nervous functioning (e.g.

Vernon, 1993). Reed (1988) suggested that genetic variation in PNCV might account for heritable differences in IQ.

Untill recently, nothing was known about causes of variation in human PNCV. The genetic background of PNCV variation was first studied in mice by Hegmann *et al.* (1973), who observed low to median heritabilities in tail PNCV (narrow-sense heritabilities of .1 to .2; broad-sense heritabilities of .2 to .3) in inbred strains and their derived generations. Tail PNCV also correlated with certain behaviours like open-field activity and defecation (Hegmann, 1979). Reed (1983) reported a broad-sense heritability of .4 for tail PNCV in genetically heterogenous mice. Reed (1988) found a significant narrow-sense heritability in mouse tail PNCV of .23. He suggested that in large natural populations of mammals, including humans, the heritability of PNCV could be considerably greater because the genetic variability of randomly-bred laboratory mouse colonies derived from inbred strains is probably much less than that of natural populations. Body length in heterogenous strain mice, for example, has a heritability of .21 ± .05, which is much smaller than the heritability of around .8 in humans. According to Reed, a heritability of .5 or more for PNCV in humans may be a reasonable estimate. In this dissertation the first results on heritability of human PNCV are reported.

Reaction Times and intelligence

In the search for biological determinants of human intelligence, the relationship between measures of speed-of-information-processing (SIP) as obtained by timed performance on experimental cognitive tasks and intelligence test scores is the most extensively studied and well established. Galton (1883) was the first to propose that Reaction Times (RTs) might be used as an index for intelligence. Early investigators were not successful in proving RTs to be a correlate of intelligence and it was not until the 1960s that RTs were seriously considered in theories of intelligence. Thorndike (1927) formulated a model for the concept of intelligence in which *mental speed* was one of the most fundamental components in accounting for individual differences in intelligence. The other two components, *persistence* (the continuation of assumed fundamental search processes) and *error checking* were thought to be more related to personality. The importance of the mental speed components to individual differences in intelligence was an item that was picked up by for example Eysenck (1967) and Furneaux (1961). The early history of the research on the relation between RTs and intelligence is extensively reviewed in Vernon (1987). Based on research on simple and choice RTs in the 1970s, Jensen introduced the 'Hick Paradigm', in which RTs were examined as

a function of response uncertainty. Response uncertainty was determined by the number of 'bits' of decision making information processing (see Jensen, 1987). In the 1980s Vernon and co-workers regressed subjects' IQ scores on a battery of RT tests of varying complexity (Vernon, 1983; Vernon & Kantor 1986; Vernon, Nador & Kantor 1985). One of the important findings in these studies was that the relation between RT and IQ cannot be attributed to common content, nor by the fact that some parts of IQ tests are timed. Typically, Reaction Time tests do not require information and reasoning skills tapped by intelligence tests (Vernon, 1983). Vernon and Kantor (1986) also demonstrated that the Reaction Time variables actually explain less of the variance of a timed intelligence test than that of an untimed administration of the same test.

Reaction Times are suggested to measure basic cognitive operations which are involved in many forms of intellectual behavior. Individual differences in intelligence are suggested to be moderately attributable to variance in the speed or efficiency with which individuals can execute these cognitive operations. A theoretical explanation for this relationship was given by the 'neural efficiency model' (Jensen, 1982; Vernon, 1983, 1985) in terms of some characteristics of the Short Term Memory ('Working Memory') system (STM) in which the basic cognitive operations are carried out. These characteristics are: the limited capacity to store information, the rapid decay of information when there is no rehearsal and the trade-off between the amount of information that can be stored and processed simultaneously. Therefore, the speed or efficiency with which individuals can execute the cognitive operations in a given task might be expected to have an effect on the success of their performance of the task.

If individual differences in the speed with which cognitive operations can be executed is attributable to individual differences in intelligence, the next question is to what extent they are attributable to differences in neurophysiological properties of the brain that may be hypothesized to underlie both the speed with which persons can process information and performance on intelligence tests. One approach to this question is to examine the heritabilities of individual differences in reaction times and the extent to which the phenotypic correlation between intelligence tests and information processing tasks are determined by underlying genetic factors.

There is some evidence that performance on Reaction Time tasks is partly determined by genetic factors. Rose, Miller and Fulker (1981) reported a heritability of 76% for a Perceptual Speed measure in college-aged twins and genetic half-siblings (MZ twin offspring). More recently, Boomsma and Somsen (1991) measured RTs in a small twin sample of adolescent twins (age range, 15 - 18

years). For Choice RT low heritabilities were observed (7 to 20%). Heritabilities of almost 50% were observed for RT measured in double task trials where subjects simultaneously performed mental arithmetic and the Choice RT task. Vernon (1989) observed a heritability of 49% for a General Speed factor based on a battery of 8 information processing tasks. The heritabilities of the speed-of-information-processing measures were observed to be positively correlated with a General intelligence factor (*g*). No homogeneous pattern of genetic and environmental structures across the RT measures was observed in a younger twin sample, aged 6 to 13 years (Petrill, Thompson & Detterman, 1995). Measures on a Stimulus Discrimination task showed the highest heritabilities (42% on average) and their composite score also showed the highest correlation with IQ (r = .42). A Simple and Choice RT tasks were totally under environmental control.

Only a few studies have examined the genetic and environmental basis of the relationship between speed-of-information-processing tasks and IQ. McGue, Bouchard, Lykken and Feuer (1984) observed that an overall speed component, for which a heritability of 46% was estimated, showed a consistent pattern of significant correlations with a General cognitive ability factor (*g*). McGue and Bouchard (1989) estimated heritabilities of 54%, 58% and 27% for a Basic-, a Spatial Speed factor and an Acquisition factor in a sample of reared apart twin pairs (mean age, 39.9 years). General Speed was observed to be moderately related to general intelligence (*g*). A genetic analysis of the relation between the Vernon (1989) RT and IQ data conducted by Baker, Vernon and Ho (1991), showed that phenotypic correlations between Verbal and Performance IQ and a General speed-of-processing factor (heritability estimated to be 45%) were entirely mediated by genetic factors. The same pattern of results were obtained by Ho, Baker and Decker (1988) for a twin sample, aged 8 to 18 years. Heritabilities for a Rapid Automatic Naming and Symbol Processing factor were estimated as .52 and .49 and the phenotypic correlation between IQ and speed of processing measures was mainly due to genetic correlations. These findings all support the notion of some common biological mechanism underlying both general intelligence and speed-of-information-processing measures.

In contrast to these findings Petrill, Luo, Thompson and Detterman (1996) found little genetic covariance between RTs and IQ scores of the Petrill, Thompson and Detterman (1995) data. The genetic variance could be represented by a General, Verbal, Performance, and Speed factor, whereas common environmental influences could be supported by one General factor. Loadings of the speed measures and all IQ subtests on the General genetic factor were modest compared to their loadings on the General common environmental factor. These results

suggest that covariance of speed-of-information-processing with IQ in this sample is predominantly determined by common environment in this younger sample.

The phenotypic associations of peripheral nerve conduction, reaction times and intelligence

There are only a few (non-genetic) studies which have investigated the relationship between PNCV, Reaction Times and IQ measures simultaneously. In two independent studies, $N = 85$ (mean age, 24.5 years) and $N = 88$ (mean age, 23.1 years), of Canadian university students, Vernon and Mori (1992) measured Reaction Times, PNCV and IQ. A psychometric test battery, the MAB [Multidimensional Aptitude Battery (Jackson, 1984)], patterned after and highly correlated with the Wechsler Adult Intelligence Scale was administered. A battery of 12 RT tests was employed including: measures of Simple RT; measures of speed with which subjects can scan information in Short Term Memory and the extent to which subjects can store information in STM while simultaneously processing other kind of information; and measures of the speed with which subjects can retrieve information from Long Term Memory. In the first study eight PNCV measures were obtained in three segments of the median nerve of the arm (wrist-elbow, wrist-finger and elbow-axilla). In the second study PNCV measures were obtained from the wrist-finger segment only. In both studies first unrotated factor scores for each of the three sets of measures (IQ, RT and PNCV) were obtained, yielding a General IQ, General RT and General PNCV measure. Vernon and Mori reported correlations of .42 and .48 between General PNCV and General IQ for the first and second study, respectively. Correlations between General IQ and General RT were -.44 and -.45. The correlations between General PNCV and General RT were -.28 for the first, and -.18 for the second study. The authors concluded that a General factor of neural efficiency is a major aspect of psychometric IQ. However, these findings have not been replicated.

Barrett, Daum and Eysenck (1990) conducted a study in 44 British adults (mean age, 26.47 years) on the correlation between PNCV in the median nerve (finger-wrist segments), intelligence scores as measured by the Raven Advanced Progressive Matrices test (administered in a 20-minute period) and a Choice RT test using the Jensen test console. This is an apparatus consisting of a panel of 8 button lights in a semicircle, equidistant from a home button (Jensen, 1985). Barret *et al.* only reported results that replicated on a second test occasions. IQ correlated -.33 with the standard deviation of the movement time and -.25 with the decision time. No correlation was found between PNCV and IQ and PNCV and RT. An

important methodological difference with the Vernon and Mori (1992) study was stimulation of the nerve below supramaximal level. Supramaximal stimulation is stimulation at a current value beyond which no further increase in nerve action potential is observed, and thus ensures activation of all nerve fibers (fast and slow) of the nerve bundle.

Reed and Jensen (1991) also failed to find a relation between median peripheral nerve conduction velocity (wrist-elbow segment) and IQ in 88 community college and 112 university male Californian students (mean age, 20.3 years). The Raven Standard Progressive Matrices was administered to the community college group and the Advanced form to the university group (without a time limit). Also, speed-of-information-processing tests were employed using the Jensen test console: e.g. a Simple RT test and a Choice RT test. Several measures of PNCV were correlated with Simple and Choice RTs (correlations between -.21 and -.34). Correlations between IQ and RTs were not reported. An important methodological difference with the Vernon and Mori (1992) study concerned temperature control of the arm. Temperature control, the key confounder of PNCV, was conducted statistically rather then experimentally and might be a reason of the contradictory findings in this study.

Rather surprising were the results of the Wickett and Vernon (1994) study, who also failed to replicate the findings of the earlier two studies of Vernon and Mori (1992), administering the same IQ test, PNCV procedure and 4 RT tests to a smaller sample of 38 females (20 to 30 years of age). Two PNCV measure (wrist to finger and wrist to elbow) were obtained and a composite RT measure was calculated based on the *z*-scores of the individual reaction time tests. General intelligence was obtained by submitting the MAB subtests to factor analysis and computing factor scores on the first unrotated factor. PNCV did not correlate with either General IQ or composite RT score. General IQ correlated negatively, but not significantly, with the composite RT score (r = -.24). Based on these puzzling findings, a reanalysis of the Vernon and Mori (1992) data was conducted, which showed a lower PNCV-IQ correlation in females, although the difference was not significant. In the first study: r = .62 for males (N = 40) and r = .28 (n.s.) for females (N = 45); in the second study: r = .54 for males (N = 38) and r = .37 for females. From the consistent pattern of lower correlations in females, Wicket and Vernon suggested that males might rely more heavily on neuronal speed to perform cognitive tasks, whereas in females other neural processes might play a predominant role.

Quantitative behavior genetics and the twin methodology

Quantitative behavior genetics investigates the relative contribution of genetic and environmental influences to individual differences in traits (phenotypes). Phenotypes are considered to be the total effect of genes and environment. A polygenic model assumes that observed phenotypes are influenced by several different loci on one or more chromosomes. The additive genetic influence, *A*, represents the sum of the effects of alleles at all loci that influence the trait. Non-additive genetic influences concern interactions between alleles on the same locus (dominance, *D*) or on different loci, producing deviations from simple linear addition. Environmental factors contributing to phenotypic variance can be partitioned into: influences shared by family members, the common environment (*C*), e.g. socio-economic status, rearing; and influences that are unique for each individual (*E*), e.g. illnesses, accidents, differential parental treatment. The total phenotypic variance (V_P) of a trait is the sum of the additive genetic, dominance genetic, common environmental and unique environmental variance and can be denoted with the equation:

$$V_P = V_A + V_D + V_C + V_E \qquad (1)$$

To unravel these sources of variance, information from genetically informative subjects is essential. Twins are very useful for this purpose. Because identical or monozygotic (MZ) twins reared together are genetically identical, and share the same family environment, differences in traits and behavior can, theoretically, only be due to unique environmental factors. Resemblance between MZ twins on the other hand is an effect of both their common genetic constitution and their common environment. Because fraternal or dizygotic (DZ) twins, which are reared together, share 50% of their genetical material on average, like other siblings, the common environment contributes fully, but genetic factors only half to their resemblance. Unique environmental influences, do not contribute to twin resemblance.

Figure 1.1 depicts a path diagram of the usual twin model for both MZ and DZ twin pairs. The figure represents an extention of equation (1) to a decomposition of observed phenotypes for both members of a twin pair. This gives the usual model denoted by the equation:

$$P_1 = aA_1 + dD_1 + cC_1 + eE_1$$

$$P_2 = aA_2 + dD_2 + cC_2 + eE_2 \qquad (2)$$

where:
P is the observed trait or behavior (phenotype); *A* is the unobserved additive genetic factor; *D* is the unobserved dominance genetic factor; *C* is the unobserved shared environmental factor; *E* is the unobserved non-shared, unique environmental factor; *a*, *d*, *c*, and *e*, are the factor loadings from P on the unobserved (latent) factors, subscript 1 refers to the first twin, subscript 2 refers to the second twin. In MZ twins, the correlation between the twins for the additive genetic factors as well as the dominance genetic factors is unity. In DZ twins these correlations are 0.5 and 0.25, respectively. No interaction is assumed between the genetic and environmental factors within an individual.

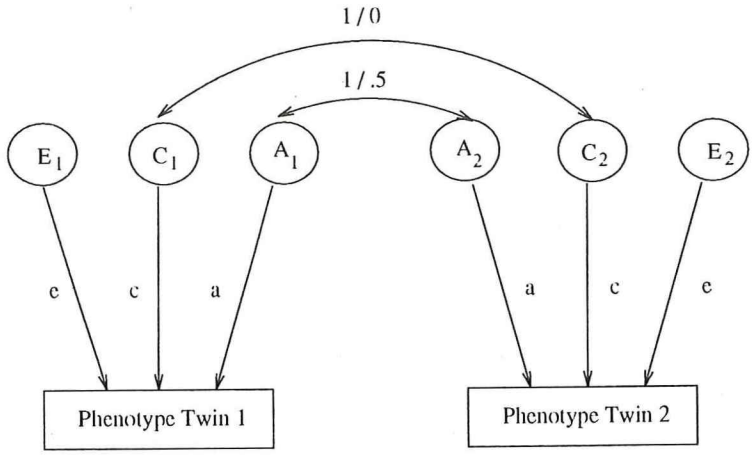

Figure 1.1 Path diagram of the quantitative genetic model. The sources of phenotypic variation considered in this example: *A*, the additive genetic component; *C*, de environmental influences shared by family members and *E* a random environmental deviation, unique to each family member. *a*, *c* and *e* are the path-coefficients representing the relative contributions of *A*, *C* and *E*, respectively. Correlations between A_1 and A_2 is 1 for MZ twins and .5 for DZ twins. The correlation between C_1 and C_2 is 1 when twins are reared together and 0 when not.

When latent factors are defined to have unit variance, a squared factor loading represents the variance explained by that specific factor ($V_A = a^2$, $V_D = d^2$, $V_C =$

c^2, $V_E = e^2$). The indices of relative contribution of genetic and environmental effects are regularly reported as a standardization in which the particular source of variance is divided by the total phenotypic variance. Heritability (h^2) is an index of the relative contribution of genetic influences to the phenotype and is calculated by dividing the genetic variance (V_A) by the total variance (V_P):
$h^2 = a^2 / a^2 + d^2 + c^2 + e^2$.

The effects of common environment and dominance genetic effects are confounded in twin studies and cannot be included simultaneously in one model. The twin correlation pattern can reveal which of the two effects is more likely. When the DZ twin correlation is less than half of the MZ correlation, dominance genetic influences are more likely, whereas common environment tends to make the DZ twin correlations greater than half the MZ correlations.

One of the assumptions in twin studies is that trait-relevant environments of MZ twin pairs are not more correlated than that of DZ twin pairs. The extent to which MZ wins are more alike than DZ twins, thus, reflects genetic influences. This equal environment assumption has received some criticism (e.g. Phillips, 1993) because shared environment might be more alike for MZ twins because they have experienced more similar environments as children (e.g. same dressing, same friends) and therefore greater similarity also reflects environmental influences. This issue can be explored by studying the effects of 'labeling' twins as identical or fraternal in misclasified groups. Performance on cognitive and personality tests showed to be little effected by labeling (Scarr & Carter-Saltzman, 1979). Another approach to address this issue is by investigating to what extent environmental differences make a difference behaviorally. Differences in environmental variables (like clothing, time spent togehther, parental treatment) did not correlate with differences in for instance cognition and personality (Loehlin & Nichols, 1976).

In the classical twin method (Falconer, 1989), heritability estimates were derived by doubling the differences between intraclass correlations for MZ twins and those for DZ twins [$h^2 = 2\ (r_{MZ} - r_{DZ})$]. This approach is not adequate for testing explicit models for individual differences and ignores information available in variances and covariances important for analyzing sex and generation differences. In the past years, this method was replaced by more advanced analysis techniques in which genetic covariance structure models are employed to special purpose software, in which data from a range of family grouping can be analyzed by means of maximum likelihood (ML) techniques. Software packages used for this modelling are LISREL (Jöreskog & Sörbom, 1986) and Mx (Neale, 1995). Some advantages were that assumptions could be made explicitly and could be tested, that parameters can be estimated with their standard errors or confidence

intervals and that the programs provide a chi-square test of the goodness-of-fit of the tested model. In genetic model fitting a series of structural equations are solved, which enables one to compare alternative models in order to estimate genetic and environmental parameters that best fit the observed (familial) twin covariations. Further, in genetic model fitting more than two groups of twins can be analyzed simultaneously, sex differences in parameter estimates and significance of parameters can be tested. Also, the univariate analysis can be extended to multivariate (multiple variables) designs (see *The Special Issue on Twin Methodology Using LISREL*, 1989; Neale & Cardon, 1992).

Multivariate genetic analyses

Multivariate genetic modelling is perhaps the most important development in behavior genetic research. In this dissertation multivariate genetic anlyses have been employed to explore the genetic and environmental components of covariation among Reaction Time variables, PNCV and IQ scores. Just as phenotypic factor analysis has been used to simplify the representation of the relationships among multiple variables, with multivariate genetic models the smallest number of genetic and environmental factors that satisfies the correlation structure can be identified. While most traits reflect both genetic and environmental influences, it is possible that associations among traits may result solely from common genes or common environment.

Outline of the thesis

Chapter 2 of this dissertation offers an introduction to the development of multivariate genetic model fitting in behavior genetic research. The advantages of structural equation modelling techniques as well as the powerful twin methodology are demonstrated by application of exploratory factor models on the phenotypic covariation among subtest scores of the Dutch translation (Stinissen *et al.*, 1970) of the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1955). This method provides more insight into individual differences in performance on the WAIS by decomposing the factor structure of the covariance of the WAIS subtests into genetic and environmental factors.

The next two chapters deal with the relationship between PNCV data and IQ measures. In chapter 3 the relation between PNCV and scores on the Raven Standard Progressive Matrices test (Raven, 1958), collected at the first test occasion, is examined. Also, the results of the first genetic study on human PNCV

are reported. Chapter 4 reports on the genetic analysis of the observed relation between PNCV and WAIS IQ scores of the data collected at the second test occasion (one and a half years later). Chapter 4 also discusses the possibility of ongoing maturation processes of PNCV, highly influenced by genetic factors, in the age interval between test occasion one (mean age, 16.1 years) and test occasion two (mean age, 17.5 years).

In chapter 5 results of multivariate analyses of reaction times and IQ measures of both test occasions are presented as well as bivariate longitudinal analyses of Reaction Times at two time points. The seventh chapter is an appendix which provides additional phenotypic correlations between Reaction Times and PNCV of test occasion I, between the WAIS subtests and PNCV and between WAIS IQ and Reaction Times of test occasion II.

Finally, chapter 8 provides an overall summary and discussion of the results and a new theory for the PNCV-IQ relationship is suggested.

2

Application of multivariate genetic models to Raven and WAIS subtests: A Dutch twin study

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ABSTRACT

An important development in behavior genetics has been the implementation of multivariate models to explore the causes of trait covariation. The association among traits may result from common genes or common environmental factors influencing multiple traits. In a multivariate genetic analysis of the relationships between multiple variables, genetical and environmental components of covariation can be separated with structural equation modelling techniques. In this paper Wechsler Adult Intelligence Scale (WAIS) subtest scores of 192 eighteen year-old Dutch twin pairs were analyzed with such multivariate genetic models. Results suggested the existence of common genetic variance for subtests loading on the Verbal and Performance scales in addition to the predominant general genetic variance for all subtests. Genetic variance not accounted for by these sources was unique to each subtest. Shared family background was not significant in explaining the environmental variance-covariance structure. Environmental effects, unique to an individual, could sufficiently be represented by one General factor and Specific factors for each subtest. Thus, the two typically observed phenotypic factors, Verbal and Performance scales, are entirely determined by underlying genetic influences. Covariance of the Raven with the WAIS subtests was solely accounted for by the General genetic factor.

Chapter 2

INTRODUCTION

Behavior genetic research has witnessed a tremendous development. Since the publication of the landmark paper by Jinks and Fulker (1970) on biometrical methods, one of the most important developments has been the extension of single trait analyses to multivariate designs. Just as phenotypic factor analysis has been used to simplify the representation of the relationships among multiple variables, multivariate genetic models have been employed to explore the genetic and environmental components of covariation and to identify the smallest number of genetic and environmental factors that explains a multivariate data structure.

One of the first multivariate extensions of genetic analysis was carried out on covariations of cognitive abilities (Loehlin & Vandenberg, 1968). Initially Vandenberg (1965) analyzed covariation matrices of twin-pair differences for latent roots in order to derive the number of independent hereditary components. Differences between members of identical twin pairs are due only to within-family environmental influences, whereas those between fraternal twins are due to genetic as well as within-family environmental influences. Vandenberg found four significant roots indicating at least four independent genetic dimensions. This method was formalized by applying an algebraic solution to obtain estimates of within-family genetic influences (Bock & Vandenberg, 1968). Loehlin and Vandenberg (1968) reported factor analyses of the covariance matrix of within-family genetic influences estimated by subtracting the within-pair identical twin covariance matrix from a corresponding fraternal twin covariance matrix. Resulting factor loadings were similar to those from the analysis of the within-pair identical twin correlation matrix, suggesting that the environmental and genetic components of cognitive abilities as measured by Thurstone's Primary Mental Abilities (PMA) test, have similar dimensions. These dimensions are manifested in the environmental covariation as a Verbal (educational) factor and in the genetic covariation as a General factor.

Eaves and Gale (1974) carried out a more detailed analysis of the genetic structure into additive and nonadditive components using the Loehlin and Vandenberg (1968) data on cognition. With a more appropriate manner of hypothesis testing they found evidence for both General and Specific genetic factors. The factor analytic formulation of genetical and environmental components of covariation by Loehlin and Vandenberg was further explored by Martin and Eaves (1977). Martin and Eaves provided a satisfacting general method based on Jöreskog's structural modelling approach (Jöreskog, 1973) to maximum likelihood estimation of confirmatory factor analytic models. They provided the framework for simulta-

neously fitting the genetic and the structural equation model to multivariate observations from relatives. Application of this method to the PMA data yielded a large, General genetic component but also at least three Specific genetic factors (verbal-, spatial- and word fluency abilities) and a General shared- and unique environmental source of variation. The genetic models of Martin and Eaves were, in a later stage, implemented in the software package LISREL (Jöreskog & Sörbom, 1986) by for example Fulker *et al.* (1983) and Boomsma *et al.* (1986). In the last decade multiple specifications were developed (e.g. *The Special Issue on twin methodology using LISREL*, 1989; Neale & Cardon, 1992). Recently, the structural equation modelling program Mx (Neale, 1995) was designed to meet specific demands of modelling genetical informative data.

There are many attractive features in exploring trait covariation rather than analyzing single measurements. While most traits reflect both genetic and environmental influences, it is very well possible that associations among traits may result solely from common genes or common environment. The aim of this paper is to demonstrate how multivariate genetic analyses of subtest scores of intelligence tests, in our case the Wechsler Adult Intelligence Scale (WAIS) and the Raven, can provide additional information about how individual differences are caused by genetic and environmental influences. Firstly, a review of phenotypic, but more important, of earlier genetic factor analytic studies of the WAIS and the Wechsler Intelligence Scale for Children (WISC) is supplied.

Phenotypic factor analytic studies of the WAIS and the WISC have revealed underlying factor patterns reflecting different cognitive constructs of intelligence. Behavioral genetic research has reported the relative genetic and environmental influences on the WAIS and WISC IQ scores, but the question to what extend the same genes and environmental factors are involved in the different factors comprised by typical subtest loadings, hence, in different aspects of intelligence, has not been frequently addressed.

One of the first phenotypic factor analyses of the WAIS subtest scores (Cohen, 1957), was conducted in four age groups ranging from 18-19 to 60-75 years of age, with large samples between 200 and 325 subjects per age group. In contrast of what has frequently been reported, four (instead of three) factors were robustly extracted across all age groups. Three of them became known as the *Cohen Factors*: the *Verbal Comprehension factor* (VC), the *Perceptual Organisation* (PO) factor and the *Memory* or *Freedom from Distractibility factor* (FD). The first factor, a General factor (G) was found to be operating in all age groups and accounted for almost 50% of the total variance. The factor structure : G, VC, PO and FD were consistent across age groups, but for age 60-75, G decreased in

favour of the Memory factor. The results observed for the youngest age group (18-19 year-olds) were: a General Structure (G); a Verbal Comprehension factor, defined by Information, Comprehension Similarity Vocabulary; a Perceptual Organisation factor, defined by Block Design, Object Assembly and Picture Arrangement and a Freedom from Distractibility factor, defined by Arithmetic and Digit Span. The factor analysis also yielded quasi-specific factors, factor D: loaded by Picture Completion, Similarity and factor E: loaded by Coding and Digit Span.

Phenotypic factor analyses of the Wechsler Intelligence Scale for Children-Revised (WISC-R) were performed by Kaufman (1975) in eleven age groups, ranging from 6.5 to 16.5 years of age, with 200 subjects for each age cohort. Principal component analysis yielded two significant factors closely resembling the Verbal scale and Performance scale at the first 6 age levels and three factors at age levels 8.5 to 15.5 years. The third factor was in agreement with Cohen's Freedom from Distractibility factor, with the highest loadings on Coding subtest at age 14.5. After rotation the three-factor solution was chosen as the most sensible for 9 of the age groups and the four-factor solutions were chosen for age 6.5 and 14.5. Kaufman (1975) concluded that there was great consistency in the three-factor structure: *Verbal Comprehension* (loaded by Information, Similarities, Vocabulary and Comprehension), *Perceptual Organisation* (loaded by Picture Arrangement, Picture Completion, Block Design and Object Assembly) and *Freedom from Distractibility* (Arithmetic, Digit Span and Coding) across the entire age range. These results provided support for Wechsler's subdivision of the test into Verbal and Performance scales and for his combination of the various verbal and nonverbal tests to obtain a Full-Scale IQ. No single factor was observed on which all subtests had loadings above a critical value, thus no general intelligence factor was identified.

The Wechsler intelligence scales have been analyzed in numerous other exploratory factor analytic studies in order to describe the components of measurable intelligence. Most of these studies analyzed data from the same standardization samples. Results of these studies are inconsistent. Intelligence as measured by the WAIS-R (Wechsler Adult Intelligence Scale-Revised) (Wechsler, 1970) in normal samples was noted to be a unitary trait (*g*-factor), or composed of two group factors VC and PO (Glass, 1982), or three group factors VC, PO and FD (Kaufman, 1975; Glass, 1982), or a composite of *g* and additional group factors: *g* and 2 factors (e.g. Blaha & Wallbrown, 1982; Silverstein, 1982; Gutkin, Reynolds & Galvin, 1984); *g* and 2, 3 and 4 factors (Parker, 1983) (see for reviews Matarazzo, 1972 and Leckliter, Matarazzo & Silverstein, 1986). Statistical methods that were most frequently applied for extracting the factor patterns were factor analyses with

orthogonal rotation (Silverstein, 1982; Gutkin *et al.*, 1984; Parker, 1983 and Glass (1982) with an oblique solution as superior to an orthogonal solution). For extracting *g* with factor analyses, different statistical techniques have been applied. The general factor was identified as: the loadings on the first unrotated principal factor (e.g. Silverstein, 1982; Parker, 1983) or principal component (e.g. Silverstein, 1982; Gutskin *et al.*, 1984), or on a primary level from a hierarchical factor solution (Blaha & Wallbrown, 1982).

The inconsistency of the number of factors that were extracted from the same data set in these factor analytic studies is basically due to the a priori restrictions that were placed upon the number of factors to be extracted, the criteria of specifying minimum eigenvalues and/or minimum residuals for factor extraction. To overcome these problems, some studies applied more or less objective statistical tests to ascertain the number of factors. For example, maximum likelihood confirmatory factor analysis was used, which permits objective evaluation of alternative models such as a different number of specified factors by means of goodness-of-fit indices. However, this method has also provided inconsistent results (e.g. one factor: O'Grady, 1983; two factors: Plake, Gutkin, Wise & Kroeten, 1987; three factors: Waller & Waldman, 1990 and Burton, Ryan, Paolo & Mittenberg, 1994 in an elderly sample). Evidently, ambiguities regarding the factor structure of the WAIS remains a fact even when the same normative sample was analyzed (O'Grady; Waller & Waldman). Waller and Waldman argued that these discrepancies may be explained by the fact that in the O'Grady study analyses were performed simultaneously across the nine cohorts of the WAIS-R (standardization sample and by the fact that a zero-correlation null model was used as baseline instead of a one-factor model.

In the present paper the advantages of structural equation modelling techniques as well as the powerful twin methodology are demonstrated. Multivariate genetic analyses of the subtest scores provide additional information about how the individual differences in WAIS IQ scores are composed by examining the factor structure of genetic and environmental covariances among the subtests. Genetic analyses of the WAIS-R and WISC-R subtests have been conducted in several ways. One way was to specify predefined theoretically Cohen factors and investigate the genetic and environmental influences on the subtests scores comprising these predefined factors.

Casto, DeFries and Fulker (1995), used a different approach on WISC-R data obtained from 574 twin pairs (7.7-16.6 years of age), pooled across control and reading-disabled subjects. Firstly, a confirmatory factor model was fitted by typically loading the subtests on the three Cohen factors and secondly, a factor

score was computed for each factor VC, PO and FD by summing the scaled scores of their component subtests. Genetic and environmental covariances among these three computed WISC-R factor scores were then assessed. A model which specified general genetic and general shared and non-shared (unique) environmental influences as well as genetic and environmental influences specific to the 3 factor scores, provided the best description of the data. Genetic variance accounted for approximately 50% of the phenotypic variance and phenotypic covariance among factors, with equal common and specific genetic influences. A similar pattern was observed for shared environmental influences. In contrast, specific factors accounted for most of the unique environmental variance.
A third approach is analyzing all subtests in a full multivariate design to explore the genetic and environmental correlations among the subtests and subsequently specifying and testing more parsimonious factor structures for the genetic and environmental effects. The few multivariate genetic studies of the WAIS and the WISC have used different approaches which hampers comparison.

The first full multivariate genetic analyses of the WAIS-R subtests was conducted by Tambs, Sundet and Magnus (1986), who explored the structure of genetic and environmental covariances among the WAIS subtest scores in a small Norwegian sample of 40 identical and 40 sex-like fraternal twin pairs (mean age, 41 years). Parameter estimates were reported for a model in which all subtests loaded on a general genetic and a shared and non-shared environmental factor as well as on specific genetic and environmental factors. A model testing the variance common to the subtests typically loading on the same phenotypical Cohen factors (Cohen, 1957) improved the fit. The major part of the covariance between subtests was due to common genetic effects. The FD factor seemed to be influenced by specific genes wile the other two factors were not. Shared environmental influences were predominantly common and modest for all subtests but Digit Span and the PO factor.

There have been two other studies in which subtest scores of the WISC-R have been analyzed with multivariate genetic techniques to explore the genetic and environmental correlations and differential genetic and environmental covariance structures among the subtests. LaBuda, DeFries and Fulker (1987) reported multivariate WISC-R results of data pooled across a reading-disabled twin sample (70 pairs) and a control twin sample (73 pairs), with an age range of 7.7 to 16.6 years. A model hypothesizing a three-factor structure for the genetic covariance matrix (with loadings constrained to the typical observed phenotypic Kaufman factor structure) with specifics; a single factor for the common environmental matrix with specifics; and a single factor plus specifics for the unique environmental matrix

best fitted the data. They concluded that the three-factor phenotypic structure typically observed in the WISC data (VC, PO and FD) may be due largely to genetic influences.

In the present study WAIS subtests scores were analyzed for 194 twin pairs with a multivariate genetic factor model in order to explore the genetic and environmental factor structure underlying the observed phenotypic covariance structure. In order to compare our results with earlier findings, models with a factor loading pattern that conformed to the Cohen factor structure as in the Tambs *et al.* (1986) and LaBuda *et al.* (1987) study were tested as well. The Raven Standard Progressive Matrices test scores, also available for our twin sample (Rijsdijk, Boomsma & Vernon, 1995) were included as a subtest in the best fitting factor model to explore the nature of the covariance structure with the WAIS subtests. The Raven (Raven, 1958) is a nonverbal test of reasoning, supposed to be a good measure of *g*, and to have only negligible loadings on any other factors.

SUBJECTS AND METHODS

Subjects were 192 Dutch twin pairs who participated in a longitudinal project which investigated variation in peripheral nerve conduction velocity and intelligence (Rijsdijk *et al.*, 1995) and genetic and environmental influences on brain development (Van Beijsterveldt *et al.*, 1995, 1996). The Raven Standard Progressive Matrices test scores were obtained at the first visit of the twins to the laboratory (mean age, 16.13; SD, .56). The Raven score was simply the number of correct answers (without a time limit). The Dutch version of the Wechsler Intelligence Scale (Wechsler, 1955) was individually administered (Stinissen *et al.*, 1970) on the second visit, 1.5 years later (mean age, 17.6; SD, .54). Mean age was equal for males and females. IQ data were available for 37 monozygotic (identical) male twin pairs (MZM), 31 dizygotic (fraternal) male twin pairs (DZM), 46 monozygotic female twin pairs (MZF), 36 dizygotic female twin pairs (DZF) and 44 dizygotic opposite sex twin pairs (DOS).

For 117 same-sex twin pairs zygosity was determined by bloodgroup and DNA typing and for the others by using items from a questionnaire concerning physical similarity and the frequency by which the twins get 74 confused by family members and strangers. For the blood and DNA typed group questionnaire data were available for 85 pairs. The percentage correctly classified zygosities based on the questionnaire information compared with blood group polymorphisms and DNA was 95%.

STATISTICAL ANALYSES

Phenotypic analyses

Sex differences in means for the WAIS subtest scores, Verbal, Performance, Full-Scale IQ and the Raven score were assessed by likelihood-ratio chi-square (χ^2) tests using the computer program Mx (Neale, 1995). These tests compare the fit of a model that constrained parameter estimates for mean scores to be equal across sexes to one which allowed them to vary in males and females, while taking into account the dependency that exists between observations from twins (Boomsma *et al.*, 1993). The difference between the χ^2 of a general model (M1) and that of a submodel (M2) ($\Delta\chi^2$) is itself a χ^2 with Δdf (degrees of freedom) ($\Delta\chi^2 = \chi^2_{M2} - \chi^2_{M1}$, with $\Delta df = df_{M2} - df_{M1}$).

Sex differences in phenotypic correlations among the WAIS subtests and the Raven were also analyzed in Mx. To the variance-covariance matrices of males and females a model was fitted in which maximum-likelihood correlations as well as the standard deviations were obtained. Firstly, the standard deviations were tested for sex differences by comparing the fit of models which constrained standard deviations to be equal across groups with models in which they are allowed to vary. With the same strategy correlations were tested for sex differences in the next step. Significance of correlations was tested by evaluating the significance of χ^2 changes of models in which correlations were constrained at zero.

Confirmatory phenotypic factor analysis was conducted on the variance-covariance matrix of the whole sample by model fitting in Mx as well. Models were fitted in which the phenotypic variance and covariance was accounted for by a specified number of group factors and also by specific factors, accounting for the variance unique to each subtest. In contrast with exploratory factor analyses, the number of factors as well as the factor loading pattern of the subtests can be specified with structural equation modelling. Significance of alternative phenotypic factor models can be compared by changes in χ^2.

Univariate genetic analyses

Decomposition of the phenotypic variance of all IQ variables was carried out by univariate genetic model fitting on variance-covariance matrices from the 5 sex-by-zygosity groups. The basic quantitative genetic model that was employed can be represented by a path model as shown in Figure 2.1, in which:

$$P_1 = aA_1 + cC_1 + eE_1$$

$$P_2 = aA_2 + cC_2 + eE_2$$

where P_1 is the phenotype of the first twin and P_2 of the second twin.

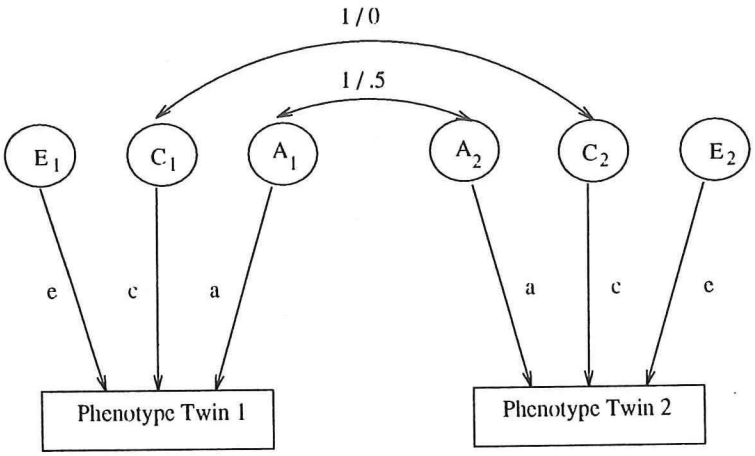

Figure 2.1 Path diagram of the quantitative genetic model. The sources of phenotypic varation: *A*, the additive genetic component; *C*, de environmental influences shared by family members and *E*, a random environmental deviation, unique to each family member. *a*, *c* and *e* are the path-coefficients representing the relative contributions of *A*, *C* and *E*, respectively. The correlation between A_1 and A_2 is 1 for MZ twins and .5 for DZ twins. The correlation between C_1 and C_2 is 1 when twins are reared together and 0 when reared apart.

Sources of phenotypic variation considered were *A*, additive genetic variation (i.e. the sum of the average effects of the individual alleles at all loci); *C* (common or shared environmental variation) and *E*, a random environmental deviation that is not shared by family members. The correlation between the genetic components (A_1 and A_2) is 1 for monozygotic twins because of their identical genetic makeup and .5 for dizygotic twins because they share 50% of their genes on average. The correlation between the shared environmental components (C_1 and C_2) is 1 if the twins are reared together (in our case) and 0 when not. The parameter estimates of the model: *a*, *c* and *e* are path-coefficients that represent the relative

contributions of the genetic, shared (between-family) and non-shared (within-family) factors, respectively. If *A*, *C* and *E* are standardized to have unit variance, the total phenotypic variance (V_P) is given by the sum of the squared path-coefficients:

$$V_P = a^2 + c^2 + e^2$$

The relative contributions of the genetic factors is called the heritability (h^2):

$$h^2 = a^2 / V_P.$$

Parameters were estimated by maximum likelihood, using the Structural Equation Modelling program Mx. Also, 80% Confidence Intervals for these heritability estimates were computed (Neale & Miller, 1996). Goodness-of-fit was assessed by likelihood-ratio χ^2 tests, alternative nested models were evaluated by changes in χ^2. All WAIS subtests scores, Verbal, Performance, Full-Scale WAIS IQ and the Raven score were tested for sex differences in genetic architecture. Because no sex differences were observed, the groups were pooled across sexes and between and within mean cross-product matrices for MZ and DZ were used for conducting multivariate genetic analyses.

Multivariate genetic analyses

In multivariate genetic analyses phenotypic covariances among subtests are decomposed into a genetic, common and unique environmental part. Multivariate analyses were conducted on the phenotypic mean-squares-between pairs (MS_B) and mean-squares-within pairs (MS_W) ($v \times v$) covariance matrices (v = number of variables). These matrices can be estimated by, for example, MANOVA. This method is not frequently used any more because of the limitations in testing for sex differences. The advantage of this method, however, is the input of much smaller matrices, which becomes of great importance when a large number of variables are tested multivariately.

The MS_W estimates the within-pairs covariance (σ_W^2). The expectation for MS_B is twice the between-pairs variance plus the within-pairs variance ($2\sigma_B^2 + \sigma_W^2$). Expected mean-squares-between and mean-squares-within pairs for MZ twin pairs and DZ twin pairs can be translated into relative magnitudes of variance for genetic and environmental influences that effect the phenotypic covariance.

As MZ twins are genetically identical, genetic variance does not contribute to phenotypic differences between members of a MZ twin pair. The MZ within-pair variance, thus reflects only unique environmental differences ($\sigma_W^2 = \mathbf{E}$). Variance components that cause differences between MZ twin pairs (and make members of one twin pair more alike) are the genetic and common environmental influences ($\sigma_B^2 = \mathbf{A} + \mathbf{C}$).
As DZ twins share half of there genes on average, DZ within-pair covariances not only reflect differences in unique environment but differences caused by a different genotype as well ($\sigma_W^2 = .5\ \mathbf{A} + \mathbf{E}$). Variance components that cause differences between DZ twin pairs are also the additive genetic and common environmental influences ($\sigma_B^2 = .5\ \mathbf{A} + \mathbf{C}$). Writing out the formulae for the expected MS_W (= σ_W^2) and MS_B (= $2\sigma_B^2 + \sigma_W^2$) for MZs and DZs based on the expected variance components leads to the following specification:

$$\Sigma MS_{MZB} = 2(\mathbf{A} + \mathbf{C}) + \mathbf{E} + 2(\mathbf{A}_s + \mathbf{C}_s) + \mathbf{E}_s \quad (1)$$

$$\Sigma MS_{MZW} = \mathbf{E} + \mathbf{E}_s \quad (2)$$

$$\Sigma MS_{DZB} = 1.5\mathbf{A} + 2\mathbf{C} + \mathbf{E} + 1.5(\mathbf{A}_s) + 2(\mathbf{C}_s) + \mathbf{E}_s \quad (3)$$

$$\Sigma MS_{DZW} = .5\mathbf{A} + \mathbf{E} + .5(\mathbf{A}_s) + \mathbf{E}_s \quad (4)$$

Notice that the expected variance components of Specific **A**, **C** and **E** factors are also included in the equations, according to the same previously outlined principals.

Multivariate genetic analyses was conducted by applying the model:

$$\Sigma_{YY} = \Lambda_Y\ \Psi\ \Lambda'_Y$$

simultaneously to the MZ and DZ between and within mean square matrices, where Σ_{YY} is the observed ($v \times v$) mean square matrix. Λ_Y is comprised of the matrices **A**, **C**, and **E** common to all subtests and $\mathbf{A}_S$, $\mathbf{C}_S$, and $\mathbf{E}_S$ ($v \times v$) diagonal matrices specific to each subtest. The weighting of **A**, **C**, **E**, $\mathbf{A}_S$, $\mathbf{C}_S$, and $\mathbf{E}_S$ by the coefficients specified in equations (1) through (4) is accomplished in the diagonal ($v \times v$) matrix Ψ (Psi). The dimensions of **A**, **C**, and **E** depend on the specified model.

Initially, a full Cholesky (or triangular) decomposition was imposed upon the between and within mean cross-product matrices to provide a starting point in the multivariate analyses of the eleven subtests. In a Cholesky decomposition the number of factors equals the number of variables. The first factor influences all variables (11 subtests). The second factor does not contribute to the first variable but effects the subsequent (10) variables, and so on. The last factor is specific to the last variable.

The genetic and environmental correlation matrices obtained from this analysis were evaluated to specify more parsimonious, alternative models in which the complexity of the genetic and environmental covariance structures were reduced by a limited number of factors. In this case the dimensions of the common **A**, **C** and **E** matrices in Λ_Y are changed to $(v \times f)$ and their relative weight in Ψ to $(f \times f)$, where f is the number of common factors. The dimensions of $\mathbf{A}_S$, $\mathbf{C}_S$, and $\mathbf{E}_S$ are not changed. A three-factor structure was imposed upon **A** and **E**. In the following steps the change in fit was assessed from the three-factor structure to a two-factor structure and to even more restricted factor models for components **A** and **E** individually. Also, factor models reported by Casto *et al.* (1995), LaBuda *et al.* (1987) and Tambs *et al.* (1986) were examined. In the final analysis the Raven test score was included as a subtest in the best fitting model to explore the common variance with the WAIS subtests.

RESULTS

Phenotypic analyses

For subtest mean scores, sex differences were observed for: Arithmetic and Picture Completion, for which males had a significant higher score than females (6.98 versus 6.51 and 6.38 versus 5.95, respectively); and for Coding for which females had a significant higher score than males (6.78 versus 7.72). However, these sex differences were small and did not weigh heavily on the total subtest scores which is reflected in the equality of means across sexes for the Verbal, Performance and Full-Scale IQ scores (VIQ, PIQ and FSIQ) (Table 2.1).

Table 2.1
Male and female estimates of means and standard deviations for the WAIS subtests, WAIS scales and the Raven test score.

	Males (N = 180)		Females (N = 208)		Sex differences
Subtests	M	(SD)	M	(SD)	$\Delta\chi^2(1)$
INF	6.09	(1.32)	5.84	(1.48)	2.51
COM	5.94	(1.67)	5.90	(1.66)	0.17
ARI	6.98	(1.90)	6.51	(1.84)	4.15*
SIM	7.07	(1.92)	7.29	(1.67)	0.56
DS	6.21	(1.87)	6.35	(1.53)	1.23
VOC	5.87	(1.65)	6.08	(1.64)	1.14
CODE	6.78	(1.84)	7.62	(1.61)	19.2*
PC	6.38	(1.68)	5.95	(1.78)	5.22*
BLO	7.24	(1.91)	7.42	(1.96)	0.14
PA	7.02	(2.01)	7.01	(1.89)	0.02
OA	6.46	(1.96)	6.64	(1.81)	0.44
VIQ	109.9	(12.7)	109.6	(11.6)	0.06
PIQ	115.7	(11.9)	117.1	(11.9)	0.87
FSIQ	113.5	(11.8)	114.0	(11.7)	0.07
Raven	4.95	(0.64)	4.94	(0.56)	0.08

Subtests: INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Span, VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. VIQ = Verbal IQ, PIQ = Performance IQ, FSIQ = Full-Scale IQ. Raven = number of correct items devided by 10. N = number of individuals. * = $\Delta\chi^2(1) > 3.84$, and implies a significant difference for 1 degree of freedom.

The mean WAIS Full-Scale IQ of 113.8 was higher and the standard deviation of 11.7 was lower than the population mean and standard deviation (M = 100; SD = 15). In a recent validation study (N = 601) of 4 subtests of the Dutch translation of the WAIS (Mulder *et al.*, 1995) it appeared that scores on all 4 tests were higher than the scores of the Dutch normative sample (Stinissen *et al.*, 1970). Bouma *et al.* (1996) suggested that this observation might be a consequence of increasing population IQ and that WAIS IQ scores based on the 1970 norms might, in fact, be somewhat overestimated.

For standard deviations of the subtests Similarity and Digit Span, higher values were observed for males (1.87 versus 1.67 and 1.82 versus 1.56, respectively). Maximum-likelihood estimates of phenotypic correlations among subtests are shown in Table 2.2.

Table 2.2
Maximum-likelihood estimates of phenotypic correlations among WAIS subtests and the Raven test score.

	INF	COM	ARI	SIM	DS	VOC	CODE	PC	BLO	PA	OA	Raven
INF	-											
COM	.55	-										
ARI	.52	.48	-									
SIM	.55	.59	.53	-								
DS	.39	.34	.46	.38	-							
VOC	.67	.66	.56	.67	.43	-						
CODE	.21	.16	.26	.14	.29[a]	.21	-					
PC	.30	.39	.30	.31	.20	.34	.22	-				
BLK	.35	.31	.47	.36	.29	.34	.19	.30	-			
PA	.28	.36	.29	.33	.21	.32	.08[ns]	.33	.32	-		
OA	.20	.25	.25	.25	.08[ns]	.21	.07[ns]	.28	.49	.26	-	
Raven	.49	.47	.51	.47	.38	.51	.25	.31	.40	.32	.25	-

Subtests: INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Span, VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. Number of individuals = 388. Mean correlation between subtests comprising the Verbal scale = .52, Mean correlation between subtests comprising the Performance scale = .25, Mean correlation between subtests from different scales = .27. [ns] = nonsignificant correlation. [a] = sex differences in correlation: .29 for males and .07 [ns] for females.

Sex differences were only observed for the correlation between Coding and Digit Span: .29 for males and .07 for females (ns). The mean correlation between subtests comprising different scales was .27 for males and .27 for females. Correlations between subtests loading on the Verbal scale and Performance scale averaged .52 and .25, respectively. The coherence of the Performance scale subtests was relatively weak, weaker than the relation among the subtests from different scales. The phenotypic correlation of the Raven score with the Verbal and Performance scale WAIS subtests was on average .47 and .30, respectively and with VIQ, PIQ and Full-Scale IQ .63, .51 and .66, respectively. Vernon (1983) reported correlations of .36 and .46 on average for the Raven with Verbal and Performance subtests, respectively and .57, .70 and .72 with VIQ, PIQ and FSIQ, respectively. In contrast with our results, the Raven test shared more variance with the performance scale.

For the phenotypic factor analysis of the WAIS subtests a model with three factors: a General factor (influencing all subtests), a Verbal factor (Information, Comprehension, Similarities, Vocabulary), a Performance factor (Picture

Completion, Block Design, Picture Arrangement, Object Assembly) and Specific factors accounting for the unique phenotypic variance for each subtest had the best fit to the data ($\chi^2_{36} = 56.37$, $p = .017$). The General factor accounted for 34% of the phenotypic variance, the second factor for 18% and the third for 22%. The subtests Arithmetic, Digit Span had insignificant loadings on the Verbal factor and Coding on the Performance factor, thus, their variance was totally explained by the General factor and by Specific subtests variance. For the subtest Coding, the variance accounted for by the General factor was, though significant, very low (9%).

Table 2.3
Twin correlations for the WAIS subtests, WAIS scales and the Raven test score.

	Sex-by-zygosity groups					Pooled groups	
Subtests	MZM (*N*=37)	DZM (*N*=31)	MZF (*N*=46)	DZF (*N*=36)	DOS (*N*=44)	MZ (*N*=83)	DZ (*N*=111)
INF	.73	.43	.80	.52	.23	.76	.36
COM	.66	.17	.73	.33	.32	.70	.27
ARI	.63	.20	.64	.45	.18	.64	.27
SIM	.72	.11	.58	.04	.22	.66	.16
DS	.65	.36	.46	.00	.37	.58	.26
VOC	.82	.16	.77	.27	.27	.79	.25
CODE	.39	.30	.47	.11	.30	.44	.29
PC	.25	.32	.28	.05	.35	.28	.24
BLK	.70	.25	.65	.57	.44	.67	.44
PA	.43	.26	.51	.11	-.11	.46	.05
OA	.69	.46	.33	.40	.21	.50	.36
VIQ	.87	.31	.87	.26	.25	.89	.27
PIQ	.74	.23	.67	.47	.26	.70	.34
FSIQ	.86	.19	.84	.44	.24	.85	.30
RAVEN	.77	.24	.50	.35	.42	.66	.39

Subtests: INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Span, VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. VIQ = Verbal IQ, PIQ = Performal IQ, FSIQ = Full-Scale IQ. *N* = number of twin pairs.

Univariate genetic analyses

The twin correlations for subtest scores, VIQ, PIQ, FSIQ and Raven scores for the 5 sex-by-zygosity as well as for the MZ and DZ group are given in Table

2.3. Univariate genetic analyses showed an *AE* no-sex-differences model to be the best for the IQ scores and for all but three subtests scores (Table 2.4). For the subtests Coding, Picture Completion and Object Assembly there was no difference in fit between an *AE* or *CE* no-sex-differences model (c^2 = 32%, 25% and 42%, respectively). Because of the consistency in absence of sex differences the 5 groups were pooled over sexes.

Tabel 2.4
Model fit indices for the univariate analyses of the WAIS subtests, WAIS scales and the Raven, fitted to the 5 different sex-by-zygosity covariance matrices.

	*ADE*sd Model df = 9		*ACE*sd Model df = 9		*ACE*nsd Model df = 12		*AE*nsd Model df = 13		*CE*nsd Model df = 13		Variance Components		h^2
Sub-tests	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*	*A*	*E*	
INF	12.55	.18	11.10	.27	16.82	.16	16.82*	.21	37.69	.00	1.502	0.491	75%
COM	15.30	.08	15.34	.08	15.70	.21	15.7*	.27	26.92	.01	0.775	0.970	65%
ARI	6.39	.70	6.34	.71	9.32	.68	9.32*	.75	21.39	.07	2.195	1.313	63%
SIM	7.76	.56	9.85	.36	14.68	.26	14.67*	.33	28.06	.01	1.813	1.319	58%
DS	13.30	.15	13.48	.14	20.43	.06	20.43*	.09	27.85	.01	1.606	1.284	56%
VOC	6.07	.73	7.84	.55	8.30	.76	8.30*	.82	34.76	.00	2.005	0.681	75%
CODE	6.80	.66	6.72	.67	11.38	.50	11.40	.58	14.14	.36	1.344	1.658	45%
PC	6.53	.07	5.03	.83	6.06	.91	7.05	.90	6.14	.94	0.960	2.026	32%
BLK	5.94	.75	2.68	.98	4.64	.97	6.02*	.95	11.50	.57	2.482	1.180	68%
PA	2.89	.97	3.69	.93	8.42	.75	8.42*	.82	14.61	.33	1.471	2.232	40%
OA	9.88	.36	6.99	.64	12.54	.40	14.46	.34	13.37	.42	1.751	1.745	50%
VIQ	7.84	.55	9.58	.39	11.19	.51	11.19*	.61	55.08	.00	122.4	23.93	84%
PIQ	2.84	.97	2.33	.99	3.84	.99	3.84*	.99	17.87	.16	93.65	43.60	68%
FSIQ	6.37	.70	7.70	.57	9.13	.69	9.13*	.76	47.80	.00	110.7	24.23	82%
Raven	26.48	.00	24.22	.00	30.20	.00	31.53*	.00	34.33	.00	0.207	0.127	62%

Subtests: INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Span, VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. VIQ = Verbal IQ, PIQ = Performal IQ, FSIQ = Full-Scale IQ. * = Best Fitting Model. For CODE, PC and OA the Additive genetic as well as the common environmental structure could be omitted from the *ACE* model without deterioration of fit; the AE and CE model fitted equally well: c^2 was 32%, 25% and 42%, respectively. (n)sd = (no-)sex-diferences. h^2 = heritability estimate.

In Table 2.5 subsequent univariate genetic analyses results for the MZ and DZ groups are shown: an *AE* model best fitted the data, but again, no difference in

fit between an *AE* and *CE* model for Coding, Picture Completion and Object Assembly was observed (c^2 = 34%, 26% and 42%, respectively). Also, the heritability estimates were in close agreement with estimates for the first analyses. The univariate estimates of heritability for the Verbal scale subtests show the additive genetic factor to account for 58%-76% of the phenotypic variance (66% on average). Subtests of the Performance scale exhibit a lower heritability on average (47%) if Coding, Picture Completion and Object Assembly are regarded as to be influenced by additive genetic rather than common environmental factors. The lowest heritabilities were observed for Picture Completion and Picture Arrangement (33% and 39%, respectively). Analyses of VIQ, PIQ and FSIQ yielded heritabilities of 84%, 69% and 82%, respectively (Table 2.5).

Table 2.5
Model fit indices of univariate analyses of the WAIS subtests, WAIS scales and the Raven fitted to pooled MZ and DZ covariance matrices.

	ADE Model df = 3		*ACE* Model df = 3		*AE* Model df = 4		*CE* Model df = 4		Variance Components		h^2
Sub-tests	χ^2	*p*	χ^2	*p*	χ^2	*p*	χ^2	*p*	*A*	*E*	
INF	9.14	.03	9.19	.03	9.19*	.06	30.61	.00	1.502	0.496	75%
COM	7.96	.05	7.99	.05	7.99*	.09	19.59	.00	1.747	0.968	64%
ARI	1.57	.67	1.86	.60	1.86*	.76	13.74	.01	2.203	1.321	63%
SIM	6.60	.09	8.28	.04	8.28*	.08	21.70	.00	1.870	1.296	56%
DS	0.51	.92	0.59	.89	0.59*	.96	8.18	.09	1.615	1.272	59%
VOC	2.81	.42	3.99	.26	3.99*	.41	30.16	.00	2.008	0.678	75%
CODE	2.59	.46	2.43	.49	2.59	.63	5.11	.28	1.520	1.628	48%
PC	14.71	.00	1.19	.76	2.06	.73	1.34	.86	0.997	2.019	33%
BLK	2.23	.53	0.44	.93	2.23*	.69	7.03	.13	2.506	1.167	68%
PA	1.75	.63	3.96	.27	3.96*	.41	10.16	.04	1.457	2.305	39%
OA	3.76	.29	1.48	.69	3.76	.44	2.20	.70	1.771	1.729	51%
VIQ	4.86	.18	6.43	.09	6.43*	.17	50.97	.00	121.44	23.68	84%
PIQ	.61	.89	0.61	.90	0.61*	.96	13.65	.01	95.38	43.37	69%
FSIQ	2.64	.45	3.54	.32	3.54*	.47	42.14	.00	110.96	24.12	82%
Raven	5.41	.14	3.65	.30	5.41*	.25	7.60	.11	.211	.125	63%

Subtests: INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Span,VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. VIQ = Verbal IQ, PIQ = Performal IQ, FSIQ = Full-Scale IQ. For the Raven, VIQ, PIQ and FSIQ a *ADE* rather than *ACE* Model was indicated, but the dominance structure was not significant. * = Best fitting model. For CODE, PC and OA the Additive Genetic (*A*) as well as the *C* structure could be omitted from the *ACE* model without deterioration of fit; the *AE* and *CE* model fitted equally well: c^2 was 34%, 26% and 42%, respectively. h^2 = heritability.

Table 2.6
Fit indices for nested sequence of multivariate models fitted to between and within mean product matrices of monozygotic and dizygotic pairs.

Model	χ^2	df	*p*	$\Delta\chi^2$	Δdf
1. Cholesky decomposition imposed upon *A*, *C* & *E*.	109.9	33	.00	-	-
2. Same as 1, without *C*.	127.9	110	.117	18	77
3. Three-factor (General, Verbal & Performal) structure imposed upon *A* & *E* (A_G A_V A_P; E_G E_V E_P) and Specifics (A_{SP}; E_{SP}).	198.6	198	.475	70.7	88
4. Two-factor structure imposed upon *A* & *E* and Specifics (A_V A_P A_{SP}; E_V E_P E_{SP})	362.6	220	.00	164*	22
5. Same as 3, but without E_V & E_P (A_G A_V A_P A_{SP}; E_G E_{SP}).	208.5	209	.497	9.9	11
6. Same as 3, but for *E* only E_{SP} (A_G A_V A_P A_{SP}; E_{SP}).	241.2	220	.156	42.6*	22
7. Same as 5, but One Factors for *A* and Specifics (A_G A_{SP}; E_G E_{SP}).	276.5	220	.006	68*	11
8. Same as 5, but without A_{SP} (A_G A_V A_P; E_G E_{SP}).	284.9	220	.002	76.4*	11
9. Same as 5, without nonsignificant loadings: A_V: ARI,DS; A_P: CODE; A_{SP}: ARI,SIM,VOC,OA; E_G: INF,ARI,DS,CODE,BLK.	211.5	221	.666	3	12
10. Same as 9, with Raven score loading on all factors (A_G A_V A_P A_{SP}; E_G E_{SP}).	260.1	263	.54		
11. Same as 10, without nonsignificant loadings for the Raven on: A_V A_P; E_G.	265.2	266	.50	3	5.1

Twin groups pooled across sexes: 83 MZ, 111 DZ. $\Delta\chi^2$ = change in chi-square, Δdf = change in number degrees of freedom, * = significant $\Delta\chi^2$.

Multivariate genetic analyses

A full Cholesky decomposition imposed upon the *A*, *C* and *E* structures was fitted to the MZ and DZ between and within mean cross-product matrices. First, the significance of the shared environmental structure was tested in this model (Table 2.6). The *C* structure could be omitted without deterioration in fit [$\Delta\chi^2(77) = 18$, $p = .99$]. The corresponding estimates of genetic and environmental correlations between subtests as well as heritabilities for each subtest for the full *AE* Cholesky model are reported in Table 2.7.

Table 2.7
Genetic (below diagonal) and non-shared environmental (above diagonal) correlations for the WAIS subtests, estimated from the *AE* Cholesky decomposition.

	INF	COM	ARI	SIM	DS	VOC	CODE	PC	BLK	PA	OA
INF	-	.01	.12	.02	.17	.18	.16	.01	.03	.01	.11
COM	.80	-	.03	.06	.20	.20	.03	.18	.04	.21	.04
ARI	.71	.73	-	.17	.13	.11	.08	.18	.22	.05	.17
SIM	.81	.94	.74	-	.04	.22	.02	.06	.13	.13	.05
DS	.48	.40	.67	.60	-	.19	.05	.17	.05	.06	.05
VOC	.83	.87	.75	.91	.56	-	.04	.07	.05	.06	.05
CODE	.24	.24	.35	.30	.34	.38	-	.02	.05	.01	.03
PC	.60	.63	.51	.62	.31	.62	.51	-	.23	.11	.04
BLK	.48	.45	.58	.49	.46	.49	.31	.42	-	.04	.24
PA	.53	.52	.54	.55	.43	.58	.22	.73	.64	-	.05
OA	.24	.41	.28	.39	.15	.35	.14	.60	.67	.54	-
h^2	.75	.62	.64	.58	.61	.72	.49	.34	.67	.39	.51
e^2	.25	.38	.36	.42	.39	.28	.51	.66	.33	.61	.49

Subtests: INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Span, VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. Mean genetic correlation between Verbal scale subtests = .72, between the Performance scale subtests = .48, between subtests from different scales = .44. Mean environmental correlation between Verbal scale subtests = .12; between Performance scale subtests = .08; between subtests from different scales = .09. Sample: 83 MZ twin pairs, 111 DZ twin pairs (same-sex and opposite-sex twin pairs).

The heritability estimates closely resemble the univariate estimates and in accordance with the univariate analyses higher heritabilities were obtained for the Verbal scale subtests (58%-75%, 65% on average) than for the Performance scale subtests (34%-67%, 48% on average). The lowest heritability estimates were again

observed for Picture Completion and Picture Arrangement (34% and 39%, respectively). The *AE* model showed a reasonable fit. Next, the genetic and environmental correlation patterns were examined in order to derive hypotheses about the underlying factor structure. The genetic correlations show a similar pattern as the phenotypic correlations. The mean genetic correlation among subtests of the Verbal scale and Performance scale were .72 and .48, respectively. The genetic correlation among subtests loading on different scales averaged .44 and was almost equal to the mean Performance scale correlation. This rather high correlation suggested a General genetic factor influencing all subtests. The mean correlation among Verbal scale subtests due to within-pair environmental influences (*E*) was small and positive (.12), whereas that among the Performance scale subtests and among different scale subtests was practically zero. The environmental correlations matrix did not exhibit a clear pattern reflecting different effects for Verbal and Performance subtests and therefore suggested a General *E* factor.

In subsequent multivariate model fitting, Model 2 (Table 2.6) was taken as a reference for testing significance of χ^2 change for the modified factor models. The *AE* Cholesky model was tested against a three-factor model (Model 3). In this model the genetic structure was composed of three factors: a General additive genetic factor, A_G (influencing all subtests); a Verbal genetic factor (A_V); a Performance genetic factor (A_P); and Specific factors constituting unique genetic variance for each subtests (A_{SP}). Similarly, the non-shared environmental influences were defined by three factors and specific factors: E_G , E_V , E_P and E_{SP}. The Verbal factors were comprised of the subtests: Information, Comprehension, Arithmetic, Similarity, Digit Span and Vocabulary; the Performance factors of the subtests: Coding, Picture Completion, Block Design, Picture Arrangement and Object Assembly; the General factors by all subtests. The three-factor model did not lead to a significant increase in chi-square [$\Delta\chi^2(88) = 70.2$, $p = .88$]. The significance of the General factors (A_G and E_G) was tested next by fitting a two-factor model (Verbal and Performance factor) with specifics for *A* and *E* (Model 4). The significant deterioration in fit [$\Delta\chi^2(22) = 164$, $p = .00$] suggested that the General factors could not be omitted.

Next, with Model 3 as a reference, more parsimonious structures for *E* were tested. Model 5 hypothesizes only the General and Specific factors to account for the unique environmental structure. This model resulted in a nonsignificant change in χ^2 (Model 5). Because the lack of pattern in the *E* correlation matrix (low intra-scale and between-scale environmental correlations) a model was tested with only the Specific factor for the *E* structure (Model 6). The significant change in chi-square indicated that the General *E* factor must be included in the model.

Like the model fitting tests for *E*, more parsimonious structures for *A* were examined. The three-factor structure for *A* was tested by specifying a single General factor and Specifics (Model 7). As may be seen from the fit of this model, a single factor model is not adequate to account for the genetic covariance matrix. Next, a three-factor model for *A* (like Model 5) was tested, but the Specific factor was dropped (Model 8). Apparently, the highly significant decline in fit proves inclusion of the Specific genetic factors necessary. Thus, Model 5, specifying a General, Verbal, Performance factor with Specific factors for the additive genetic matrix and a General factor with Specific factors for the within-pair environmental matrix, best accounted for the covariances among the subtests. The fit of Model 5 was good ($\chi^2_{209} = 208.5$, $p = .497$).

In order to compare the present results with multivariate genetic analyses results of the WISC (LaBuda *et al.*, 1987), a model was fitted with the Cohen factor structure imposed upon *A* with Specifics (A_{VC} , A_{PO} , A_{FD} and A_{SP}) and with a General factor with Specifics imposed upon E (E_G and E_{SP}). In contrast with LaBuda *et al.* (1987), this model did not fit the data adequately, as can be seen by the significant change in chi-square [$\chi^2_{220} = 328.9$, $p = .00$; $\Delta\chi^2(11) = 120.4$, $p = .00$]. This incompatibility could be explained by the fact that a general genetic factor is crucial in explaining our data. In our adolescent twin sample shared environmental influences could be left out in our model, whereas in the WISC data these influences were significant. The first multivariate analyses results of the WAIS (Tambs *et al.*, 1986) yielded a model with a General factor and the Cohen factors for *A* (A_G , A_{VC} , A_{PO} , A_{FD}) and a General factor with Specifics for *E* (E_G and E_{SP}). This model adds a general genetic factor to the LaBuda *et al.* (1987) model and, consequently, when fitted to our data gave a better fit [$\chi^2_{220} = 268.3$, $p = .014$]. Compared to Model 5, however, this model did not fit adequately [$\Delta\chi^2(11) = 59.8$, $p = .00$]. Just as with the LaBuda *et al.* (1987) model, this bad fit could possibly be explained by the insignificant shared environmental structure in our data. Instant comparison with the Casto *et al.* (1995) model was impossible because of their different approach of using summed factor scores for the genetic analyses. Thus, only factor (VC, PO and FD) specific *E* influences were considered in the Casto model which contrasts with the significant subtest Specific *E* factors in our data.

In the final step the significance of loadings in the factor structure of Model 5 was tested. All general additive genetic influences were significant. For the Verbal additive genetic factor (A_V) loadings from Arithmetic and Digit Span were nonsignificant; for A_P the loading of Coding and for A_{SP} loadings of Arithmetic, Similarities, Vocabulary and Object Assembly were nonsignificant. All specific

environmental influences were significant, probably accounting for the error variance specific to each subtest, but for E_G the loadings of Information, Arithmetic, Digit Span, Coding and Block Design were nonsignificant. In Model 9 all 12 nonsignificant loadings were set to zero [$\Delta\chi(12) = 3$, $p = .99$].

The question how the shared variance of the Raven and the WAIS is mediated was addressed by including the Raven scores as a subtest in the multivariate design in order to examine the loading pattern on the latent *A* and *E* factors. The Raven was included in Model 10 (Table 2.6) and allowed to load on all genetic and environmental factors ($\chi^2_{263} = 260.1$, $p = .54$). However, loadings on A_V, A_P and E_G were very weak and could easily be omitted without significant increase in chi-square ($\chi^2_{266} = 265.2$, $p = .50$) (Model 11). But what if, in addition to the specific genetic variance, the Raven taps a quite different cognitive processing structure than those underlying Verbal or Performance scales of the WAIS? Therefore, a model was tested which allowed the Raven to load on a distinct (fourth), orthogonal genetic factor. This did not improve the fit of the model ($\chi^2_{266} = 341.6$, $p = .00$). Going back to model 11, covariance of the Raven test score with the other WAIS subtests was solely accounted for by the General genetic factor. The mean genetic correlation of the Raven with the verbal subtests was higher than with the performance subtests (.73 and .51, respectively). Genetic and environmental correlations among WAIS subtests as well as heritability estimates did not alter significantly when the Raven was included in the multivariate analysis (Table 2.8). Heritability estimate for the Raven (65%) and the WAIS subtests along with information about their precision in the form of likelihood based 80% confidence intervals are reported in Table 2.9.

Table 2.8
Genetic and non-shared environmental correlations for the WAIS subtests and the Raven test score. Estimates are based on Model 11.

	INF	COM	ARI	SIM	DS	VOC	CODE	PC	BLK	PA	OA	Raven
INF	-	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
COM	.79	-	.00	.14	.00	.14	.00	.24	.00	.21	.11	.00
ARI	.79	.79	-	.00	.00	.00	.00	.00	.00	.00	.00	.00
SIM	.87	.91	.87	-	.00	.05	.00	.09	.00	.08	.04	.00
DS	.58	.57	.73	.63	-	.00	.00	.00	.00	.00	.00	.00
VOC	.86	.90	.84	.99	.61	-	.00	.09	.00	.08	.04	.00
CODE	.37	.37	.46	.40	.34	.39	-	.00	.00	.00	.00	.00
PC	.58	.58	.74	.64	.54	.62	.34	-	.00	.14	.07	.00
BLK	.52	.52	.66	.57	.48	.55	.30	.66	-	.00	.00	.00
PA	.53	.53	.67	.58	.49	.56	.31	.59	.63	-	.07	.00
OA	.33	.33	.41	.36	.30	.35	.19	.58	.80	.57	-	.00
Raven	.69	.69	.87	.76	.63	.73	.40	.64	.57	.58	.36	-

Subtests: INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Span, VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. Sample: 83 MZ twin pairs, 111 DZ twin pairs (same-sex and opposite-sex twin pairs).

Table 2.9
Percentages genetic and environmental variance and heritabilities with 80% convidence intervals for the WAIS subtests and the Raven test score.

	% Variance accounted for by the genetic and environmental factors								
Subtests	A_G	A_V	A_P	A_{SP}	h^2	80% CI	E_G	E_{SP}	e^2
INF	48	10	-	18	76	71 - 81	-	24	24
COM	38	12	-	11	61	54 - 67	14	25	39
ARI	58	-	-	-	58	53 - 64	-	42	42
SIM	42	13	-	-	55	49 - 60	2	42	45
DS	32	-		28	60	52 - 67	-	40	40
VOC	52	22	-	-	74	69 - 78	1	25	26
CODE	15	-	-	9	49	38 - 58	-	75	51
PC	16	-	3	11	30	19 - 40	11	59	70
BLK	30	-	23	16	69	63 - 74	-	31	31
PA	17	-	4	18	39	29 - 49	8	53	61
OA	8	-	41	-	49	41 - 57	2	49	51
Raven	49	-	-	16	65	59 - 71	-	35	35

Note. All values reperesent percentages. A_G = General genetic factor, A_V = Verbal genetic factor, A_P = Performance genetic factor, A_{SP} = Specific genetic factor, E_G = General environmental factor, E_{SP} = Specific environmental factor. h^2 = heritability.

Estimates of Model 11 (Figure 2.2) indicate that the variance in the subtest Arithmetic is only accounted for by General genetic and Specific environmental factors and the nonsignificant loading on the Verbal genetic factor suggests that Arithmetic may not be a typical verbal tests (see also Table 2.9). The same holds for Digit Span which also loaded non-significantly on A_V. For the performance scale it was the subtest Coding which did not seem to share variance with the other performance subtests. These findings indicated some congruence with the third extracted Cohen factor (Cohen, 1957) Freedom from Distractibility (A_{FD}) on which Arithmetic, Digit Span and Coding typically load. A model was specified in which the subtests Arithmetic, Digit Span and Coding were allowed to load on a fourth genetic factor (A_{FD}) instead of being equalized to zero ($\chi^2_{218} = 210.5$, $p = .63$). Because this fourth factor might also arise from underlying environmental influences a model was tested with an additional E_{FD} factor, loaded by these three subtests ($\chi^2_{218} = 209.9$, $p = .64$). The fit of these two models, compared to that of Model 9, indicated that the nonsignificant loadings of Arithmetic, Digit Span and Coding on the verbal genetic factor and their moderate genetic correlation were due to neither a common influence of a distinct genetic Freedom of Distractibility factor, nor to a distinct environmental Freedom of Distractibility factor.

DISCUSSION

Results of the present study provide information about the underlying factor structures constituting individual differences in WAIS subtest scores. By means of multivariate genetic analyses the phenotypic associations among the subtests were decomposed into a part due to genetic and a part due to environmental factors. The relative contributions of these factors and the extent to which individual differences in the subtests are determined by the same factors were estimated. The genetic correlations among subtests comprising the Verbal scale and Performance scale indicated substantial communality within these scales. The covariance structure of the additive genetic matrix could be adequately explained by: a General factor (on which all subtests loaded), a Verbal, a Performance and Specific factors. The covariance structure of the unique environmental matrix indicated one General factor with Specific factors to account for the environmental variance.

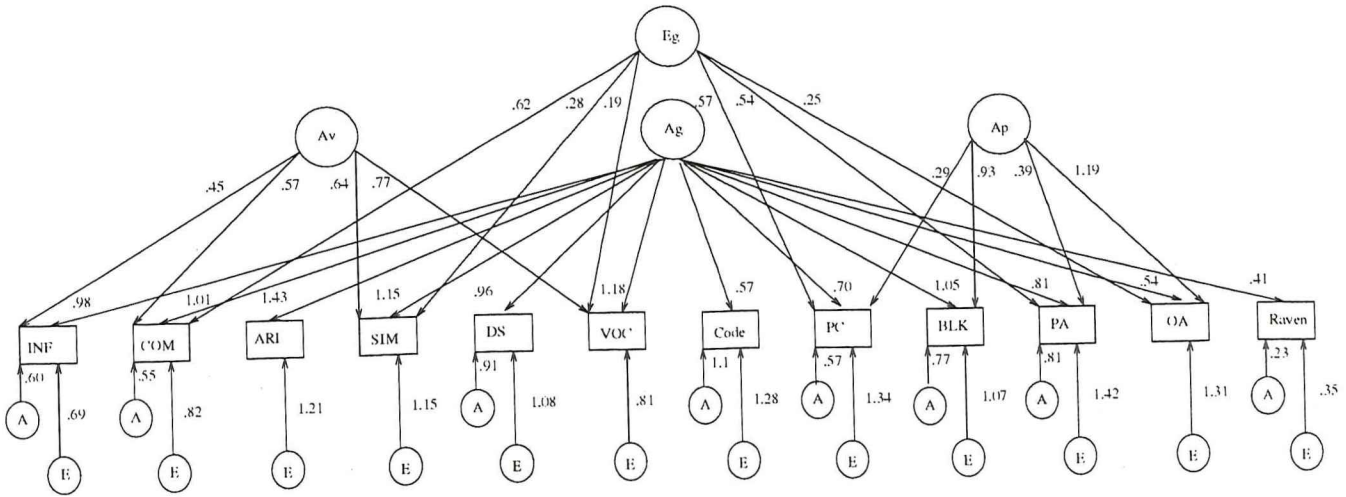

Figure 2.2
Path-coefficients, representing the variances accounted for by the General- (A_G), Verbal- (A_V), Performance genetic (A_P) factors; the General environmental factor (E_G) and the Specific genetic (A) and specific environmental (E) factors.
Estimates are based on Model 11.

In contrast with earlier findings (Tambs *et al.*, 1986; LaBuda *et al.*, 1987 and Casto *et al.*, 1995), the influences of shared-family environment were nonsignificant. The significant shared environmental influences for individual differences in the WAIS-R subtest scores of the Tambs *et al.* study were low, however, and were suggested to be interpreted with caution because of the small sample size and relative low phenotypical correlations observed among subtests. The significant shared environmental variance of the WISC-R data in the other two studies was not surprising given the mean age of the samples (12.5 and 11.2 years, respectively). The effects of shared environment are suggested to decrease as children begin their formal education, and non-shared family environment becomes more important as children become adolescents (Scarr, 1983; Thompson, 1993, Boomsma, 1993).

Verbal scale subtests were strongly influenced by the General genetic factor and moderately by the Verbal genetic and Specific genetic factors. Performance scale subtests were more or less equally influenced by the General, Performance and Specific genetic factors. The General environmental influences were low for all subtests and the major part of the environmental variance was explained by environmental influences specific to each subtest. Heritabilities for the Verbal subtests were between 55% and 77% and for the Performance subtests between 30% and 70%.

The Raven is a widely used nonverbal test and claimed to measure analytic intelligence, the ability to reason and solve problems involving new information, without relying to heavily on acquired knowledge and skills. This implies a high loading on *g*, and thus on the general rather than the group factors. Covariance with the WAIS IQ subtests and other tests of mental ability was, therefore expected to be mediate by general rather than group factors. The next question is, whether this covariance is mediated by general genetic or by general environmental influences. The covariance between the WAIS and the Raven was solely accounted for by the General genetic factor. By revealing additional information about underlying genetic and environmental factor structures, multivariate genetic analysis has helped answering the question about the nature of the General factor of intelligence (*g*). The construct *g* refers to the variance component of individual differences in IQ that is common to all tests of mental ability. The psychometric aspects of *g* are well established empirically, and now research is focusing on the biological basis of *g* (Jensen, 1993). In this search establishment of a genetical basis of *g* is of great importance. The covariation among the WAIS subtests and the covariation between the subtests and the Raven in our data is predominantly

influenced by a General genetic factor and support the notion of a biological basis of *g*.

As shown in this paper, genetic covariance structure models can be fitted to phenotypic data from genetically informative subjects by means of stringent maximum likelihood (ML) techniques. Not very long ago such a strict adherence to ML techniques could only be accomplished by taking recourse to special purpose software. Nowadays, ML-based quantitative genetic modelling can be accommodated by commercially available software, such as LISREL or Mx. Multivariate genetic covariance structure analysis can also be accommodated in these programs in a natural way. The multivariate extension of genetic linear structural equation models has recently made apparent a number of possible generalizations of these models. These generalizations involve applications to the genetic analysis of repeated measures or longitudinal data, and the estimation of single-subject common genetic and environmental factor scores, the study of genotype × environment interaction (Molenaar & Boomsma, 1987; Molenaar *et al.*, 1990) and the decomposition of phenotypic means (Dolan, Molenaar & Boomsma, 1992). Behavior genetics has now even moved beyond estimation of heritabilities: likelihood based confidence intervals (CI) provide information about the precision of the estimates (Neale & Miller, 1996). Confidence intervals can provide information about differences in heritability between variables. If two intervals are non-overlapping, which is the case for example for Information and Arithmetic, one may conclude that heritabilities of these subtests are significantly different.

The advantage of multivariate genetic analysis is that it can reveal additional information about underlying genetic and environmental factor structures that can be quite different from the observed phenotypic factor structure (Heath *et al.*, 1989a, 1989b). In our data this is demonstrated by the fact that the phenotypic factor structure was only mirrored in the genetic component in variance but not in the unique environmental structure. Another obvious advantage is indicated by the difference in fit between the phenotypic factor analysis ($\chi^2_{36} = 56.4$, $p = .02$, which reflects a bad fit) and that of model 11 ($\chi^2_{266} = 265.1$, $p = .50$, which reflects a good fit). Therefore, genetic research focusing upon the analysis of scale scores or factor scores derived by traditional (phenotypic) factor analysis, might be misleading (Heath *et al.*, 1988). Differences in heritability estimates of scale scores can arise through differences in subtest reliability, subtest loadings on one or more underlying genetic common factors, or in subtest specific genetic factors. With multivariate genetic analysis, however, these different possibilities can be resolved with information contained in the intertwin, intersubtest correlations about

genetic and environmental correlations between subtest scores (Heath *et al.*, 1989; Heath & Martin, 1990).

Quantitative genetic theory offers a strong foundation for the application of structural equation models in behavior genetics and genetic epidemiology because unambiguous causal relationships can be specified. For example, genes 'cause' a certain variable like cognitive abilities or blood pressure and parental genes determine those of children and not vice versa (Rao, 1991). Quantitative genetic research, by means of multivariate genetic analyses, has established the importance of genetic factors in many complex behaviors such as personality and cognitive abilities and has also provided an empirical guide and conceptual framework for the application of molecular genetics by identifying the most heritable domains of behavior and the specific genes that contribute to genetic variance in complex behaviors (Plomin, Owen & McGuffin, 1994).

Beyond the current study, the power of the multivariate genetic approach is applied to the search for quantitative trait loci (QTL). Until very recently genes that underlie continuously distributed quantitative characteristics such as behavior, were thought impossible to map and identify. With the availability of highly polymorphic DNA markers and improvements in linkage methodology, the localization of genes underlying complex traits has become possible. Several strategies have been developed to map QTL, that are based on identifying marker alleles that are inherited identical by descent (IBD). The methods that study the genetic linkage of a quantitative trait and a polymorphic marker in data from for example sibling pairs, suppose that if a marker is co-segregating with a quantitative trait, then siblings whose trait values are more alike, are more likely to receive the same alleles IBD at a closely linked marker locus than siblings whose resemblance for the trait is less. However, even with large numbers of highly polymorphic markers the power to detect a single locus that influences quantitative traits is low (e.g. Blackwelder & Elston, 1982). One strategy to increase the power to detect QTL is to reduce the environmental variance in the trait under study. This can be accomplished by using multivariate observations to estimate (extreme) individual genotypic values at a QTL, that pleiotropically affects more than one trait. The genetic scores (instead of phenotypic observations) are investigated in relation to the genetic markers (Boomsma, 1996).

It is not clear to what extent the relations between IQ and its biological correlates are genetically or environmentally mediated. Multivariate genetic analyses of specific cognitive abilities suggest that genetic influences substantially overlap, although some genetic effects are unique to each ability. These findings imply that there may be a common set of genes associated with these cognitive

abilities (PLomin, Owen & McGuffin, 1994). Application of molecular genetic techniques are now being considered to look for multiple loci that affect quantitative traits such as intelligence. Molecular genetics might profit from focusing on results of multivariate genetic analyses which indicate what cognitive abilities have in common. Recently the first allelic association study to identify QTL associated with high versus low IQ (Plomin *et al.*, 1994) has been conducted. Frequency differences were investigated in 60 DNA markers, related to genes thought relevant for neural functioning, in a low and high performing group of children. The findings were not replicated (Plomin *et al.*, 1995) due to limited statistical power. Despite skeptism, however, QTL research on IQ and other human behavior is progressing. An important advance in QTL research on cognitive disabilities was made in the context of reading disability (Cardon *et al.*, 1994). Identification of the functional genes that cause the disorder can improve risk assessment and early diagnosis.

3

Genetic analysis of peripheral nerve conduction velocity in twins[1]

F.V. Rijsdijk, D.I. Boomsma and P.A. Vernon

ABSTRACT

We studied variation in peripheral nerve conduction velocity (PNCV) and intelligence in a group of sixteen year-old Dutch twins. It has been suggested that both brain nerve conduction velocity and PNCV are positively correlated with intelligence (Reed, 1984) and that heritable differences in NCV may explain part of the well established heritability of intelligence. The Standard Progressive Matrices test was administered to 210 twin pairs to obtain IQ scores. Median nerve PNCV was determined in a subgroup of 156 pairs. Genetic analyses showed a heritability of .65 for Raven test scores and .77 for PNCV. However, there was no significant phenotypic correlation between IQ score and PNCV.

INTRODUCTION

Understanding the nature of human intelligence must include knowledge of the underlying neurophysiological factors and processes that contribute to variance in this trait. Among features like the electroencephalogram (Courchesne, 1978), regional cerebral blood flow (Phelps *et al.*, 1982; Risberg, 1986) and cortical glucose metabolism (Chase *et al.*, 1984), peripheral nerve conduction velocity (PNCV) has been investigated as a potential biological determinant of intelligence. Nerve conduction velocity is the speed with which electrical impulses are transmitted along

[1] This chapter is a slightly revised version of publication in *Behavior Genetics*, 1995, 25, 341-348.

nerve fibres and across synapses.

Peripheral nerve conduction velocity is a well established, extensively studied neurological trait in humans for diagnosing neuromuscular and neurological diseases (Desmedt, 1980 ; Oh, 1993). Nothing is known about causes of variation in PNCV in humans. In animal studies low to median heritabilities have been observed. Hegmann *et al.* (1973) found a significant heritability in mouse tail NCV (narrow-sense heritabilities of .1 to .2; broad-sense heritabilities of .2 to .3). Tail PNCV also correlated with certain behaviours like open-field activity and defecation (Hegmann, 1979). Reed (1988) found a significant narrow-sense heritability in mouse tail PNCV of .23. He suggested that in large natural populations of mammals, including humans, the heritability of PNCV could be considerably greater because the genetic variability of randomly bred laboratory mouse colonies derived from inbred strains is probably much less than that of natural populations. Body length in heterogenous-strain mice, for example, has a heritability of .21 ± .05, which is much smaller than the heritability of around .8 in humans. According to Reed, a heritability of .5 or more for PNCV in humans may be a reasonable estimate.

Three components of nerve action potentials can be distinguished. Onset PNCV and peak PNCV measure the conduction speed in the fast-conducting (large-diameter) nerve axons and the average-conducting (average-diameter) nerve axons, respectively, while end PNCV involves slow-conducting (small-diameter) axons (MA & Liveson, 1983; Oh, 1993). Onset PNCV is commonly used in studies examining the relation between IQ and PNCV, because it reflects conduction of the fast nerve fibres. A high IQ is suggested to be a consequence of faster speed-of-information-processing (SIP) and, hence, of faster and more efficient central nervous functioning (e.g. Vernon, 1993). Reed (1988) suggested that genetic variation in NCV might account for heritable differences in IQ.

Twin and family data support the existence of genetic influences upon human cognitive abilities. Approximately 50%-60% of the phenotypic variance in IQ is associated with genetic differences among individuals (Bouchard & McGue, 1981; Plomin, 1991; Boomsma, 1993). Reed (1984) hypothesized that NCV and intelligence might be correlated as a result of genetic variability in the structure and amount of transmission proteins which set limits on information processing rates and, hence, on intelligence. Higher NCV may allow higher SIP and thereby contribute to higher IQ test scores (Vernon, 1993, Reed, 1984).

Recently, Vernon and Mori (1992) reported correlations of .43 and .46 between PNCV in the median nerve and IQ score on the MAB (Multidimensional Aptitude Battery) in two independent samples (N = 85 and N = 88) of Canadian

university students. However, Barrett et al. (1990) found no correlation between median PNCV and Raven Advanced Progressive Matrices in 44 British adults and Reed and Jensen (1991) also failed to find a relation between median nerve conduction velocity and IQ in 200 Californian students.

The present study was designed to study the heritability of PNCV in humans; to determine the correlation between PNCV and a measure of intelligence; and to investigate to what extent this correlation is influenced by genetic factors. IQ scores were determined for 210 sixteen year-old Dutch twin pairs by the Raven Standard Progressive Matrices Test. Complete data for median nerve conduction velocity were available from a subgroup of 156 pairs.

SUBJECTS AND METHODS

Subjects

Four hundred twenty-six adolescent Dutch twins (mean age, 16.13; SD, 0.56) participated in the experiment. Mean age was equal for males and females. Addresses of the twins were obtained from municipal authorities. Subjects had earlier participated in a large questionnaire study on personality and lifestyle factors such as physical activity level, alcohol consumption (Koopmans *et al.*, 1993) and smoking (Boomsma *et al.*, 1994). A subsample of the twins who enrolled in this questionnaire study currently take part in a longitudinal EEG and ERP study in which genetic and environmental influences on brain development are examined. This PNCV-IQ study was part of the EEG/ERP project. NCV and IQ data presented in this paper were collected at the first visit of the twins to the laboratory.

IQ data were available for 38 MZM, 36 DZM, 51 MZF, 37 DZF and 48 DOS twin pairs. For IQ data three outliers (1 DZM, 1 MZF and 1 DZF) were removed because of questionable test circumstances (e.g. noisy, distracting room). Nerve conduction data were available for 25 MZM, 20 DZM, 42 MZF, 30 DZF and 39 DOS twin pairs. Missing NCV data for one or both twins in a pair were due to technical and procedural problems (e.g. difficulty in palpation of the nerve). To date, for 104 same-sex twins zygosity was determined by blood and DNA typing, for the other same-sex pairs by a questionnaire filled in by the mother. Questions were asked about physical similarity (face, hair structure, and eye, hair and skin color) and about the frequency of confusion of the twins by family members and strangers. In 16 cases zygosity was determined by a questionnaire completed by the twins themselves. In the subgroup of 104 same-sex twin pairs, questionnaire

data were available for 86 pairs. The percentage correctly classified zygosities of the questionnaire compared with blood group polymorphism was 88%.

Intelligence Test

The Raven Standard Progressive Matrices Test (Raven, 1958) was administered without a time limit. The IQ score was simply the number of correct answers.

Physical exercise

Reed (1993) has suggested that physical exercise could be a covariate of peripheral NCV and should be controlled for in studies examining correlations between PNCV and IQ. Data on sports participation and average weekly physical activity level were obtained from the questionnaire study for 216 subjects; 85 males and 131 females (Koopmans *et al.*, 1994).

Nerve conduction velocity

PNCVs were determined for the wrist-elbow segment of the median nerve of the right arm. The median nerve is a mixed motor and sensory nerve.

Action potential acquisition apparatus

Subjects were tested in an electrically shielded sound proof cabin. Orthodromic electrical stimulation of the median nerve was accomplished using a ELTRON G-F 437 (Enraf Nonius) stimulator. The stimulator, two surface electrodes provided positive, 0.05 msec long, constant current electrical pulses. Current stimulation was available from 0 to 75 mA. A skin thermistor probe, placed on the middle of the arm, provided continuous temperature readings. The probe and stimulator were under control of an Olivetti M28 PC, which also controlled a heating pad, wrapped around the arm. The stimulator was only effective if arm temperature was 33°C and the heating pad was switched off. A Nihon Kohden AB-601G Bioelectric pre-amplifier unit was used for signal amplification. Filters were set at an upper frequency limit of 1 KHz and at a lower limit with a time constant of 3 msec. The pre-amplifier was connected to a digital sampling oscilloscope (DSO) PM 3355 (Philips), sampling at 50 KHz per channel. All signals were monitored directly on the DSO and via a GPIB-PC2/2A Handler (National Instruments) on the PC termi-

nal. Recording and reference electrodes were standard EEG silver-chloride 9 mm disc electrodes filled with NaCl electrode gel.

Action potential acquisition procedure

Phase 1. After locating the nerve via palpation, the stimulating electrodes were placed at the elbow, anode most distal. The stimulating current was slowly increased to determine whether the innervated fingers of the median nerve were effected (thumb, index, middle and lateral part of the ring finger).

Phase 2. The skin on all test sites was cleaned with alcohol and lightly abraded with a scrub paste. The stimulating electrodes were placed at the wrist with a centre-to-centre distance of 30 mm (anode most proximal). A recording electrode (most distal) and a reference electrode were applied in the elbow (30 mm centre-to-centre distance) and together with a ground electrode connected to the preamplifier. Impedances between electrodes were below 5 KΩ.

The current value beyond which the amplitude of the nerve action potential no longer increased was used as the supra maximal level (SML). At the SML all nerve fibres of the median nerve are being stimulated. The subjects were given 2 series of 8 stimuli at a rate of 1 per second with the SML, each series yielding a signal averaged action potential (AP).

NCV computation

From the two APs 3 latencies (components) were determined: the time from shock onset to the first deviation from baseline (onset latency); to the peak (peak latency) and to the end (end latency). Dividing wrist-elbow distance in millimetres (centre-to-centre distance between the recording electrode and the closest pole of the stimulating electrode) by the average latencies of the two APs (milliseconds) gave the onset PNCV (ONCV), peak PNCV (PNCV) and end PNCV (ENCV) for the nerve segment.

Statistical analyses

The effect of sex on mean IQ and PNCV measures was assessed by likelihood-ratio chi-square tests using the computer program LISREL7 (Jöreskög & Sörbom, 1988). These tests were used to compare the fit of a model that constrained parameter estimates for mean IQ and PNCVs to be equal across sexes to one which allowed them to vary in males and females, while taking into account

the dependency that exists between observations from twins (Boomsma *et al.*, 1993).

Genetic analysis

Genetic model fitting was carried out on variance-covariance matrices of the 5 different sex-by-zygosity groups. Genetic models specified variation in phenotype to be due to genotype and environment. Sources of variation considered were *A*, additive genetic variation (i.e. the sum of the average effects of the individual alleles at all loci); *D*, dominance genetic variation (interaction of alleles at a given locus, summed over all loci) and *E*, a random environmental deviation that is not shared by family members. We assume that the phenotypic variance can be expressed as a simple additive function of additive genetic effects (*A*), dominance genetic effects (*D*) and specific environmental effects (*E*);

$V_P = V_A + V_D + V_E$.

The relative contributions of genetic and environmental influences to individual differences were estimated by maximum likelihood, using the computer program Mx (Neale, 1991). PRELIS, the preprocessor of LISREL, was used to compute the variance-covariance matrices of the observations. Sex differences in covariance structure were examined by comparing the fit of an *ADE* model with the parameters constrained to be the same for males and females to the fit of an unconstrained *ADE* model. Goodness-of-fit was assessed by likelihood-ratio χ^2 tests. The overall χ^2 tests the agreement between the observed and the predicted variances and covariances in the 5 groups. A large χ^2 (and a low probability) indicates a poor fit, while a small χ^2 (accompanied by a high *p*-value) indicates that the data are consistent with the model. Submodels were compared by hierarchic χ^2 tests, in which the χ^2 for a reduced model is subtracted from that of the full model. The degrees of freedom (df) for this test are equal to the difference between the df for the full and the reduced model (Neale & Cardon, 1992).

RESULTS

Figure 3.1 shows the distribution of the raw scores for onset PNCV and the Raven test. The raw scores for onset PNCV showed acceptable symmetry (skewness .344; kurtosis .053) (Figure 3.1A). The Raven test score distribution (Figure 3.1B) was negatively skewed (skewness -.977; kurtosis 1.66), and a quadratic transformation was used to obtain a more symmetric distribution (skewness -.485; kurtosis .273).

Height, temperature, age (Oh, 1993; Stetson *et al.*, 1992) and physical exercise level (Reed, 1994) are possible confounders of PNCV. Arm temperature was controlled for and showed no correlation with PNCV. The PNCV measures also showed no correlation with age and physical exercise level for males and females. All three PNCV measures were correlated with height in males (.20, .21 and .27; $p < .05$), but not in females.

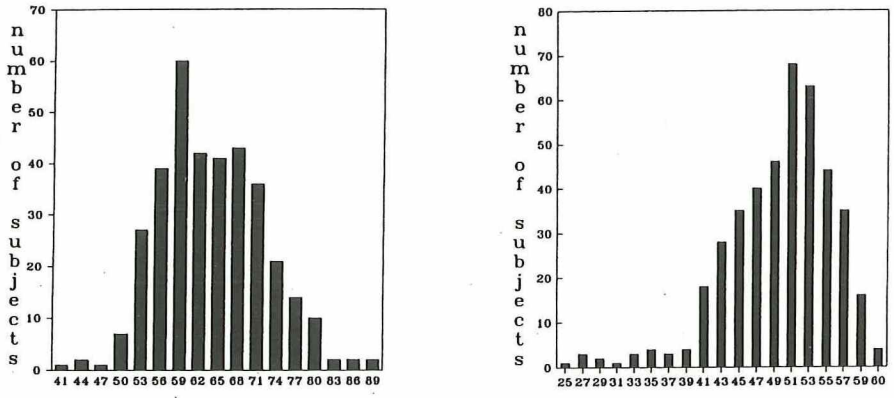

Figure 3.1
(A) Onset PNCV distribution. The *X* axis represents the nerve conduction velocity (m/s).
(B) Raven test score distribution. The *X* axis represents the number of correct items.

In Table 3.1 the means and standard deviations for the Raven test score, the PNCV measures and height are presented. There are no differences between males and females for the Raven test score, peak PNCV, end PNCV measures and SML. Males and females differed for onset PNCV [$\chi^2(1) = 10.87$] and height [$\chi^2(1) = 135.85$].

Table 3.1
LISREL estimates of means and standard deviations for the Raven, PNCV measures and height.

	Males		Females		Sex differences
	M	SD	M	SD	$\Delta\chi^2(1)$
Raven	49.3	6.4	49.3	5.6	.37
Onset PNCV (m/s)	62.3	7.7	65.2	8.3	10.87*
Peak PNCV (m/s)	49.9	6.0	49.9	5.2	.55
End PNCV (m/s)	39.5	5.1	39.5	4.4	.65
SML (mA)	38.3	10.6	38.3	9.3	1.75
Height (cm)	176.9	7.8	168.3	5.3	135.8*

Raven = number of correct items. SML = Supra Maximal Level (mA = milli Ampére).
* = $\Delta\chi^2(1) > 3.84$ and implies significant difference between males and females. For PNCV, SML and Height: 129 males and 183 females. For the Raven: 196 males and 224 females.

The PNCV means of 63.8 m/s (onset PNCV) and 49.7 m/s (peak PNCV) for the total population (N = 312) agree with values reported in the literature for adults (age range, 20 - 60) : 64.5 ± 4.28 and 55.99 ± 3.30 respectively (Oh, 1993). Onset PNCV showed high correlations with the other two PNCV measures; 0.88 ($p <$ .001) with peak PNCV and 0.71 ($p <$ .001) with end PNCV. For onset PNCV a test-retest reliability of 0.80 was found in a group of 13 university students, measured two weeks apart.

Table 3.2
Twin correlations for the Raven, PNCV measures and height.

	Raven	onset PNCV	peak PNCV	end PNCV	Height
MZM	.76*	.72*	.75*	.73*	.98*
DZM	.22	.15	.14	.14	.37*
MZF	.52*	.74*	.68*	.70*	.88*
DZF	.31*	.46*	.40*	.43*	.17
DOS	.50*	.17	.12	-.05	.58*

* = $p <$ .05. For Raven-IQ: 38 MZM, 36 DZF, 51 MZF, 37 DZF and 48 DOS twin pairs. For PNCV measures and height: 25 MZM, 20 DZM, 42 MZF, 30 DZF and 39 DOS twin pairs.

No significant correlations between the PNCVs and the Raven test scores were observed for males or females. The correlation between the Raven test scores and Supra Maximal Level was also non-significant. Removing subjects with a Raven score less than 40 correct items, did not improve the correlations between the PNCVs and Raven test score.

The twin correlations for the Raven test score, the PNCV measures and height are given in Table 3.2, showing higher MZ than DZ correlations for all measures. The pattern of the male twin correlations (high MZ and low DZ correlations) for the Raven test score suggests dominance genetic effects. Therefore, a univariate *ADE* model for males and *AE* model for females was tested against the *AE* sex-differences model. For IQ the dominance component could be omitted from the model without a significant detoriation in fit and the reduced *AE* no-sex-differences model gave the most parsimonious explanation of the data ($\chi^2_{13} = 23.93, p = .032$). Heritability for the Raven test was 65% ($V_A = 20.02$; $V_E = 10.95$). The height-PNCV relationship was examined by a Cholesky triangular decomposition with height entered as the first variable and the NCV phenotypes as the second variable. Figure 3.2 shows the model for one member of a twin pair, where A_C and E_C are the genetic and environmental influences common to height and PNCV, and A_S and E_S are the genetic and environmental influences specific to PNCV. The effects of A_C and E_C on height are represented in the parameter h_c and e_c and the effects of A_C and E_C on PNCV in h'_c and e'_c. In Table 3.3 bivariate analyses results are presented. Models which tested dominance genetic effects did not show a better fit than models where the dominance factor was omitted. A model without sex differences did not show a good fit to the data because of the significant difference in heritability for height between males and females. Therefore a model was tested which constrained the total genetic and environmental variance in PNCV to be equal for males and females and allowed the variation in height to vary across gender. Thus, for PNCV $[(h'_c)^2 + (h_s)^2]_{\text{males}} = [(h'_c)^2 + (h_s)^2]_{\text{females}}$ and $[(e'_c)^2 + (e_s)^2]_{\text{males}} = [(e'_c)^2 + (e_s)^2]_{\text{females}}$, implying no sex differences in heritability for PNCV. This model showed the best fit for onset, peak and end PNCV. In Table 3.4 the standardized parameter estimates for the best fitting models are presented. The covariation of height with the PNCV phenotypes was genetically mediated in females and influenced by *A* and *E* in males. However, the overall covariation of height and PNCV was small. The heritabilities for onset PNCV, peak PNCV and end PNCV before controlling for height were 76%, 68%, and 64%, respectively and after controlling for height 76%, 70% and 66% in females and 76%, 74% and 70% in males, respectively. Heritabilities for height were 86% for females and 96% for males.

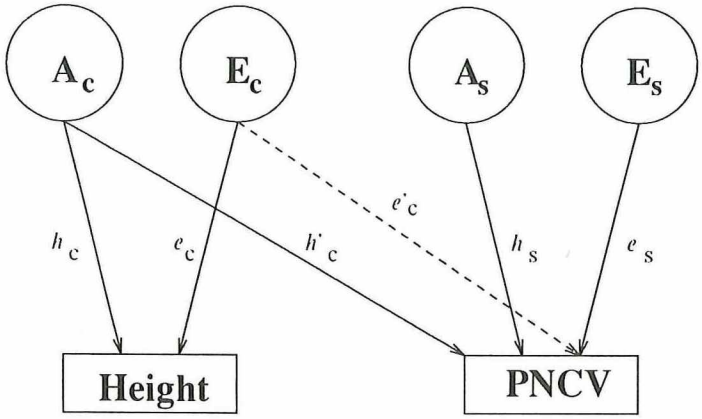

Figure 3.2
Cholesky triangular decomposition for height with PNCV. A_C and E_C reflect the genetic and environmental influences common to height and PNCV. A_S and E_S reflect the genetic and environmental influences specific for PNCV.

Table 3.3
Bivariate genetic model fitting results of height with PNCV measures.

		onset PNCV		peak PNCV		end PNCV	
Model	df	χ^2	*p*	χ^2	*p*	χ^2	*p*
*ADE*sd PNCV & height	32	30.94	.52	33.66	.39	40.24	.15
ADE_{males} $AE_{females}$	35	32.16	.62	34.69	.48	40.24	.25
*AE*sd PNCV & height	38	34.79	.62	38.82	.43	46.90	.15
*AE*sd height	40	36.89*	.61	40.25*	.46	48.86*	.16

For all PNCV measures the best fitting model included a constraint for keeping the total genetic and environmental variance for PNCV equal for males and females, while for height variances were allowed to vary across gender. sd = sex-differences, * = best fitting model.

Table 3.4
Genetic and environmental specific and common effects of the bivariate model of height with PNCV measures.

	Genetic & environmental specific effects for PNCV				Genetic & environmental common effects for PNCV				Genetic & environmental common effects for height			
	Females		Males		Females		Males		females		Males	
	h_s	e_s	h_s	e_s	h'_c	e'_c	h'_c	e'_c	h_c	e_c	h_c	e_c
Onset PNCV	7.112	3.991	6.970	3.925	0.705	0.0	1.579	0.721	4.958	2.007	7.832	1.587
Peak PNCV	4.679	3.049	4.652	2.739	0.586	0.0	0.769	1.342	4.958	2.012	7.816	1.584
End PNCV	3.766	2.682	3.735	2.415	0.725	0.0	0.872	1.168	4.954	2.016	7.800	1.586

For all PNCV measures the total genetic and the total environmental variance are equal for males and females: $((h_s)^2+(h'_c)^2)_{\text{males}} = ((h_s^2)+(h'_c)^2)_{\text{females}}$; $((e_s)^2+(e'_c)^2)_{\text{males}} = ((e_s)^2+(e'_c)^2)_{\text{females}}$.

DISCUSSION

This study is the first to determine the heritability of PNCV in humans. As Reed (1988) predicted, a large heritability of 76% was found for onset PNCV which would make PNCV an interesting quantitative genetic trait that could potentially explain genetic differences on human intelligence.

The test-retest correlation of .80 for onset PNCV ($N = 13$) implies a reliability index of .64 (r^2). The onset PNCV heritability of .76, therefore, suggests nearly all reliable variation in PNCV to be heritable.

For the Raven test score we obtained a heritability estimate of 65%. Although the genetic model for the total score on the Raven did not show a very good fit to the data, the heritability estimate is in line with most of the other studies on adolescent and adult IQ (for reviews see Plomin (1988, 1991); Boomsma (1993) and Vernon (1993).

However, no significant correlation between PNCV and IQ was found in our sample. The mean PNCVs are in agreement with the values reported in the literature (Oh, 1993) for the same nerve segment and technique, but our standard deviations for both males and females were higher (7.7 and 8.3 versus 4.3 and 6.0; and 5.2 versus 3.3 for onset and peak PNCV, respectively). These standard deviations were also higher than those reported by Vernon and Mori (1992). However,

it does not seem likely that these differences in standard deviations can explain the absence of a correlation between PNCV and IQ.

Reed (1993) found increased brain NCV and peripheral NCV in mice as a result of environmental enrichment and physical exercise. Because human data also indicate increased PNCV as a result of increased activity, physical exercise level is proposed to be an important covariate which should be taken into account when studying the relationship between PNCV and IQ. Reed suggested that lack of information on physical exercise status may explain, at least in part, the contradictions among studies that correlate median nerve PNCV with IQ level. We, however, found no correlation between physical activity level and PNCVs.

Our results contrast sharply with those observed in two samples by Vernon and Mori (1992). They found correlations between PNCV and IQ of .43 ($N = 85$) and .46 ($N = 88$). In our study, arm temperature was experimentally controlled and supramaximal stimulation was used to measure PNCV just as in the studies of Vernon and Mori. A possible explanation for the lack of correlation between PNCV and IQ, therefore, is the use of the Raven IQ test. This lack of correlation is consistent with results from Jensen and Reed (1991), who found no correlation between median nerve arm PNCV and IQ scores in two groups of students. In their university students, IQ was measured with the Raven Advanced Progressive Matrices and for their community college students, the Standard version was used. Barrett *et al.* (1990) also reported no correlation between the advanced form of the Raven test and PNCV.

The correlations of .43 and .46 between PNCV and IQ found by Vernon and Mori were obtained using the MAB. The MAB is a group test of intelligence patterned after and highly correlated with the WAIS-R (.91 for Full-Scale IQ, Jackson, 1984). The correlation of the Raven Advanced Progressive Matrices with the WAIS Full-Scale IQ is .72 (Vernon, 1983) and is even lower with verbal IQ and performance IQ (.57 and .69, respectively). The fact that Raven IQ and WAIS IQ only have around 50% of their variance in common may account for the absence of a phenotypic correlation between Raven IQ score and PNCV. (Though see Wickett & Vernon (1994), who failed to find a significant correlation between MAB IQ scores and PNCV in a sample of adult females). Our subjects are currently participating in a second PNCV study in which the WAIS is administered. The results from this study will resolve the issue of wether use of the Raven IQ test is an explanation for the failure to confirm the positive correlation between peripheral conduction velocity and IQ level.

4

Genetic mediation of the correlation between peripheral nerve conduction velocity and IQ[1]

F.V. Rijsdijk & D.I. Boomsma

ABSTRACT

Variation in peripheral nerve conduction velocity (PNCV) and intelligence was studied in eighteen year-old Dutch Twins. It has been suggested that both brain nerve conduction velocity and PNCV are positively correlated with intelligence (Reed, 1984) and that heritable differences in nerve conduction velocity may explain part of the well established heritability of intelligence. The relationship between IQ, obtained with the Wechsler Adult Intelligence Scale, and median nerve PNCV was examined in 159 twin pairs. Genetic analyses showed a heritability of 81% for IQ and 66% for onset PNCV. The small but significant phenotypic correlation between IQ and onset PNCV (.15) was entirely mediated by common genetic factors. Analyses of difference scores for PNCV of this study and PNCV from the same subjects collected at age sixteen, suggest that there might still be development in PNCV in this age interval. This maturation is highly controlled by genetic factors. It is suggested that variation in IQ that is associated with nerve conduction velocity, only becomes apparent after the developmental processes in peripheral nerves are completed. This is in line with the suggestion of increasing heritability of IQ in adulthood.

[1] Accepted for publication by *Behavior Genetic*, 1997, 27 (2).

INTRODUCTION

The strong heritability for psychometric intelligence is well established. Twin and family data support the existence of genetic influences upon human cognitive abilities. Approximately 50%-60% of the phenotypic variance in adult IQ is associated with genetic differences among individuals (Bouchard & McGue, 1981; Plomin & Rende, 1991; Boomsma, 1993; Bouchard, 1993). Since genetic polymorphisms code for biological differences, these findings give strong evidence for the existence of biological determinants of intelligence differences between individuals. This biological intelligence is influenced by genes which code for neurophysiological and biochemical factors and processes in the brain, but can also be modified by environmental factors. Despite the considerable practical applications of psychometric IQ it remains an uncertain mixture of capacity and acquired knowledge and a more complete understanding of the nature of human intelligence should include knowledge of biological intelligence (Eysenck, 1993).

Among a great number of biological variables, peripheral and central nerve conduction velocity have been investigated as potential biological determinants of intelligence. Nerve conduction velocity (NCV) reflects the speed with which electrical impulses are transmitted along nerve fibres and across synapses. Reed (1984) hypothesized that the heritability of IQ may be a result of genetic variability in the structure and amount of 'transmission proteins' which set limits on information processing rates and on intelligence. Transmission proteins include enzymes involved in myelin sheathing and neurotransmitters (which are synthesised by specific enzymes). Genetic variability in the structure and amount of transmission proteins may determine information processing rates. Reed (1988) suggested that peripheral nerve conduction velocity (PNCV) as a quantitative genetic trait may model central nerve conduction velocity. PNCV is a relatively easy obtainable measure of nerve conduction speed. In humans, it is a well established, extensively studied neurological trait, used for diagnostic purposes in neuromuscular and neurological diseases (Desmedt, 1980 ; Ma & Liveson, 1983; Oh, 1993). The genetic background of PNCV variation was first studied in mice populations by Hegmann *et al.* (1973), who observed low to median heritabilities in tail PNCV (narrow-sense heritabilities of .1 to .2; broad-sense heritabilities of .2 to .3). Reed (1988) also found heritabilities of .23 ± .05 for tail PNCV in mice. In humans, the genetic architecture of PNCV was studied in twins (Rijsdijk *et al.*, 1995) and was, as predicted by Reed (1988), a substantially heritable trait. The heritability for median nerve conduction velocity, computed for onset latencies of orthodromically assessed compound mixed nerve action potentials, was 76%.

Variation in PNCV has been studied in relation to individual differences in intelligence.

Table 4.1 provides an overview of the results of studies conducted on peripheral NCV and IQ. Vernon and Mori (1992) reported correlations between PNCV in the median nerve and IQ score on the MAB [Multidimensional Aptitude Battery, (Jackson, 1984)] in two independent samples of Canadian university students: .43 (N = 85) and .46 (N = 88). They concluded that a general factor of neural efficiency is a major aspect of psychometric IQ. However, Barrett *et al.* (1990) found no correlation between median NCV and Raven Advanced Progressive Matrices in 44 British adults. Wickett and Vernon (1994) also failed to replicate the findings of the earlier studies of Vernon and Mori (1992), submitting the same IQ test and PNCV procedure to a smaller sample of 38 females (20 to 30 years of age). Reanalyses of the data of 1992, yielded sex difference in the relationship between PNCV and IQ, with a pronounced correlation in males. Wickett and Vernon speculated that males may rely more heavily on neural speed to perform cognitive tasks, whereas for females other neural processes might play the predominant role.

In addition to these studies of peripheral NCV and IQ, two other studies investigated the relation between peripheral NCV, central NCV and IQ simultaneously. Reed and Jensen (1991) divided latencies of visual evoked potentials (VEP) by head length to obtain an indicator of central NCV. The latency of a VEP reflects the speed of conduction along the primary visual pathway (retina-thalamus, v1). Reed and Jensen found no correlation between visual pathway NCV and IQ (though, an earlier report (1989) from the same project gave correlations of .27 and .37 between visual pathway NCV and IQ). There was no correlation between peripheral NCV and the visual pathway NCV, nor between peripheral NCV and IQ (N = 200).

Reed and Jensen (1993) also studied the relation between central NCV, peripheral NCV and IQ by means of Somatosensory evoked potentials (SEPs). SEPs are electrical signals recorded from the scalp over the relevant part of the somatosensory cerebral cortex following stimulation of some peripheral nerve. Three SEPs are usually observed following one single stimulation of the median nerve at the wrist. N13 is generated in the region of the cervical spinal cord, N19 is generated in the thalamus and P22 is generated in the somatosensory cortex. The Latency of the N13 represents peripheral conduction time. The latency difference P22 - N19 represents the thalamus - parietal cortex transmission time and reflects brain conduction time. The P22 - P19 latency difference correlated negatively with IQ (r = -.22). Peripheral latency (wrist to cervical spinal cord) did not correlate

with IQ. This finding was in agreement with the previous study of the same population (Reed & Jensen, 1991), where no correlations were found between median nerve NCV and IQ. Inadequate temperature control in both studies (statistically instead of physically) should be considered when evaluating these findings as temperature is regarded the most important source of error that can affect the assessment of peripheral NCV (e.g. Kimura, 1984; Rivner, 1990; Oh, 1993; Letz, 1994). Reed and Jensen did not report on the correlation between peripheral and central tract latencies, nor did they report on velocity measures for the peripheral and central tracts.

Several studies have examined the relation between other measures of central conduction speed and IQ. A rational for these investigations is given by the myelin hypothesis (Miller, 1994), which postulates that higher intelligence is associated with larger brain size. Positive correlations between brain size and intelligence have been found in studies using magnetic resonance imaging, (e.g. Wickett *et al.* 1994; Willerman *et al.*, 1991; Raz *et al.*, 1993, Schultz *et al.*, 1993). Miller proposed that thicker myelin sheaths could be the major explanation for the positive correlation between brain size and IQ. Thicker myelin sheathed nerves are faster, prevent accidental signalling in adjacent neurons and therefore are associated with faster speed-of-information-processing and higher intelligence (Miller, 1994).

Clearly, there are studies which found a significant relationship between peripheral NCV and IQ and between central NCV and IQ but in the studies that investigated the three measures simultaneously, there was no evidence that peripheral NCV was correlated with central NCV. However, besides experimental artifacts like temperature control, the absence of a peripheral to central NCV correlation may be real. There are differences in peripheral and central nervous system properties that should be considered. Myelin, the membrane characteristic of nervous tissue that is responsible for transmission velocity, is formatted and maintained by oligodendrocytes in the central nervous system. In the peripheral nervous system the Schwann cells are the myelin-forming cells. These cells differ in a number of ways, e.g. in the way of controlling the formation of myelin, in the coding for production of myelin, in their origin and in their biochemics and structure. A single oligodendrocyte maintains as many as 30-50 internodes of myelin. In contrast, a single Schwann cell envelopes just one internode. (Kandel *et al.*, 1991). The genes in Schwann cells that encode myelin are turned on by the presence of axons, whereas expression of the genes in oligodendrocytes that encode for central myelin depend on the presence of astrocytes, the other major glial cell type in the central nervous system (Kandel *et al.*, 1991). Oligodendrocytes orig-

inate from precursor cells in the ventricle zone of the neural tube, whereas Schwann cells are derived from migrating neural crest cells (e.g. Jacobson, 1991). Given these differences, peripheral and central neurophysiological processes might not be fully comparable. However, there are a number of clinical studies providing evidence that diseases of and inflictions upon the nervous system, show negative effects on both peripheral and central conduction. Clinical PNCV studies in for example lead, zinc and copper exposed workers (Araki *et al.*, 1987); in patients with primary hypothyroidism (a hormone dysfunction) (Abbott *et al.*, 1983) and in HIV-1 patients (Pinto *et al.*, 1992) show slowing in both peripheral and central NCV when patients are compared with controls, even though there was no clinical evidence of neurological impairment.

Table 4.1
Studies on the relationship between peripheral nerve conduction velocity and IQ.

	Correlation IQ-PNCV	Segment Median Nerve	Mean PNCV (m/s)	IQ-test	Temperature controle	Age range (mean age)	N
Vernon & Mori (1992)	.41*[a]	Wrist-Fingers Wrist-Elbow Elbow-Axilla	63.9	MAB	experimentally	18-42 (24)	85
Vernon & Mori (1992)	.46*	Wrist-Fingers	60.1	MAB	experimentally	18-38 (23)	88
Barret et al. (1990)	-.00[b]	Fingers-Wrist	39.7	RAPM	experimentally	18-41 (25.6)	44
Reed & Jensen (1991)	.04[c] -.07	Wrist-Elbow	68.9 67.1	RSPM & RAPM	statistically	18-25 (20.3)	200 (males)
Wickett & Vernon (1994)	.02[d] -.12	Wrist-Elbow Wrist-Fingers	60.5 59.0	MAB	experimentally	20-30 (24.6)	38 (females)
Rijsdijk et al. (1995)	-.02	Wrist-Elbow	63.7	RSPM	experimentally	14.8-18 (16.1)	312
This study	.15*	Wrist-Elbow	59.5	WAIS	experimentally	16.4-19.5 (17.6)	346

RSPM = Raven Standard Progressive Matrices; RAPM = Raven Advanced Progressive Matrices; MAB = Multidimensional Aptitude Battery; WAIS = Wechsler Adult Intelligence Scale.
[a] : 8 PNCV measures of these segments were aggregated into a single one, GNCV. The Correlation between GNCV and IQ is reported. [b] : mean correlation of 4 PNCV measures with IQ, [c]: correlations of two samples: community college (RSPM) and university students (RAMP), [d]: correlations with PNCV of two segments. N = Number of subjects, * = significant correlation.

Inspired by the original findings of Vernon and Mori we designed a study to investigate the relationship between PNCV and intelligence longitudinally in a sample of Dutch twins. We investigated to what extend the variation in IQ is attributed to variation in PNCV and to what extend the PNCV-IQ covariation is mediated by genetic and/or environmental factors. At the first test occasion at age 16, no correlation was found between scores on the Raven Standard Progressive Matrices (Raven, 1958) and PNCV measured in the median nerve (Rijsdijk *et al.*, 1995). This paper reports the correlation between PNCV in the median nerve and intelligence, determined by the Wechsler Adult Intelligence Scale (WAIS) in the same twin pairs at age 18. Using the WAIS IQ test was suggested to increase the probability of replicating the findings of Vernon and Mori, because the WAIS is highly correlated with the MAB [r = .91 for Full-Scale IQ (Jackson, 1984)]. This is in contrast with the Raven Advanced Progressive Matrices which has a common variance of only 50% with WAIS Full-Scale IQ [r = .72 (Vernon, 1983)]. In our sample the common variance between the Raven Standard Progressive Matrices and the WAIS Full-Scale IQ was even lower; 44% (r = .66). We also looked at the stability of the correlations between PNCV measured at age 16 and at age 18.

SUBJECTS AND METHODS

Subjects

This PNCV study was part of a longitudinal project in which genetic and environmental influences on brain development were examined (Van Beijsterveldt *et al.*, 1995, 1996). At age 16, 213 twin pairs participated in the study; at age 18, 196 pairs came back for a second time. The 17 twin pairs who dropped out did not differ significantly in IQ score compared to the others. PNCV and IQ data presented in this paper were collected at the second visit of the twins to the laboratory. Mean age (17.6, SD = .54) was equal for males and females. Subjects also participated in a large questionnaire study on health, personality and lifestyle factors such as smoking and sports participation (Koopmans *et al.*, 1994).

For 117 twin pairs zygosity was determined by blood and DNA typing and for the others by questionnaire data concerning physical similarity and the frequency by which the twins get confused by family members and strangers. For the blood and DNA typed group questionnaire data were available for 85 pairs. The percentage correctly classified zygosities based on the questionnaire information compared with blood group polymorphism and DNA was 95%.

IQ data were available for 37 MZM, 31 DZM, 46 MZF, 36 DZF and 44 DOS twin pairs. Data for median NCV were available for a subgroup of 34 MZM, 22 DZM, 40 MZF, 27 DZF and 36 DOS complete pairs. For another 28 twin pairs, PNCV data were available for only one twin of a pair (15 males and 13 females). In the bivariate genetic analysis and the analyses of the phenotypic correlations between PNCV and IQ, data from these incomplete pairs were included. Missing PNCV data for one or both twins in a pair were due to technical and procedural problems (e.g. difficulty in palpation of the nerve and ambiguous latency readings).

Intelligence test

The Dutch translation of the Wechsler Intelligence Scale (WAIS) was administered (Stinissen *et al.*, 1970).

Physical exercise

Questionnaire data on sports participation and other physical activities (e.g. cycling as transportation means) were available for 163 twin pairs and examined in relation to peripheral NCV. Physical activity level was proposed to be a covariate for peripheral NCV that should be controlled for when examining the relationship between PNCV and IQ (Reed, 1993).

Nerve conduction velocity

PNCVs were determined for the wrist-elbow segment of the median nerve, of the right arm. The median nerve is a mixed motor and sensory nerve. Supramaximal stimulation was used, i.e. stimulation of the nerve at a current value beyond which the amplitude of the nerve action potential no longer increases. From each subject two Compound Nerve Action Potentials (CNAP) were obtained; each CNAP was signal-averaged over 8 nerve stimulations. For each CNAP three components were distinguished: onset-, peak- and end latency. Reliability for PNCV measures was obtained by correlating the latencies of the two CNAPs. For the phenotypic correlations and the genetic analyses the two onset-, peak- and end latencies were averaged. The distance between the active stimulating and recording electrodes (wrist-elbow distance in millimetres) was divided by the mean onset, peak and end latencies (milliseconds), yielding one onset-, peak-, and end nerve conduction velocity measure per subject.

Onset and peak PNCV reflect the conduction in the fast-conducting (large diameter) nerve axons and the average-conducting (average diameter) nerve axons, respectively, while end PNCV involves slow-conducting (small diameter) axons (MA & Liveson, 1983; Oh, 1993). Onset PNCV is commonly used in studies examining the relation between IQ and PNCV, because it reflects conduction of the fast nerve fibres.

Two important errors can bias nerve conduction velocity assessment: latency readings and errors in surface measurement of the length of the nerve (Oh, 1993). To correct for the first type of error, compound nerve action potentials with ambiguous onset latencies were excluded from the sample. Temperature was experimentally controlled and kept at a constant level (33°C). For a detailed description of the action potential acquisition apparatus, -procedure and PNCV computation, see Rijsdijk *et al.* (1995).

Statistical analyses

The effect of sex on mean IQ and PNCV measures was assessed by likelihood-ratio χ^2 tests using the computer program LISREL Vll (Jöreskög & Sörbom, 1988). These tests compare the fit of a model that constrained parameter estimates for mean IQ and PNCVs to be equal across sexes to one which allowed them to vary in males and females, while taking into account the dependency that exists between observations from twins (Boomsma *et al.*, 1993). Phenotypic correlations between PNCV, IQ and age were estimated using LISREL Vll. To the variance-covariance matrices of the 5 sex-by-zygosity groups and the two singleton groups a model was fitted in which correlations as well as the standard deviations were estimated. Sex and zygosity differences in correlations were tested by comparing the fit of models which constrain correlations to be equal across groups with models in which correlations are set free. Significance of correlations was tested by comparing the fit with models in which correlations are constrained at zero.

Genetic analyses

Quantitative genetic model fitting was carried out on variance-covariance matrices to decompose the phenotypic variance. Sources of phenotypic variation considered were *A*, additive genetic variation (i.e. the sum of the average effects of the individual alleles at all loci); *D*, dominance genetic variation and *E*, a random environmental deviation that is not shared by family members. Dominance genetic effects, rather than *C* (common or shared environmental variation) were

considered, because of the high MZ versus DZ twin correlations. This model assumes negligible effects of assortative mating, and genotype-environment correlation and/or interaction. Relative contributions of the genetic and environmental influences to observed individual differences were estimated by maximum likelihood, using the computer program Mx (Neale, 1995). Also, 80% confidence intervals for the heritability estimates were computed (Neale & Miller, 1996). Goodness-of-fit was assessed by likelihood-ratio χ^2 tests.

Bivariate genetic analysis was used for modelling the relationship between PNCV and IQ. Two sets of latent *A*, *D* and *E* factors were specified: common factors influencing both PNCV and IQ and specific factors influencing IQ only. Figure 4.1 shows the model for one member of a twin pair, where A_C and E_C are the genetic and environmental influences common to PNCV and IQ, and A_S and E_S are the genetic and environmental influences specific to IQ. The effects of A_C and E_C on PNCV are represented by the parameters h_c and e_c and the effects of A_C and E_c on IQ by the parameters h'_c and e'_c.

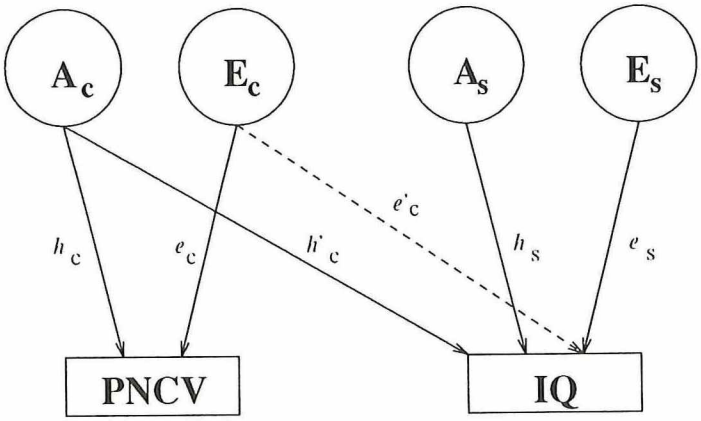

Figure 4.1
Bivariate genetic model for PNCV and IQ. A_C and E_C reflect the genetic and environmental influences common to PNCV and IQ; A_S and E_S reflect the genetic and environmental influences specific for IQ.

RESULTS I

Raw score distributions of the WAIS Full-Scale IQ and onset PNCV showed acceptable symmetry (skewness -.3 and .002; kurtosis -.42 and -.21, respectively), as did the distributions of WAIS Verbal IQ (VIQ), WAIS Performance IQ (PIQ), peak PNCV and end PNCV.

In Table 4.2 the means and standard deviations for WAIS Full-Scale IQ, VIQ, PIQ, and PNCV measures are presented. The onset PNCV mean of 59.6 m/s (SD = 3.4) for the total sample (N = 346) agrees with values reported in the literature for adults (age range, 20-60, temperature above 31) : 55.99 ± 3.3 (Oh, 1993). The observed mean WAIS Full-Scale IQ of 113.6 was higher and the standard deviation of 11.2 was lower than the population mean and standard deviation (M = 100; SD = 15). In a recent validation study (N = 601) of 4 subtests of the Dutch translation of the WAIS (Mulder *et al.*, 1995) it appeared that scores on all 4 tests were higher than the scores of the Dutch normative sample (Stinissen *et al.*, 1970). Bouma *et al.* (1996) suggested that this observation might be a consequence of increasing population IQ and that WAIS IQ scores based on the 1970 norms might be somewhat overestimated. There were no differences between males and females in mean scores for IQ, and for onset and peak PNCV. Mean end PNCV showed a significant sex difference [$\chi^2(1) = 26.1$]. Reliabilities for the PNCV measures obtained by the correlations for onset-, peak- and end latency between the two initial CNAPs available for every subject were .97, .98 and .98, respectively.

Table 4.2
Estimates of means and standard deviations for WAIS IQ scores and peripheral nerve conduction velocity measures.

	Males N = 163		Females N = 183		Sex differences
	M	SD	M	SD	$\Delta\chi^2(1)$
WAIS VIQ	110.2	12.5	109.7	11.7	0.14
WAIS PIQ	115.9	11.9	116.8	11.7	0.35
WAIS FSIQ	113.7	11.7	113.9	11.7	0.01
Onset PNCV (m/s)	59.3	3.3	59.9	3.6	3.34
Peak PNCV (m/s)	50.3	2.8	49.9	2.8	0.90
End PNCV (m/s)	43.2	2.4	41.8	2.3	21.03*

WAIS = Wechsler Adult Intelligence Scale; VIQ = Verbal IQ; PIQ = Performance IQ; FSIQ = Full-Scale IQ. PNCV = peripheral nerve conduction velocity. * = $\Delta\chi^2(1) > 3.84$, and implies a significant difference between males and females.

Potential confounders of PNCV are age, height, temperature, (Oh, 1993; Ma & Liveson, 1983; Rivner *et al.*, 1990; Stetson *et al.*, 1992) and physical exercise status (Reed, 1993). Age, height and physical exercise status, based on sports activity and daily cycling exercise did not show a correlation with PNCV. Arm temperature was experimentally controlled for and showed no correlation with PNCV. Table 4.3 shows the maximum-likelihood estimates of the phenotypic correlations between the PNCV measures and IQ scores. All PNCV-IQ correlations could be equated across twins, zygosity and sex without decline in fit. All PNCV-IQ correlations were significant.

Table 4.3
Maximum-likelihood estimates of the penotypic correlations between peripheral nerve conduction velocity and WAIS IQ.

	WAIS FSIQ	WAIS VIQ	WAIS PIQ
Onset PNCV	.15	.15	.15
Peak PNCV	.16	.17	.14
End PNCV	.18	.14	.15

WAIS = Wechsler Adult Intelligence Scale; FSIQ = Full-Scale IQ; VIQ = Verbal IQ; PIQ = Performal IQ; PNCV = peripheral nerve conduction velocity. All correlations are significant.

The twin correlations for the IQ scores, and the PNCV measures are given in Table 4.4, showing higher MZ than DZ correlations for all measures. The pattern of the female twin correlations (high MZ versus low DZ correlations) for WAIS VIQ, peak PNCV and end PNCV suggests dominance genetic effects. Therefore, a univariate *ADE* model for females and *AE* model for males was tested against the *ADE* sex-differences model. For all three variables the dominance structure could be dropped without worsening of fit and the reduced *AE* no-sex-differences model gave the best explanation of the data. For onset PNCV it was the correlation pattern for males that suggested a dominance genetic structure to be involved. This dominance structure could be omitted and further reduction of the model also showed the *AE* no-sex-difference model to have the best fit. The correlation pattern for WAIS Full-Scale IQ and WAIS PIQ suggested dominance genetic influences for both males and females, but the reduced *AE* no-sex-differences again showed the best fit to the data. Table 4.5 gives the univariate estimates and heritabilities for PNCV and IQ measures for the subsample with both PNCV and IQ data (159 pairs). Likelihood based confidence intervals (CI) provide information about the

precision of the estimates (Neale & Miller, 1996). In Table 4.5 the 80% CI for the heritability estimates for all variables are reported. Non-overlapping intervals, which is the case for example for WAIS Verbal IQ and WAIS Performance IQ, indicate that heritabilities are significantly different. Heritability for WAIS Full-Scale IQ was 81% and for onset PNCV the heritability was 66%. WAIS IQ data were available for a larger group (194 pairs). The heritability for WAIS Full-Scale IQ for this sample was 82% (Rijsdijk & Boomsma, submitted).

Table 4.4
Twin correlations for PNCV measures and WAIS IQ scores.

		Onset PNCV	Peak PNCV	End PNCV	WAIS VIQ	WAIS PIQ	WAIS FSIQ
MZM	(N = 34)	.80	.78	.79	.88	.74	.86
DZM	(N = 22)	.21	.41	.52	.47	.30	.37
MZF	(N = 40)	.63	.71	.71	.85	.65	.82
DZF	(N = 27)	.31	.19	.10	.30	.24	.34
DOS	(N = 36)	.39	.52	.45	.24	.20	.19

PNCV = peripheral nerve conduction velocity; WAIS = Wechsler Adult Intelligence Scale; VIQ = Verbal IQ; PIQ = Performal IQ; FSIQ = Full-Scale IQ. N = number of pairs with both PNCV and WAIS IQ data.

Table 4.5
Univariate estimates of genetic (a) and environmental (e) path coefficients and heritabilities with 80% confidence intervals for PNCV and IQ measures.

	χ^2 (df=13)	p	a	e	h^2	80% CI for h^2
Onset PNCV	15.08	.30	2.72	1.94	66%	58%-73%
Peak PNCV	14.04	.37	2.31	1.46	71%	64%-77%
End PNCV	13.88	.38	1.95	1.22	72%	65%-78%
WAIS VIQ	13.72	.44	10.95	5.02	83%	78%-86%
WAIS PIQ	3.62	.99	9.43	6.60	67%	59%-74%
WAIS FSIQ	10.18	.68	10.46	5.08	81%	76%-85%

PNCV = peripheral nerve conduction velocity; WAIS = Wechsler Adult Intelligence Scale; VIQ = Verbal IQ; PIQ = Performal IQ; FSIQ = WAIS Full-Scale IQ. The best fitting model for all variables was an AE no-sex-differences model.

Onset PNCV and the WAIS Full-Scale IQ score were used to investigate the PNCV-IQ relationship, using the genetic model presented in Figure 4.1. In Table 4.6 the bivariate analysis results are presented. An *ADE* model with sex differences did not show a better fit than a model in which the parameters were equated across males and females. In the next step the common dominance genetic factor could be omitted without worsening of fit. In the reduced *AE* no-sex-differences model the common unique environmental influences of PNCV on IQ (e'_c) could be fixed at zero without deterioration in fit [$\Delta\chi^2(1) = .22$, $p = .64$], whereas the common genetic influences (h'_c) could not be constrained at zero [$\Delta\chi^2(1) = 4.15$, $p = .04$]. These results indicate that all common variance in PNCV and IQ can be explained by common additive genetic factors ($\chi^2_{51} = 58.4$, $p = .22$). This model gave a good fit to the data. Thus, the PNCV-IQ relationship is purely based on common genetic mediation. The genetic correlation (r_g) between PNCV and IQ as estimated by Mx was .20. The heritability for onset PNCV was .66 with a 80% CI of .58 - .73. Heritability for WAIS Full-Scale IQ score .81 with a 80% CI of .75 - .84. The phenotypic correlation between onset PNCV and WAIS Full-Scale IQ based on the Mx estimates was .15. In Table 4.7 the parameter estimates of specific and common genetic and environmental influences for the best fitting model are presented.

Tabel 4.6
Bivariate model fitting results for onset PNCV with WAIS Full-Scale IQ.

Model	χ^2	df	*p*
ADE sd	48.73	38	.11
ADE nsd	56.13	47	.17
AE nsd	58.26	50	.19
AE nsd, no e'_c *	58.40	51	.22
AE nsd, no h'_c	62.41	51	.13

e'_c = environmental path from PNCV to IQ. h'_c = genetic path from PNCV to IQ. (n)sd = (no-)sex-differences. * = Best fitting model: *AE* no-sex-differences and no common environmental influences.

Tabel 4.7
Genetic and environmental specific and common effects of the bivariate model of PNCV and WAIS Full-Scale IQ.

Genetic & environmental specific effects for IQ		Genetic & environmental common effects for IQ		Genetic & environmental common effects for PNCV	
h_s	e_s	h'_c	e'_c	h_c	e_c
10.121	5.121	2.054	0.00	2.718	1.960

h_c and e_c are the components of the common genetic and environmental factors influencing PNCV; h'_c is the component of the common genetic structure, reflecting the genetic mediation of the correlation between PNCV and IQ; $e'_c = 0$, means no environmental correlation between PNCV and IQ; h_s and e_s are the components of the genetic and environmental specific factors exclusively influencing IQ.

DISCUSSION I

For WAIS Full-Scale IQ a heritability estimate of 81% was observed. This is in line with or somewhat higher than most family and twin studies. As Reed (1988) predicted, human peripheral NCV was found to be a substantial heritable trait (66%). Reed suggested that PNCV as a heritable trait, to some extend could explain part of the genetic variation in human intelligence and consequently the PNCV-IQ relationship should be mediated by genetic factors. A low but significant correlation between peripheral NCV and IQ was found in our sample and this correlation was solely mediated by common genetic factors. The genetic correlation between onset PNCV and IQ was .20.

Peripheral NCV, when measured in the same subjects at age 16, showed a heritability of 76%. No correlation was found between Raven Standard Progressive Matrices test scores and peripheral NCV. The lack of correlation between IQ and peripheral NCV was also found in other studies using the Raven test (Jensen & Reed, 1991 and Barrett *et al.*, 1990). The use of the Raven IQ test was proposed as a possible explanation for the lack of correlation between PNCV and IQ, because the correlations of .43 and .46 between PNCV and IQ found by Vernon and Mori were obtained using the Multi Aptitude Battery (MAB). The WAIS test was used in the present study to enlarge the probability of replicating the results of Vernon and Mori (1992), though, Wicket and Vernon (1994) failed to replicate a significant correlation between the MAB IQ scores and PNCV in a sample of adult females. However, the correlation of the Raven IQ scores of our first study with PNCVs of the second study ($r = .17, p < .05$) was higher then the correlation

between WAIS Full-Scale IQ and PNCVs of the second study, suggesting that lack of correlation was not due to the Raven test.

Results for both test occasions revealed the peripheral NCV measure to be a substantial heritable trait, 76% and 66%, respectively. However, the test-retest correlations of the PNCV measures were very low, for onset PNCV .13 ($p < .05$), for peak PNCV .08 (ns) and for end PNCV .20 ($p < .05$). PNCV data at both age 16 and 18 were available for 293 individuals. No changes were made in acquisition procedure, apparatus, experimenter and nerve conduction velocity computation. Possible statistical artifacts like non-normality, that might explain this lack of correlation were extensively tested by means of randomization tests. Randomization tests do not imply assumptions about binormality and the significance (p-value) of a statistical test is derived from the empirical distribution of p-values bases on (part of) all possible combinations. When results of a randomisation test of for example test-retest correlation are similar to the probability value of the classical test, the possibility of a wrong decision based on the classical test, when a non-binormal distribution leads to a distorted p-value, is ruled out. No difference in the probability values for the test-retest correlations of latencies, wrist-elbow distance and PNCVs were obtained in either way. These results imply that lack of stability in the PNCV data is not caused by statistical artifacts as non-binormality and justify the use of parametrical tests.

The twin correlation pattern, especially the high MZ correlations, also suggests that the lack of test-retest correlation, is not solely due to measurement errors and technical pitfalls. Moreover, the low DZ PNCV twin correlations relative to MZ correlations suggest that high MZ twin correlations are not the result of correlated measurement errors. Additional evidence for PNCV measurement consistency or reliability can be obtained by split-half correlations for the 3 latencies between the two initial compound nerve action potentials available for every subject. Reliability for onset-, peak- and end latency was .97, .98 and .98, respectively. The same reliability indices were observed for the 3 latencies of the first test occasion: .97, .99 and .99, respectively.

We speculate that the lack of correlation between age 16 and 18 might be explained by ongoing maturation processes in this age-range. Nerve conduction velocity increases in a logarithmic function. From birth to approximately age 4-6, peripheral NCV increases rapidly as a result of the myelination process and the increase in the number of large axonal fibres (Cruz Martinez *et al.*, 1978; Wagner & Buchthal, 1972; Gamstorp & Shelburne, 1965). The existence of double peaks in the sensory nerve action potential (up to age 6), indicates the presence of two groups of fibres with different degrees of maturation. No further increase in PNCV

is noted between 4-6 and 16 years of age. PNCV decreases in the late twenties. The rate of decrease for mixed PNCV per decade is approximately 4 m/sec in the median nerve (Oh, 1993).
It is reasonable to assume that, with respect to PNCV development, individual growth curves show the same morphology but have different slopes, for example, the speed of maturation might differ per individual. It is also reasonable to assume that maturation processes might be more alike in MZ twins compared to DZ twins.

We, therefore, decided to examine whether ongoing maturation processes in this age sample might explain our findings of 1) a significant correlation of PNCV with both Raven and WAIS IQ at age 18 but not at age 16; 2) a low test-retest correlation between PNCV assessed at ages 16 and 18 and 3) high MZ correlations (and high heritabilities) at both ages 16 and 18. A genetic analysis of PNCV difference scores (PNCV assessed at test occasion II - PNCV assessed at test occasion I) was carried out. Second, the relation of PNCV and IQ was studied in subjects who showed positive and negative difference scores. Negative difference scores might indicate that PNCV has not yet reached the highest value and positive difference scores might reflect a phase in which this value was reached and PNCV is then declining. It is possible that the PNCV-IQ relation is only fully observable, once PNCV has reached its highest value.

RESULTS II

To study the maturation hypothesis a difference score between onset Nerve Conduction Velocity of the second and the first test occasion was calculated (difONCV). DifONCV was normally distributed (M = -3.7; SD = 8.1; skewness = -.16; kurtosis = -.23) with about 70% of the observations between one standard deviation from the mean (Figure 4.2). The difference scores for peak PNCV (difPNCV) and end PNCV (difENCV) were also normally distributed (skewness = -.02 and .00, kurtosis = .15 and .5, respectively). In subjects with positive difference scores, PNCV is still increasing from age 16 to 18. In subjects with negative difference scores, PNCV has supposedly reached the highest value and is decreasing. This later group is in a relatively stable maturation phase or in a phase representing PNCV decrease. There were sex differences for mean difONCV and mean end PNCV difference score (difENCV). Mean difONCV for males was -1.5 and for females -4.3 [$\chi^2(1) = 7.2$]. Mean difENCV for males was 4.3 and for females 2.9 [$\chi^2(1) = 5.9$]. There was no sex difference in mean peak difference

score [M = 1.1, $\chi^2(1) = 3.2$]. No significant age differences were seen between the groups with positive and negative difference scores.

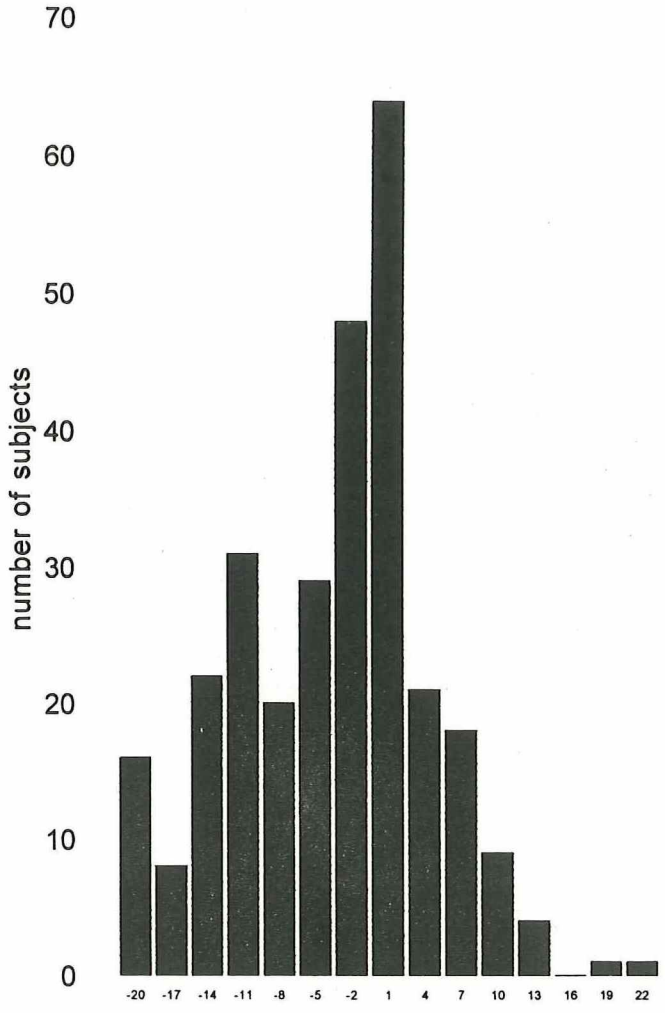

Figure 4.2
Distribution of the difference scores for onset PNCV between age 18 and 16 (difONCV). The *X* axis represents the difONCV scores.

The twin correlations for difONCV suggest genetic determination (Table 4.8). The higher MZ compared to DZ twin correlations suggested dominance genetic effects. In contrast to the PNCV measure the dominance structure was significant for PNCV difference scores. For difONCV the *ADE* model with sex differences could be simplified by dropping the female dominance structure [$\Delta\chi^2(1) = 0.10$, $p = .75$], whereas the male dominance structure was significant and could not be dropped [$\Delta\chi^2(1) = 8.16$, $p = .00$]. For males, 86% of the variance in difONCV was explained by dominance genetic factors, about zero by additive genetic factors and about 14% by unique environmental influences. For females, 87% of the variance was explained by additive genetic factors and 13% by unique environmental factors. For peak- and end PNCV difference scores the *AE*-female and *ADE*-male model also was the best fitting model. For males, the additive genetic variance in difPNCV and difENCV were also about zero and the dominance genetic variance 83% and 75%, respectively. For females the additive genetic variance in difPNCV and difENCV were 73% and 74%, respectively.

The correlations between onset PNCV and WAIS Full-Scale IQ for subjects with positive difference scores ($N = 104$) was .08, whereas in the other group ($N = 189$) the correlation was higher (.21). The results for the groups with positive and negative difference scores for Peak PNCV and end PNCV were: .04 ($N = 169$) versus .23 ($N = 124$) and .08 ($N = 223$) versus .34 ($N = 70$), respectively. Although the correlations between onset PNCV and IQ for the positive and negative difference score groups were not significantly different, the consistent pattern across PNCV measures of low correlations in the group with positive difference scores as opposed to higher correlations in the group with negative difference scores might support the notion that an association between PNCV and IQ only becomes apparent once PNCV has reached its highest value.

Table 4.8
Twin correlations and heritabilities with 80% confidence intervals for PNCV difference scores.

	MZM (N=22)	DZM (N=15)	MZF (N=33)	DZF (N=21)	DOS (N=29)	h^2_m	80% CI for h^2_m	h^2_f	80% CI for h^2_f	χ^2 (df=10)
difONCV	.85	.12	.83	.38	.01	86%	78%-91%	87%	81%-91%	8.13
difPNCV	.85	.13	.69	.39	.05	84%	75%-89%	73%	61%-81%	9.64
difENCV	.78	.05	.73	.35	-.22	75%	61%-84%	74%	62%-82%	12.65

difONCV, difPNCV and difENCV = Difference scores between Onset-, Peak and End PNCV measured at age 18 and at age 16. Best fitting model for all variables was *ADE* for males and *AE* for females. N = number of twin pairs. h^2_m, h^2_f = heritability for males, females.

GENERAL DISCUSSION

The results of the genetic analysis of the difference scores between the PNCVs of the first and second test occasion are remarkable. Nearly all of the variance in difONCV can be explained by genetic influences. These results imply that an individual's PNCV, measured on the second test occasion at age 18, is better predicted by the increase or decrease of the PNCV value of his co-twin than by his or her own PNCV score at age 16. If the difONCV value can be considered a maturation index, these results give evidence that PNCV is still increasing for some individuals in this age interval. It might be that the variance in IQ explained by PNCV is a consequence of nerve maturation in the late adolescent years. Our data suggest that the existence of a correlation of PNCV and IQ might depend on whether nerve conduction has reached its highest value. The correlation of the Raven test scores measured at age 16 with PNCVs of the present study was higher then the correlation between WAIS-IQ and PNCVs of the second study. This suggests that the PNCV measures obtained at age 16 were not correlated with IQ because of ongoing maturation processes. If individual differences in PNCV only become determinants of IQ once PNCV has reached its highest value, then we would predict additional genes that influence IQ and thus, higher heritabilities in IQ. This hypothesis of additional genetic variance is in line with the observation of further increase of IQ heritability in adults. The MZ IQ correlations appear to peak at about 16 to 20 years of age, although there is very little adult data on heritability in IQ (Bouchard, 1993).

The maturation hypothesis might explain why Vernon and Mori (1992) observed high correlations between peripheral NCV and IQ in both studies. The mean age of their samples were 24 and 23 years, respectively. In this age group PNCV is supposed to be in a stable phase, in which the PNCV-IQ correlation can be observed. The mean age of the samples in the Barret *et al.* (1990) and the Wickett and Vernon (1994) studies was also high, but the sample sizes were to small to detect even a low significant correlation of .3. Also, the Barrett *et al.* (1990) study did not use supramaximal nerve stimulation, a requirement to make sure all nerve fibres are stimulated in the tested nerve. The mean age of the sample of the Reed and Jensen (1991) study was higher than in our own study (20 years of age) and the number of subjects was large (N = 200), but the absence of experimental control of temperature could be the major reason why they did not find a correlation between PNCV and IQ.

The question remains, how to interpret the low but significant correlation between PNCV and IQ and the fact that this correlation is solely mediated by

common genetic factors. According to Jensen and Sinha (1993), trait variation due to multiple factors (like intelligence test scores) are unlikely to show large correlations with any single causal factor. Small significant correlations that are consistently replicable could be of theoretical interest especially if the intercorrelation among a number of biological and psychometric variables show a consistent pattern. Genetic analyses are considered to play an essential role in the theoretical interpretation of intercorrelations between biological and behavioral variables. Peripheral NCV was shown to be a considerable heritable trait and the correlation with intelligence test scores, even though small, is genetically mediated. As for replicability, peripheral NCV measures for the first and present study do not correlate, and it is proposed that the reasons for this lack is based on unstable, still increasing nerve conduction velocities in the tested age interval.

5

The genetic basis of the relation between speed-of-information-processing and IQ

F.V. Rijsdijk, P.A. Vernon and D.I. Boomsma

INTRODUCTION

In the search for determinants of human intelligence the relationship between measures of timed performance on experimental cognitive tasks and scores on psychometric tests of intelligence is the most extensively studied and well established. Experimental cognitive tasks, usually defined as Reaction Time tasks, are supposed to be a reflection of the speed-of-information-processing. The idea of studying Reaction Times (RTs) as correlates of intelligence goes back to Galton (1883), but it was not until after the 1960s that a great deal of research on RTs and intelligence was (successfully) conducted. One of the major contributors to this area is Jensen (e.g. 1979, 1987). The history of the research on RTs is extensively reviewed in Vernon (1987).

Speed-of-information-processing (SIP) typically involves Long Term Memory (LTM) retrieval and Short Term Memory (STM) scanning and is often derived from RT tasks consisting of highly overlearned stimuli, such as digits and letters. Operations on these RTs do not seem to involve the complex sort of reasoning skills required by intelligence tests. Therefore, the relationship between SIP and intelligence measures does not seem to be attributable to common content shared by these tests, nor to the fact that some parts of IQ tests are timed (Vernon, 1983). Moreover, Vernon and Kantor (1986) showed that the reaction time variables actually explain less of the variance of a timed intelligence test than that of an untimed administration of the same test.

Speed-of-information-processing is suggested to measure the efficiency with which subjects can perform basic cognitive operations which underlie other kinds of intellectual behavior, like the kinds involved in performance on psychometric

tests. The correlations of individual RTs and IQ typically are in the -.2 to -.4 range, and can be increased by combining the performance measures from several different RT tasks. When combined in multiple regression analyses the correlation between IQ and speed-of-information-processing becomes quite substantial, accounting for almost 50% of the phenotypic variance of IQ (Vernon, 1989). Individual differences in intelligence, thus, are suggested to be moderately attributable to variance in the speed or efficiency with which individuals can execute basic cognitive operations.

A theoretical explanation for the relationship between RTs and IQ was given by the 'neural efficiency' model (Jensen, 1982; Vernon, 1983, 1985), in terms of three characteristics of the short term memory system or 'working memory' in which the basic cognitive operations are carried out. First, this STM system has a limited capacity to store information and only about seven discrete units or chunks of information can be hold at any one time. Second, there is rapid decay of information when there is no continued rehearsal and third, there is a trade-off between the amount of information that can be stored in working memory at one time and the amount of information that can be processed simultaneously. To overcome these limiting properties of working memory and to prevent the capacity threshold from being exceeded, a fourth property was proposed: speed-of-information-processing. The speed or efficiency with which individuals can execute basic cognitive operations at each step in solving a given problem might, therefore, be expected to have an effect on the success of their performance. Because of the well established negative correlation between conventional psychometric tests and timed performance on experimental cognitive (Reaction Time) tasks, these tasks are suggested to be a good instrument for testing the neurological basis of individual differences because they have a true ratio scale and do not depend on a norm or reference group for interpretation (Jensen, 1993). Individual differences on SIP measures are not attributable to specific knowledge and acquired skills.

As is indicated by twin and family studies, individual differences in intelligence are considerably determined by genetic influences. If individual differences in the speed with which cognitive operations can be executed are responsible for individual differences in intelligence, the next question is to what extent they are attributable to differences in neurophysiological properties of the brain that may be hypothesized to underlie both the speed with which persons can process information and their intelligence. One approach to this question is to examine the heritabilities of individual differences in SIP and the extent to which the phenotypic correlation between intelligence tests and SIP is determined by underlying genetic factors. The phenotypic association between IQ and SIP could

be entirely mediated by environmental factors. It is likely, however, that some common features of both SIP and IQ are determined by the same neurophysiological processes and thus are influenced by the same or correlated genetic factors. Behavioral genetic studies have yielded moderate heritability estimates for basic cognitive tasks. These studies in which the genetic basis of speed-of-information measures was reported are discussed below and next, the few studies examining the genetic basis of the relation between RTs and IQ.

In an adult twin study, conducted by McGue, Bouchard, Lykken and Feuer (1984), the heritability of speed-of-information-processing measures was investigated. In a sample of 105 subjects, including 34 MZ and 13 DZ reared apart twin pairs or triplets (mean age, 38.8 years), a Reaction Time test battery and a battery of psychometric tests of mental ability were administered. Factor analysis of the RT tests yielded three information processing components, accounting for 67% of the total variance. The three factors were labelled Overall Speed of Response, Speed of Information Processing and Speed of Spatial Processing. Significant MZ intraclass correlations were observed only for the Overall Speed of Response factor (r = .46). The Overall Speed component underlying the reaction time tasks accounted for a large portion of the variance in the information processing measures and correlated -.31 with WAIS Full-Scale IQ. This component was, thus, suggested to be strongly related to psychometric measures of g, for which substantial genetic effects were observed.

Another adult twin study on speed-of-information-processing measures, Vernon (1989), reported a heritability of 49% in 50 MZ and 52 DZ twins for a General Speed of Response factor based on 8 complex reaction time tests. The age range in this sample was quite large, between 15 and 57 years (mean age, 24 years) This heritability index was derived by means of Falconer's Formula [$h^2 = 2(r_{mz} - r_{dz})$]. The RT tests were highly correlated with the Multidimensional Aptitude Battery IQ score (MAB). The MAB is an IQ test closely pictured after the WAIS. Vernon observed that heritabilities of the RT measures were positively related to: the degree of loading on the general Speed of Response factor (r = .39); the extent to which each RT task correlated with a General intelligence factor g (r = .60) and the tests' relative complexity (r = . 68). Vernon (1991) reported correlations of -.44 between a general IQ and a general SIP factor from 2 studies that also measured peripheral nerve conduction velocity.

Rose, Miller and Fulker (1981) estimated heritability to be 76% for a Perceptual Speed measure in 74 MZ and 127 DZ college-aged twins and genetic half-siblings (MZ twin offspring). Boomsma and Somsen (1991) measured RTs in a small sample of 12 MZ and 12 DZ adolescent twins (age range, 15 - 18). For

Choice RT higher heritabilities were reported for shorter than (20%) for longer (7%) interstimulus intervals. Heritabilities of almost 50% were seen for reaction times in Double Task trials where subjects simultaneously performed mental arithmetic and a Choice RT task.

In a study conducted by McGue & Bouchard (1989), an information-processing battery and psychometric battery of special mental abilities were administered to a sample of 49 MZ and 25 DZ twin pairs reared apart (mean age, 39.9 years). Heritabilities of 54% and 58% were observed for a Basic and for a Spatial Speed factor. For the special mental abilities, the Verbal factor showed a heritability of 57% and the spatial factor 71%. No bivariate genetic results were reported. The first conclusion in this paper was that in even relatively simple tasks, information processing reflects a General Speed factor that is moderately related to the General intelligence factor (*g*). The second conclusion was that, as the actual content of information processing tasks and psychometric tests becomes more similar, the correlation between the two rises.

Petrill, Thompson and Detterman (1995) suggested that heritability and common environment for elementary cognitive tasks might differ in younger populations. They examined a battery of elementary cognitive ability tasks in a school-aged sample of 149 MZ and 138 same-sex DZ twin pairs (age range, 6 - 13 years, mean age, 9.55 years). Scores on the RT tasks were age and sex corrected. Univariate model fitting did not yield a homogeneous pattern of genetic and environmental influences across the RT measures. Simple and Choice RTs were primarily determined by common environmental factors, while a Stimulus Discrimination task appeared to be more influenced by genetic factors. Measures on the Stimulus Discrimination task showed the highest heritabilities on average (42%) and their composite score also showed the highest correlation with IQ (r = .42), but there was no consistent pattern of tasks with higher heritabilities also showing higher correlations with IQ.

Only a few studies have been conducted to investigate the genetic and environmental sources of the relationship between speed-of-information-processing and IQ. A multivariate genetic analysis of the relation between RTs and the WAIS Full-Scale IQ score was carried out by Ho, Baker and Decker (1988) in 30 MZ and 30 DZ pairs (age range, 8 - 18 years). Speed measures were Rapid Automatic Naming and Symbol-Processing Speed factors. Heritabilities for these factors were 52% and 49%, heritability for IQ was 78%. Results indicated that the phenotypic correlation between IQ and speed of processing measures (both r's .42) were largely attributable to correlated genetic effects. Genetic correlations were .46 and .67, respectively. The authors concluded that the results supported the notion of

some common biological mechanism underlying both general intelligence and speed-of-information-processing measures.

A bivariate analysis of the Vernon (1989) RT and IQ data in 50 MZ and 32 same-sex DZ pairs (15 - 57 years) was reported by Baker, Vernon and Ho (1991). The heritability of the General Speed of Processing factor was estimated to be 45%. Phenotypic correlations of Verbal and Performance IQ with the General Speed of Processing factor were both -.59 and were entirely mediated by genetic factors. Genetic correlations were estimated to have absolute values of .92 and 1.0, respectively. Baker *et al.* concluded that the results emphasize the importance of common, heritable, biological mechanisms underlying the speed-IQ association.

More recently, Petrill *et al.* (1996) conducted a multivariate analysis on 6 measures (3 speed and 3 percent-correct variables) of the elementary cognitive tasks and the 11 subtests of the WISC-R, employing the same data as in their earlier study (Petrill *et al.*, 1995). The genetic variance could be represented by a General-, a Verbal-, a Performance-, and a Speed factor. Common environmental influences could be supported by one General factor. Loadings of the 3 speed measures and of all WISC-R subtests on the General genetic factor were modest compared to their loadings on the General common environmental factor. These results indicated that covariance of speed-of-information-processing with IQ in this sample is predominantly determined by common environment. Given the age range of this sample (6 - 13 years), these results would be in accordance with observations of the important effects of common environment on IQ in this age interval. However, the fact that all RT data were regressed on sex and age makes these findings more difficult to interpret.

Genetic studies of reaction time tasks thus suggest moderate to high heritability estimates in adult and adolescent samples and the correlation of RT with IQ is probably influenced by genetic factors. In the present study, results of a longitudinal study on Reaction Times and intelligence are reported. On the first test occasion a Reaction Time test battery and the Raven Standard Progressive Matrices (Raven, 1958) were administered to a group of 16 year-old Dutch twins. On the second test occasion (one and a half years later) the same Reaction Time test battery (slightly modified) and the Dutch translation of the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1955) were administered. Phenotypic as well as genetic factor models were fitted to the covariance structure among these tests in order to derive the significance of General and Group factors. The phenotypic and the genetic relationship between reaction times and IQ scores were examined in a multivariate design in which all variables were included. This approach is in contrast to the two studies (Ho *et al.*, 1988; Baker *et al.*, 1991), in which

phenotypically formed factor scores of speed and IQ measures were employed in the genetic analyses. A major disadvantage of using phenotypic factor scores is that phenotypic factor analysis may yield quite a different factor pattern than is observed for the genetic and environmental matrices when genetic analysis is conducted on the complete set of variables. Variability in reaction time tasks and designs in the few genetic RT-IQ studies hampers comparability of results. In the Petrill *et al.* (1996) study the phenotypic and genetic relationships among elementary cognitive tasks and the WISC-R subtests were examined in a multivariate design including all variables, rather than factor scores. Thus, as for design and intelligence test, the present study and the Petrill *et al.* (1996) study are the most comparable and, to some degree, this enables one to compare the results in two age groups. The longitudinal nature of our data also makes it possible to compare the RT results of two time points and to test whether new genetic influences on the RTs enter at age 18 compared to age 16.

SUBJECTS AND METHODS

Subjects

Subjects were 213 Dutch twin pairs who participated in a longitudinal project which investigated variation in peripheral nerve conduction velocity and intelligence (Rijsdijk *et al.*, 1995) and genetic and environmental influences on brain development (Van Beijsterveldt *et al.*, 1995, 1996). A reaction time test battery as well as the Raven Standard Progressive Matrices test were employed at the first visit of the twins to the laboratory (mean age, 16.13; SD, .56). On the second visit, one and a half years later (mean age, 17.6; SD, .54), the Dutch version of the Wechsler Adult Intelligence Scale (WAIS) was individually administered. Also, the same reaction time test battery (slightly modified) was employed. Seventeen pairs did not participate the second time. This group did not significantly differ in IQ score compared to the other participants. Mean age was equal for males and females. IQ and reaction time data on the first test occasion were available for 34 monozygotic male twin pairs (MZM), 33 dizygotic male twin pairs (DZM), 48 monozygotic female twin pairs (MZF), 32 dizygotic female twin pairs (DZF) and 44 dizygotic opposite sex twin pairs (DOS). On the second test occasion data were available for 33 MZM, 30 DZM, 41 MZF, 31 DZF and 39 DOS pairs.

For 117 same-sex twin pairs zygosity was determined by bloodgroup and DNA typing and for the others by using items from a questionnaire concerning physical similarity and the frequency with which the twins get confused by family members

and strangers. For the blood and DNA typed group questionnaire data were available for 85 pairs. The percentage correctly classified zygosities based on the questionnaire information compared with blood group polymorphisms and DNA was 95%.

Reaction time test battery of test occasion I

Five reaction time tasks were administered via a personal computer with an attached response console containing a home key and two response keys, equidistant (15 cm) from the home key. Principals of response routine were stated in a general instruction: the home key had to be pressed in order to initiate each new trial and was not to be released until the test stimulus was presented and the subject had made a decision which response key to operate. Only index and middle finger of the preferred hand were used. Subjects were instructed to respond as quickly and accurately as they could. Each of the tests began with instruction and rehearsal trials. In this paper the sum of the Decision Time (time from onset of the stimuli to the release of the home key) and the Movement Time (time from releasing the home key to pressing the response key) was employed as the measure for speed of performance (msec). For each task, a mean Reaction Time was computed for each subject after outlier trials, exceeding three standard deviation units above or below an initially computed individual mean, were removed. In addition to this individual screening of outliers per RT task, all subjects with mean RTs exceeding ± 3 standard deviation units from the group means were excluded. Subjects with less than 50% correct responses on a RT task were excluded as well. For test occasion I, 14 subjects and for test occasion II, 23 subjects were excluded.

Donders Simple Reaction Time (SRT)

Each trial was started by pressing the home key, which, after a 1000 msec intertrial time, initiated the presentation of a 500 msec visual warning stimulus (a plus sign) on the centre of the screen. A variable blank interval separated warning signal offset from the presentation of a visual reaction stimulus. The variable time interval was composed of a 500 msec base time plus a random number between 0-500 msec and was implemented to prevent automatic reactions. The reaction stimulus represented either one digit from the set {'1', '2', '3', '4', '5', '6'} or one letter from the set {'A', 'B', 'C', 'D', 'E', 'F'}, both requiring right-key responses. The reaction stimulus disappeared as soon as the subject responded, or when a maximum time of 1500 msec had expired. When maximum time was

exceeded or when the wrong key was pressed, subjects were given a 500 msec visual feedback (the word 'wrong') in the centre of the screen.
Subjects started with 12 practice trials. The number of test trials was 72, containing an equal number of digits and letters.

Donders Two Choice Reaction Time (CRT)

This task was the same as the first task, except that the reaction stimulus representing a digit required a right-key response and a reaction stimulus representing a letter required a left-key response.
Subjects started with 12 practice trials (6 digits and 6 letters). The 72 test trials were composed of an equal number of digits and letters.

Sternberg Short Term Memory scanning (STM)

Each trial was started by pressing the home key, which (after an intertrial time of 2000 msec) initiated a one-by-one display of a number of digits on the centre of the screen. There were five conditions: the number of digits (1 to 5) in the memory set. The 5 digits were drawn from the set { '0', ... , '9' }. Each digit was displayed for 1000 msec. Time between subsequent digits was 1000 msec. After offset of the last digit a 1000 msec visual warning signal (dot) was presented. A blank interval separated the presentation of the warning signal from the presentation of the visual probe stimulus. The probe stimulus (a single digit) was either one from the memory set (positive trial), requiring a right-key response, or not (negative trial), requiring a left-key response. The probe stimulus disappeared as soon as the subject responded, or when a maximum time of 2000 msec had expired. When maximum time was exceeded or whenever a key was pressed, subjects were given a 500 msec visual feedback by presentation of a white square on either the left or right half of the screen (indicating the position of the correct key).
Subjects started with 10 practice trials. The number of test trials was 100, 20 for each condition (memory-set size) with an equal number of positive and negative trials ('yes'/'no' responses).

Posner Letter Identification: Name Identification (NI)

Each trial was started by pressing the home key, which (after an intertrial time of 1000 msec) initiated the presentation of a 500 msec warning signal (a plus sign). A blank 400 msec interval separated the offset of the warning signal from

the presentation of the visual reaction stimuli. The reaction stimuli were two letters from the set {'A', 'B', 'E', 'N', 'O', 'S'}. A pair of identical letters required a right-key response and two different letters a left-key response. The reaction stimuli disappeared as soon as the subject responded, or when a maximum time of 1500 msec had expired. When maximum time was exceeded or whenever a key was pressed, subjects were given a 500 msec visual feedback by presentation of the words 'wrong or 'right' on either the left or right half of the screen (indicating the position of the correct key). Feedback was also given whenever the home-key was released too soon, together with a 100 msec auditory penalty signal (500 Hz). Subjects started with 12 practice trials. The number of test trials was 60, with an equal number of positive and negative trials ('yes'/ 'no' responses).

Posner Letter Identification: Category Identification (CI)

This task is the same as the Name Identification, but the reaction stimuli, from the set {'A', 'B', 'E', 'N', 'O', 'S'} had to be matched on the category they belong to: vowels or consonants. A pair of letters belonging to the same category required a right-key response and a pair belonging to different categories, a left-key response.

Subjects started with 12 practice trials. The number of test trials was 60, with an equal number of positive and negative trials ('yes'/ 'no' responses).

Reaction time test battery Test Occasion II

The same five Reaction Time tasks were administered with a few modifications. The number of test trials was reduced to 60 trials per task. For the Sternberg STM task this reduction implicated the removal of two conditions (memory-set size 2 and 4). These changes were made to shorten the administration time. Other adjustments were made in order to ensure maximum motivation. For each task a *target reaction time value* was established, based on the observed means of test occasion 1. After each response, the reaction time was displayed on the screen and subjects were given feedback whenever their reaction time was slower than the target reaction time value for that specific task. Also, every correct response was rewarded with 5 cents.

Intelligence tests

On test occasion 1 the Raven Standard Progressive Matrices Test (Raven, 1958) was administered without a time limit. The IQ-score was simply the number of correct answers. On test occasion 2 the Dutch translation of the Wechsler Adult Intelligence Scale (Stinissen *et al.*, 1970) was administered.

Statistical analyses

Phenotypic analyses

The effect of sex on mean and standard deviation of IQ and RT measures was assessed by likelihood-ratio χ^2 tests with the structural equation modelling program Mx (Neale, 1995). This was accomplished by specifying a model for the means as well as the covariances of the 5 sex-by-zygosity groups. The fit of a model that constrained parameter estimates of means and standard deviations for each variable to be equal across sexes was compared to one which allowed them to vary in males and females, while taking into account the dependency that exists between observations from twins (Boomsma *et al.*, 1993). The chi-squared statistic is computed by subtracting the χ^2 for the full model (e.g. one specifying two different means for males and females) from that for the reduced model. The degrees of freedom for this test is equal to the difference between the df (Δ df) of the two models (Neale & Cardon, 1992).

Sex differences in phenotypic correlations among the WAIS subtests, Raven and the RT measures were also examined in Mx. To the covariance matrices of males and females a model was fitted in which maximum-likelihood correlations as well as the standard deviations were obtained.
The model imposed upon the covariance matrices can be denoted as:

$$\Sigma_{YY} = \mathbf{S} * \mathbf{R} * \mathbf{S}',$$

where Σ_{YY} is the observed v x v covariance matrix, **S** is a v x v diagonal matrix in which the standard deviations are estimated, and **R** is a v x v symmetric matrix in which the correlations among variables are estimated (v = number of variables). Firstly, the standard deviations were tested for sex differences by comparing the fit of models which constrained standard deviations to be equal across groups with models in which they were allowed to vary, while correlation estimates were set free. Next, the same strategy was followed for testing sex differences in correlations, while standard deviations were constrained to be equal for males and

females. Significance of a single correlation was tested by evaluating the significance of the χ^2-change of the model in which the correlation (the specific element in matrix $\mathbf{R}$) was fixed at zero.

Confirmatory phenotypic factor analysis was conducted on the variance-covariance matrix of the whole sample by model fitting in Mx as well. Models were fitted in which the phenotypic variances and covariances were specified to be accounted for by a General factor, a number of Group factors and by Specific factors, accounting for the variance unique to each subtest. The model imposed upon the covariance matrix can be denoted as:

$$\Sigma_{YY} = \mathbf{F} * \mathbf{F}' + \mathbf{E} ,$$

where Σ_{YY} is the observed v x v covariance matrix, $\mathbf{F}$ is a v x f full matrix in which the loadings on the General and Group factors are estimated, and $\mathbf{E}$ is a v x v diagonal matrix in which the unique variance of each variable is estimated (v = number of variables; f = number of Group factors). Group factors are comprised of a subgroup of variables which share a common variance, not shared by the other variables. In contrast with exploratory factor analyses, the number of factors as well as the factor loading pattern of the variables on the different factors can be specified (in $\mathbf{F}$). Significance of alternative phenotypic factor models can be tested by changes in χ^2.

Longitudinal genetic analysis

Variation in phenotype is a function of variation in genotype and in environment. Sources of variation considered were *A*, additive genetic variation (i.e. the sum of the average effects of the individual alleles at all loci), *C*, environmental variation shared by family members in the same household and *E*, random, environmental variation that is not shared by family members. The phenotypic variance can be expressed as a simple additive function of the effects of *A*, *C* and *E*:

$$V_P = V_A + V_C + V_E .$$

Decomposition of the phenotypic variance/covariance of the RT variables was carried out in 5 bivariate genetic analyses, in which the RT of test occasion I was selected as first, and that of test occasion two as the second variable. In the bivariate design (see Figure 5.1) the *A*, *C* and *E* matrices were composed of a common factor (A_C, C_C and E_C) influencing the RT of test occasion I and II, and a specific factor, influencing only the second RT (A_S, C_S and E_S). For example,

the loading of the first RT on the common genetic factor is represented by the path coefficient a_c and that of the second RT by a'_c. The loading of the second RT on the A_S factor is represented by a_s. A_S represents new genetic influences on the second time point. The relative contributions of genetic and environmental influences to individual differences were estimated by maximum likelihood, conducted on raw data files, using Mx. This method is especially useful for handling incomplete data, for example subjects with missing values for one RT task are not excluded from the sample and, thus, the loss of valuable data is minimized. Goodness-of-fit of alternative nested models, in which parameters were constrained across sexes and models in which the *A* or *C* structure was dropped, were assessed by change in chi-square, which was calculated as twice the highest log-likelihood minus the lowest log-likelihood.

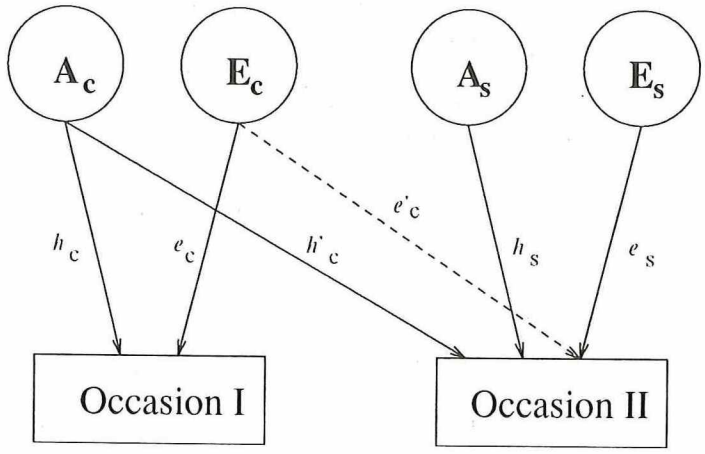

Figure 5.1
Longitudinal genetic model for Reaction Times of test occasion I and II. *A*, *C* and *E* are the additive genetic, the shared-environmental and the unique environmental component. A_C, C_C and E_C represent influences common to the RTs of test occasion I and II. A_S, C_S and E_S represent influences specific to the RTs of test occasion II.

Multivariate genetic analyses

Because the sex differences observed in the bivariate RT analyses were small (and no sex differences were observed for test occasion II when analyzed

separately), the multivariate RT-IQ analyses of both occasions were conducted on the mean-squares-between pairs (MS_B) and mean-squares-within pairs (MS_W) covariance matrices for the MZ and DZ twin pairs. This method is especially useful for handling large numbers of variables in multivariate designs, because of the application of much smaller input matrices, v x v (instead of $2v$ x $2v$), where v is the number of variables.

To examine the covariance among the RTs and IQ scores, models with a number of Group factors and Specific factors were specified for the **A**, **C** and **E** structures and fitted to the MS_B and MS_W matrices of the MZ and DZ twin pairs. The dimensions of the **A**, **C** and **E** matrices were (v x f), where f is the number of Group factors. The dimensions of the Specific factors $\mathbf{A}_{SP}$, $\mathbf{C}_{SP}$, and $\mathbf{E}_{SP}$ were v x v, and represent the variance specific to each variable. To examine the covariance among the RTs and the Raven (test occasion 1), a two-factor model with Specific factors was hypothesized for the **A**, **C** and **E** structures. The two factors were a General factor loaded by all variables and a Reaction Time factor accounting for the common variance of the RTs, not shared by the Raven. The first model for the RTs and the 11 WAIS subtests (test occasion 2), was a four-factor model with Specific factors, specified for the **A**, **C** and **E** structures. The four factors were a General factor, a Verbal factor, a Performance factor and a Reaction Time factor. Significance of further reduction of these models was tested by changes in chi-square. Heritability estimates for Reaction Times and WAIS subtests as well as their 80% Confidence Intervals (Neale & Miller, submitted) were computed based on the best fitting genetic factor model.

RESULTS

Phenotypic analyses of test occasion I

The distribution of the Raven score was negatively skewed (skewness, -.98), and a quadratic transformation was conducted to obtain a more symmetric distribution (skewness, -.49). RT distributions for Simple RT, Choice RT, STM RT, Name Identification and Category Identification, all showed acceptable symmetry (skewness, .39, .46, .60, .47 and .02, respectively).

Maximum-likelihood estimates of the phenotypic correlations among the Reaction Time tasks and Raven could be constrained to be equal for males and females without significant increase in chi-square [$\Delta\chi^2(21) = 32.59$, $p = .051$]. Correlations were equal for males and females and were all significant (Table 5.1). The mean correlation among the RT tasks was .68. Correlations between Raven

and Simple RT, Choice RT, STM RT, Name Identification and Category Identification were -.21, -.22, -.24, -.27 and -.28, respectively.

Tabel 5.1
Maximum-likelihood estimates of phenotypic correlations among Reaction Times and Raven, means and standard deviations (occasion I, age 16).

Subtests	SRT	CRT	STM	NI	CI	Raven
SRT	-					
CRT	.70	-				
STM	.57	.71	-			
NI	.64	.81	.76	-		
CI	.49	.66	.67	.74	-	
Raven	-.21	-.22	-.24	-.27	-.28	-
Means	448.25	649.31	784.27	642.57	814.12	49.8
SD	61.97	72.32	156.99	80.79	109.97	56.23

Subtests: SRT = Simple Reaction Time, CRT = Choice Reaction Time, STM = Short Term Memory RT, NI = Name Identification, CI = Category Identification. Correlation estimates were equal for males and females and were all significant.

Phenotypic factor analysis was employed to explored a more simple structure to account for the covariances among the RTs. The correlation pattern among the RTs did not suggest more than one Reaction Time factor, therefore, a General factor accounting for the shared variance of the Raven with the RTs, a Reaction Time factor, accounting for the shared variance among the RTs and Specific factors, accounting for the unique variance for each variable were specified. The fit of this first model ($\chi^2_4 = 14.13$, $p = .01$) significantly declined when the Reaction Time factor was omitted ($\chi^2_9 = 46.27$, $p = .00$). The first model exhibits rather high loadings on the Reaction Time factor for STM RT, Name and Category Identification, whereas the loadings of Simple RT and Choice RT were low and could be fixed at zero without significant change in chi-square ($\chi^2_6 = 15.71$, $p = .02$), meaning that the simple RTs did not share any common variance with the more complex RTs, other than the part they all share with the Raven test. This loading pattern suggested the possibility of two Reaction time factors, one associated with the more simple RT performance (loaded by Simple and Choice RT) and one associated with more complex information processing. To examine this more detailed Reaction Time structure a model was fitted with, in addition to the

General factor, a Simple Reaction Time factor and a Complex Reaction Time factor ($\chi^2_4 = 12.23$, $p = .02$). However, the Complex factor was only significantly loaded by the STM RT not by Name and Category Identification, and could be dropped from the model. The model with a General and Simple Reaction Time factor showed the best fit to the data ($\chi^2_7 = 14.71$, $p = .04$). These results suggest that the complex RTs do not share any common variance other than that which they share with the Raven. The information processing underlying these complex RTs tap that acquired for solving the Raven Progressive matrices. The General factor accounted for 76% of the phenotypic RT variance (on average), and for 9% of the phenotypic variance of the Raven (Table 5.2). The Simple Reaction Time factor explained 22% of the Simple RT variance and 7% of the Choice RT variance.

Table 5.2
Best phenotypic factor model for Reaction Times and Raven (occasion I, age 16).

	% Variance Accounted for		
	General factor	RT factor	Specific factors
Simple RT	45	22	33
Choice RT	74	7	19
STM RT	67	-	33
Name Identification	87	-	13
Category Identification	63	-	37
Raven	9	-	91

Phenotypic analyses of test occasion II

All RT distributions showed acceptable symmetry (skewness, .35, .28, .27, .10, .09) for Simple RT, Choice RT, STM RT, Name Identification and Category Identification, respectively. WAIS subtest scores all showed symmetric distributions as well (for a detailed analysis of the WAIS subtest scores, see Rijsdijk & Boomsma, 1996).

Maximum-likelihood estimates of phenotypic correlations among the Reaction Time tasks and WAIS subtests could be equalized across sexes [$\Delta\chi^2(136) = 155.19$, $p = .13$]. The correlations are reported in Table 5.3.

Tabel 5.3
Maximum likelihood estimates of phenotypic correlations among WAIS subtests and reaction time tasks; Means and SD (occasion II, age 18).

Subtests	INF	COM	ARI	SIM	DS	VOC	CODE	PC	BLK	PA	OA	SRT	CRT	STM	NI	CI
Information	-															
Comprehension	.55	-														
Arithmetic	.50	.48	-													
Simmilarity	.54	.60	.52	-												
Digit Symbol	.37	.32	.45	.36	-											
Vocabulary	.67	.65	.55	.68	.43	-										
Coding	.22	.16	.26	.13	.22	.21	-									
Pict Compl	.30	.39	.30	.32	.20	.34	.19	-								
Blok Design	.32	.30	.45	.33	.28	.32	.16	.29	-							
Pict Arrangem	.30	.36	.31	.35	.23	.34	.05^{ns}	.33	.33	-						
Obj Assembly	.21	.25	.26	.27	.09^{ns}	.24	.02^{ns}	.27	.51	.25	-					
Simple RT	-.28	-.18	-.22	-.14	-.23	-.24	-.16	-.19	-.21	-.16	-.09^{ns}	-				
Choice RT	-.20	-.12	-.15	-.03^{ns}	-.21	-.16	-.26	-.15	-.16	-.15	-.02^{ns}	.56	-			
STM RT	-.28	-.18	-.25	-.15	-.25	-.21	-.28	-.18	-.23	-.20	-.06^{ns}	.49	.62	-		
Name Ident	-.23	-.17	-.19	-.12	-.21	-.18	-.25	-.18	-.20	-.12	-.07^{ns}	.52	.74	.70	-	
Categ Ident	-.25	-.14	-.19	-.12	-.19	-.20	-.20	-.14	-.23	-.08^{ns}	-.11	.38	.58	.61	.74	-
Means	6.17	5.98	7.08	7.14	6.31	5.95	6.81	6.44	7.30	7.00	6.45	249.99	499.92	505.99	518.43	636.91
SD	1.39	1.66	1.83	1.79	1.66	1.63	1.70	1.71	1.93	1.95	1.89	66.60	45.52	73.36	46.08	60.27

ns = non-significant correlations.

Nine correlations were non-significant and noteworthy are the ones between the subtest Object Assembly and 4 of the RTs. Object Assembly is one of the two timed performance subtests in which faster performance is rewarded with a higher score. This provides some evidence that the relationship between SIP and intelligence measures does not seem to be attributable to the fact that some parts of IQ tests are timed. The mean correlation among the Verbal subtests was .51. The mean correlation among the Performance subtests (.24) was even lower than the mean correlation between the Verbal and Performance subtests (.28). RT tasks were almost equally correlated with the Verbal and Performance subtests, -.19 and -.16, respectively. Strikingly, the RTs showed an even higher intercorrelation (.59) than the Verbal subtests. The mean correlations of the Simple RT, Choice RT, STM RT, Name Identification and Category Identification with the 11 WAIS subtests were: -.19 , -.15, -.21, -.18 and -.17, respectively.

Five factors and Specific factors were hypothesized to underlie the phenotypic covariance structure of the 16 variables (based on the results in Rijsdijk & Boomsma, 1996). The five factors were a General factor (loaded by all RTs and WAIS subtests), an IQ factor (loaded by the WAIS subtests), a Verbal, a Performance and a Reaction Time factor. The Verbal and Performance factors were parameterized according to the regular subdivision of the WAIS subtests, the Verbal factor was loaded by the first 6 subtests comprising the Verbal scale and the Performance factor was loaded by the last five subtests comprising the Performance scale. This five-factor model did not fit the data adequately ($\chi^2_{77} = 112.79$, $p = .005$). In this model the loadings of Arithmetic and Digit Symbol on the Verbal factor, the loading of Coding on the Performance factor, Object Assembly on the General factor and the Simple RT on the Reaction Time factor were non-significant and could be fixed at zero ($\chi^2_{82} = 114.27$, $p = .01$). This is also apparent when the phenotypic correlation pattern is examined more closely to identify departures from subtest loadings on the regularly parameterized factors. The subtest Coding showed very low correlations with the other Performance subtests. The same holds for Digit Span and Arithmetic on the Verbal scale. A model in which these three tests were loaded on a separate sixth factor ($\chi^2_{77} = 108.07$, $p = .01$), did not improve the fit compared to one in which they were fixed at zero. These tests do not seem to share any significant common variance with each other or with subtests of the other scales, thus, variances for these individual tests were predominantly accounted for by the General and Specific factors.

Table 5.4
Best phenotypic factor model for Reaction Times and WAIS subtests (occasion II, age 18).

	% Variance accounted for					
	General factor	IQ factor	Verbal factor	Perfor-mance factor	RT factor	Specific factors
Information	12	31	13	-	-	44
Comprehension	4	40	12	-	-	44
Arithmetic	9	47	-	-	-	44
Similarities	1	49	11	-	-	39
Digit Symbol	9	22	-	-	-	69
Vocabulary	6	45	26	-	-	22
Coding	21	13	-	-	-	66
Picture Completion	6	15	-	3	-	76
Block Design	5	21	-	24	-	50
Picture Arrangement	4	17	-	3	-	76
Object Assembly	-	11	-	51	-	38
Simple RT	53	-	-	-	-	47
Choice RT	57	-	-	-	11	32
STM RT	49	-	-	-	12	39
Name Identification	49	-	-	-	38	13
Category Identification	28	-	-	-	36	36

The subtest Coding correlated more highly (on average) with the RTs than with the other Performance subtests. Because the score of Coding is directly associated with speed of performance and this subtest in all respects more resembles an RT task, one might expect this subtest to have more common variance with the other RTs and, consequently, to have higher loadings on the Reaction Time factor. This also holds for the Verbal subtest Digit Span, which shows more similarity with the STM RT tasks. When Coding and Digit Span were allowed to load on a sixth factor together with the RTs, the fit, compared with the first model, improved significantly ($\chi^2_{73} = 88.96$, $p = .11$). The first model can be regarded as a submodel of this 6 factor model. For simplicity the first model is maintained to illustrate the phenotypic factor pattern. In Table 5.4 the percentages of phenotypic variance explained by the different factors are reported for all significant loadings. The general factor accounted for 47% of the phenotypic RT variance (on average) and for just 7% of the phenotypic variance of the WAIS subtests (on average),

with the highest percentage for Coding (21%). Performance on this subtest seems to tap quite different skills or cognitive abilities. The Reaction Time factor explained 19% of the RT variance on average, with a zero loading for Simple RT, which does not share any common variance with the other RTs except for the part shared with IQ. The average correlation between RTs and Verbal scale subtests was -.19 and with Performance scale subtests -.16. Different from test occasion I, STM showed the highest correlations with the subtest scores: -.21 on average.

Table 5.5A
Twin correlations for Reaction Times of test occasion I and II.

	Test occasion I					Test occasion II				
	MZM (*N*=34)	DZM (*N*=33)	MZF (*N*=48)	DZF (*N*=32)	DOS (*N*=44)	MZM (*N*=33)	DZM (*N*=30)	MZF (*N*=41)	DZF (*N*=31)	DOS (*N*=39)
Simple RT	.58	.50	.47	.12	.32	.36	.59	.36	.07	.30
Choice RT	.56	.54	.56	.10	.24	.37	.33	.57	.05	.29
STM RT	.40	.35	.52	.49	.15	.24	.22	.28	.20	.22
Name Identification	.55	.55	.46	.11	-.01	.29	.16	.51	.14	.07
Category Identification	.46	.37	.48	.10	.22	.44	.32	.34	-.05	.28

N = number of twin pairs.

Table 5.5B
Maximum-likelihood estimates of twin correlations for the Reaction Times of test occasion I and II with 95% CIs.

	Test Occasion I					Test Occasion II				
	MZM	DZM	MZF	DZF	DOS	MZM	DZM	MZF	DZF	DOS
SRT	.67 (.45-.81)	.60 (.34-.77)	.48 (.24-.66)	.07 (-.25-.38)	.30 (.02-.54)	.37 (.06-.61)	.60 (.34-.77)	.34 (.08-.56)	.01 (-.31-.31)	.35 (.08-.57)
CRT	.64 (.41-.79)	.64 (.39-.79)	.56 (.34-.72)	.12 (-.20-.41)	.19 (-.10-.45)	.37 (.07-.61)	.32 (.00-.59)	.55 (.33-.71)	.04 (-.28-.35)	.25 (-.03-.50)
STM	.45 (.17-67)	.51 (.22-.71)	.09 (-.18-.35)	.34 (.03-.59)	.13 (-.15-.40)	.31 (-.00-.56)	.21 (-.12-.50)	.34 (.07-.55)	.20 (-12-.49)	.18 (-.11-.44)
NI	.60 (.35-.77)	.60 (.34-.77)	.47 (.22-.65)	.10 (-.22-.40)	-.01 (-.29-.27)	.35 (.04-.60)	.10 (-.24-.40)	.51 (.27-.68)	.08 (-.24-.39)	.06 (-.23-.34)
CI	.45 (.17-.67)	.43 (.13-.66)	.53 (.30-.70)	.21 (-12-.49)	.21 (-.08-.46)	.41 (.11-.64)	.32 (-.01-.60)	..42 (.17-.62)	-.09 (-.40-.23)	.26 (-.02-.50)

Number of pairs for each group is number of data records in the raw-data files = total number of pairs for each group, for MZM : 39, DZM : 36, MZF : 52, DZF : 38, DOS : 48.

Longitudinal genetic analyses of RTs from test occasion I and II

Maximum-likelihood estimates of phenotypic correlations between the Reaction Time tasks of test occasion I and II could be equalized across sexes [$\Delta\chi^2(45) = 52.84$, $p = .20$]. The correlations are reported in Table 5.6. All correlations were significant. The mean test-retest correlation was .54, with the highest value for STM RT (.59). The twin correlations for RT measures of test occasion I and II for the 5 sex-by-zygosity groups are given in Table 5.5A. Table 5.5B reports the maximum-likelihood estimates of the twin correlations based on the raw data. Longitudinal genetic analyses results are reported in Table 5.7. The twin correlations suggest little genetic influences for males. However, the large CI around these correlations may explaine why the *C* structure could be omitted from the *ACE* sex-differences model for all RTs. In a further reduction, the parameters for males and females could be constrained to be equal for males and females for all but the Choice RT and the Name Identification RT, resulting in an *AE* no-sex-differences model. Sex differences for the STM RT task were marginal. Heritabilities of the RTs on test occasion I were substantial and ranged from 40% to 72%, with the highest value for males on the Choice RT. On test occasion II a decrease in heritability was observed for almost all RTs, with the largest decreases for males on the Choice and Name Identification RT.

Tabel 5.6
Maximum-likelihood estimates of phenotypic correlations between Reaction Times of test occasion I and II.

Subtests	SRT_I	CRT_I	STM_I	NI_I	CI_I
SRT_{II}	.53				
CRT_{II}	.40	.58			
STM_{II}	.39	.53	.59		
NI_{II}	.39	.51	.41	.50	
CI_{II}	.31	.41	.34	.43	.50

Subtests: SRT = Simple Reaction Time, CRT = Choice Reaction Time, STM = Short Term Memory RT, NI = Name Identification, CI = Category Identification. Subscripts: I, II = test occasion I, II. Correlation estimates were equal for males and females and were all significant.

The significance of new genetic influences was tested by omitting the specific genetic factor (A_S) from the *AE* no-sex-differences model (Table 5.8). This factor

was significant for the Simple and Choice RT and marginally significant for the STM RT, which implies that there are no new genetic effects for the more complex RTs. When this A_S influence was fixed to zero, the heritabilities of STM RT, Name and Category Identification for test occasion II decreased to 23%, 32% and 36%. New environmental effects (including measurement errors of test occasion II) were highly significant as was indicated by the hugh increase in χ^2 when the E_S influence was fixed at zero. Genetic and environmental influences from occasion I on occasion II (a'_c and e'_c) were significant for all RTs.

Table 5.7
Bivariate moddel fitting results of Reaction Times of test occasion I and II, fitted on raw data files of the 5 sex-by-zygosity groups ($\Delta\chi^2$ for *ACE*sd model is based on comparison with the saturated model).

	Models (df)							
	*ACE*sd		*AE*sd		*AE*nsd		Heritabilities	
	$\Delta\chi^2_6$	*p*	$\Delta\chi^2_6$	*p*	$\Delta\chi^2_6$	*p*	h_I^2	h_{II}^2
Simple RT	4.74	.58	4.89	.56	6.5*	.37	64%	42%
Choice RT	1.96	.92	6.09*	.41	20.9	.00	f: 49% m: 72%	f: 50% m: 43%
STM RT	0.13	.99	6.00	.42	12.9*	.04	50%	34%
Name Identification	1.55	.96	11.84*	.07	17.2	.01	f: 40% m: 62%	f: 47% m: 26%
Category Identification	1.71	.94	3.59	.73	8.8*	.19	51%	42%

n(sd) = (no-)sex-differences. * = Best fitting model. h_I^2 = heritabilities at test occasion I (age 16), h_{II}^2 = heritabilities at test occasion II (age 18). f = females , m = males.

Univariate genetic results of the WAIS subtests and the Raven have been reported previously (Rijsdijk & Boomsma, 1996) and are summarized in Tabel 5.9. For the subtests Coding, Picture Completion and Object Assembly an *AE* and *CE* model fitted equally well. Heritabilities for individual differences in WAIS subtest scores in this population are quite high and ranged from 33% to 75%. Heritabilities for Verbal IQ, Performance IQ and Full-Scale IQ were 84%, 69% and 82%.

Because the sex differences for the 5 RTs were small, but especially to account for the large number of variables, the multivariate RT-IQ analyses for test occasion I and II were both conducted on the mean-square within and between covariance matrices pooled across sexes.

Table 5.8
Model fitting results for common and specific genetic and environmental influences of Reaction Times at test occasion I and II.

	Models (df)									
	*AE*nsd		*AE*nsd no a'_c		*AE*nsd no e'_c		*AE*nsd no a_s		Heritabilities	
	$\Delta\chi^2_6$	*p*	$\Delta\chi^2_1$	*p*	$\Delta\chi^2_1$	*p*	$\Delta\chi^2_1$	*p*	h_I^2	h_{II}^2
Simple RT	6.5	.37	27.5	.00	19.6	.00	8.1	.00	64%	42%
Choice RT	20.9	.00	32.5	.00	18.1	.00	8.8	.00	63%	47%
STM RT	12.9	.04	87.7	.00	30.7	.00	4.2	.04	50%	34%
Name Identification	17.2	.01	26.8	.00	6.4	.01	1.3*	.26	52%	32%
Category Identification	8.8	.19	26.9	.00	6.8	.01	2.8*	.10	49%	36%

h_I^2, h_{II}^2 = heritabilities on test occasion I and II. n(sd) = (no-)sex-differences. * = non-significant increase in χ^2.

Table 5.9
Model fit indices of univariate analyses of the WAIS subtests and the Raven test fitted to pooled MZ and DZ covariance matrices.

	ACE Model df=3		*AE* Model df=4		*CE* Model df=4		Variance Estimates		h^2
Subtests	χ^2	*p*	χ^2	*p*	χ^2	*p*	*A*	*E*	
Information	9.19	.03	9.19*	.06	30.61	.00	1.502	0.496	75%
Comprehension	7.99	.05	7.99*	.09	19.59	.00	1.747	0.968	64%
Arithmetic	1.86	.60	1.86*	.76	13.74	.01	2.203	1.321	63%
Similarities	8.28	.04	8.28*	.08	21.70	.00	1.870	1.296	56%
Digit Span	0.59	.89	0.59*	.96	8.18	.09	1.615	1.272	59%
Vocabulary	3.99	.26	3.99*	.41	30.16	.00	2.008	0.678	75%
Coding	2.43	.49	2.59	.63	5.11	.28	1.520	1.628	48%
Pict Completion	1.19	.76	2.06	.73	1.34	.86	0.997	2.019	33%
Block Design	0.44	.93	2.23*	.69	7.03	.13	2.506	1.167	68%
Pict Arrangement	3.96	.27	3.96*	.41	10.16	.04	1.457	2.305	39%
Object Assembly	1.48	.69	3.76	.44	2.20	.70	1.771	1.729	51%
Verbal IQ	6.43	.09	6.43*	.17	50.97	.00	121.44	23.68	84%
Performance IQ	0.61	.90	0.61*	.96	13.65	.01	95.38	43.37	69%
Full-Scale IQ	2.64	.45	3.54*	.47	42.14	.00	110.96	24.12	82%
Raven	3.65	.30	5.41*	.25	7.60	.11	.211	.125	63%

* = Best fitting model. For Coding, Picture Completion and Object Assembly the additive genetic as well as the common environmental structure could be omitted from the *ACE* model without deterioration of fit; the *AE* and *CE* model fitted equally well: c^2 was 34%, 26% and 42%, respectively. h^2 = heritability.

Table 5.10
Fit indices for nested sequence of multivariate models fitted to between and within mean product matrices of MZ and DZ pairs (occasion I, age 16).

Model	χ^2	df	*p*	$\Delta\chi^2$	Δdf	Δp
1. Cholesky *ACE*	29.12	3	.00			
2. Cholesky *AE/CE*	35.85 47.03	24	.06 .00	6.73 17.91	21	.99 .65
3. Two-Factor Model + Specifics for *A*, *C*, & *E* : A_G A_{RT} A_{SP} etc.	34.25	33	.41			
4. Same as 3, without *C*	47.66	50	.57	13.41	17	.71
5. Same as 4, without E_{RT}	63.81	55	.19	16.15	5	.00
6. Same as 4, without A_{RT}	57.89	55	.37	10.23	5	.07
7. Same as 6, without non-significant loadings of Raven on E_G; SRT on E_G; CRT on E_G E_{SP}	60.37	59	.40	2.48	4	.65

Twin groups pooled across sexes: 80 MZ, 108 DZ pairs. $\Delta\chi^2$ = change in chi-square, Δdf = change in number degrees of freedom, $\Delta p < .05$ means significant change in χ^2. Factor Subscripts : G = General, RT = Reaction Times, SP = Specific.

Multivariate genetic analyses of test occasion I

In Table 5.10 the results of the multivariate genetic analysis of the Raven and RTs are presented. To examine the covariances among the RTs and Raven, initially, a Cholesky decomposition was imposed upon *A*, *C* and *E*. The *C* as well as the *A* structure could be dropped without significant decline in fit [$\Delta\chi^2(21) = 6.73$, $p = .99$ and $\Delta\chi^2(21) = 17.91$, $p = .65$]. Factor analysis was explored to identify a more simple structure to account for the covariances among the RTs. A two-factor model with Specifics, imposed upon *A*, *C* and *E* was specified (model 3). The two factors were a General factor loaded by the Raven and all RTs, and a Reaction Time factor. The Specific factors accounted for variance specific to each subtest. In model 4 the *C* structure was dropped, resulting in a more parsimonious *AE* model [$\Delta\chi^2(17) = 13.41$, $p = .71$]. In further reduction the genetic Reaction Time factor could be omitted (model 6) [$\Delta\chi^2(5) = 10.23$, $p = .07$], whereas (in model 5) the environmental Reaction Time factor proved to be significant [$\Delta\chi^2(5) = 16.15$, $p = .006$]. Finally, in model 7, all nonsignificant loadings were excluded from model 6 [$\Delta\chi^2(4) = 2.48$, $p = .78$]. The fit of this model was moderate (χ^2_{59}

= 60.4, p = .40). The non-significant loadings were loadings of the Raven on E_G, of the Simple RT on E_G and of the Choice RT on E_G and E_{SP}. The non-significant loading of the Raven on E_G implies that the correlation between the Raven and the RTs is solely mediated by common genetic factors. The genetic correlations between the Raven and RTs were -.40, -.43, -.43, -.43 and -.40. The genetic correlation among the RTs (.75) was higher than the environmental correlation (.49).

Path coefficients of the best fitting model (model 7) are represented in Figure 5.2. Percentages of genetic and environmental variance and heritability estimates with information about their precision in likelihood based 80% confidence intervals are reported in Table 5.11. The RT heritabilities are considerable, ranging from 50% to 58%, with the heritability for Simple RT as high as that for the Raven (58%). The General genetic factor accounted for almost 45% of the total RT variance, on average, whereas for just 12% of the total variance of the Raven. The General environmental factor accounted for 21% of the Reaction Time variance. The Reaction Time factor was only loaded by the STM, Name Identification and Category Identification RTs, suggesting a shared unique environmental variance associated with more complex information processing.

Tabel 5.11
Percentages genetic and environmental variance and heritability estimates with 80% CI for the Reaction Times and the Raven.

	Genetic factors (%)				Environmental factors (%)				
Subtests	A_G	A_{SP}	h^2	80% CI	E_G	E_{RT}	E_{SP}	e^2	80% CI
Simple RT	44	14	58%	49%-66%	13	-	29	42%	34%-51%
Choice RT	51	6	57%	48%-65%	43	-	-	43%	35%-52%
STM RT	44	6	50%	42%-58%	12	13	25	50%	42%-58%
Name Identification	47	6	52%	43%-60%	24	14	10	48%	40%-57%
Category Identification	39	11	50%	40%-58%	11	16	23	50%	42%-60%
Raven	12	46	58%	50%-65%	-	-	42	42%	35%-51%

Multivariate genetic analyses of test occasion II

To examine the covariance among the RTs and WAIS subtests, initially a Cholesky decomposition was imposed on the *A*, *C* and *E* structures and fitted to

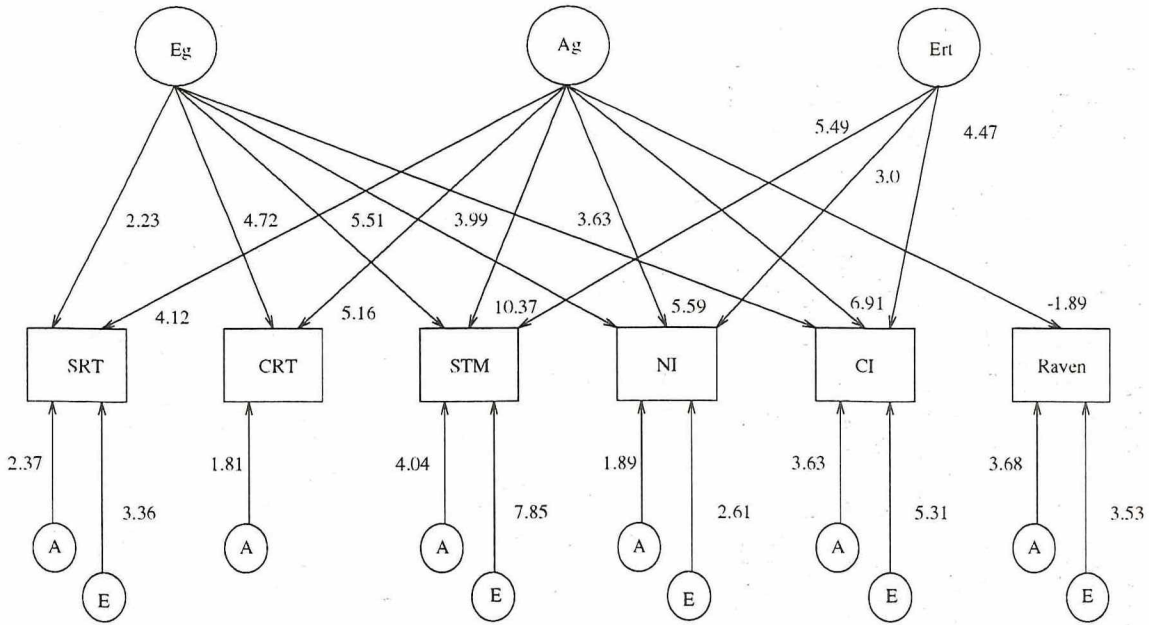

Figure 5.2
Path coefficients of the multivariate genetic model for the RTs and Raven on test occasion I (age, 16): A general genetic factor influencing all variables; a general environmental factor only influencing the RTs; an environmental RT factor; and specific *A* and *E* factors, unique to each variable.

the MS_B and MS_W matrices of the MZ and DZ twin pairs. Both the *C* and *A* matrices could be omitted without significant decrease in chi-square (Table 5.12). The loading pattern of the *A* matrix suggested the existence of at least a general factor to account for the covariation of the WAIS subtests with the RTs, an IQ factor to account for the common variance of the WAIS subtests that is not shared by the RTs (and thus not expressed in the General factor). Based on previous findings, and according to the regular subdivision of the WAIS, a Verbal and Performance factor were specified as well and finally, a fifth factor was hypothesized to account for the covariance among the RTs. Specific factors accounted for variance specific to each subtest. This model (model 3) did not fit the data well, as is indicated by the low *p*-value ($\chi^2_{367} = 411.57$, $p = .05$). In subsequent model fitting, the *C* structure was omitted from model 3 and χ^2 change for this reduced factor model appeared to be non-significant [$\Delta\chi^2(59) = 55.27$, $p = .05$]. In model 5 the Verbal and Performance factor in the *E* matrix proved to be non-significant [$\Delta\chi^2(11) = 8.54$, $p = .66$] and in model 6 the IQ factor could be dropped as well. Thus, a General factor, a Reaction Time factor and Specific factors were sufficient to explain this unique environmental matrix. As can be concluded from models 8, 9 and 10, in the genetic covariance matrix all five factors (A_G, A_{IQ}, A_V, A_P, A_{RT}) and Specific factors were significant and could not be omitted, thus, model 6 was accepted as the best fitting model. Note that the fit of this model was extremely poor, though. The loadings of the more complex RTs on the A_G were quite low and suggested the possibility of a second (complex) RT factor in the *A* matrix. This was not the case: the fit of a model with two RT factors declined significantly. Because it is conceivable that the genetic and environmental mediation of the SIP-IQ relationship may differ for Verbal and nonverbal abilities, a model was specified with two additional factors in both the *A* and *E* matrix (an extention of model 3). These two factors were a Verbal-RT factor and a Performance-RT factor ($\chi^2_{384} = 450.2$, $p = .01$). Model 3, regarded as a reduction of this model, showed a nonsignificant decline in fit [$\Delta\chi(42) = 16.37$, $p = 9.99$] and, thus, proved the insignificance of these additional factors.

Finally, all non-significant loadings were excluded from model 11. These were the loadings of Digit Symbol and Coding on A_{IQ}; Coding and Picture Arrangement on A_P; Category Identification on A_{RT}; Similarities, Block Design and Name identification on A_{SP}; Information, Vocabulary, Coding, and all 5 RTs on E_G. In accordance with the test results of occasion I, the zero loadings of the RTs on E_G imply that the observed phenotypic correlations between the RTs and all 11 subtests of the WAIS were entirely determined by genetic factors.

Table 5.12
Fit indices for nested sequence of multivariate models fitted to between and within mean product matrices of MZ and DZ pairs (occasion II, age 18).

Model	χ^2	df	p	$\Delta\chi^2$	Δdf	Δp
1. Cholesky *ACE*	297.61	88	.00	-	-	-
2. Cholesky *AE/CE*	338.59	224	.00	40.98	136	.99
	388.69	224	.00	91.08	136	.99
3. Five-factor Model + Specifics (*ACE*) A_G A_{IQ} A_V A_P A_{RT} A_{SP} etc.	411.57	367	.05	-	-	-
4. Same as 3, without *C*	466.84	426	.08	55.27	59	.05
5. Same as 4, without E_V E_P	475.38	437	.10	8.54	11	.66
6. Same as 5, without E_{IQ}	493.29	448	.07	17.91	11	.08
7. Same as 6, without E_{RT}	516.65	453	.02	23.36	5	.00
8. Same as 6, without A_V	508.57	454	.04	15.28	6	.01
9. Same as 6, without A_P	515.48	453	.02	22.19	5	.00
10. Same as 6, without A_{RT}	513.23	453	.03	19.91	5	.00
11. Same as 6: A_G A_{IQ} A_V A_P A_{RT} A_{SP}; E_G E_{RT} E_{SP} Without the non-significant loadings	498.08	464	.13	4.79	16	.99

Twin groups pooled across sexes: 74 MZ, 100 DZ pairs. $\Delta\chi^2$= change in chi-square, Δdf = change in number degrees of freedom, $\Delta p < 0.05$ means significant change in χ^2.

Percentages of variance accounted for by the different genetic and environmental factors and heritability estimates with 80% confidence intervals are reported in Table 5.13. The heritabilities for the WAIS subtest are in close agreement with the univariate estimates seen in Table 5.9. The General genetic factor, on average, shows to be more important for the RTs, explaining 22% of the genetic variance, compared to the WAIS subtests. The genetic Reaction Time factor is predominantly loaded by Simple RT, whereas the environmental RT factor is highly loaded by the more complex RTs. Simple RT showed the highest heritability (56%), heritabilities of the Name and Category Identification RTs were quite low (25% and 22%). For the WAIS subtests, the average genetic correlation was higher among the Verbal subtests (.74) than among the Performance subtests (.44), while the mean environmental correlations were around zero. The mean genetic correlation among the RTs was quite high (.77) and so was the mean environmental correla-

tion (.53), which may, in part, have resulted from correlated measurement errors. The mean genetic correlations between RTs and Verbal and Performance subtests were -.46 and -.42.

Tabel 5.13
Percentages genetic and environmental variance and heritability estimates with their 80% CI for the Reaction Times and WAIS subtests.

% Variance accounted for by genetic and environmental factors based on Model 11													
Subtests	A_G	A_{IQ}	A_V	A_P	A_{RT}	A_{SP}	h^2	80% CI	E_G	E_{RT}	E_{SP}	e^2	80% CI
Information	31	13	14	-	-	16	74%	68-79%	-	-	26	26%	21-32%
Comprehension	13	27	16	-	-	7	63%	56-70%	2	-	35	37%	31-44%
Arithmetic	33	2	11	-	-	15	61%	52-68%	13	-	26	39%	33-48%
Similarities	11	20	27	-	-	-	58%	42-63%	4	-	38	42%	37-48%
Digit Symbol	26	-	10	-	-	23	59%	50-66%	1	-	40	41%	34-50%
Vocabulary	22	22	32	-	-	2	78%	73-83%	-	-	22	22%	17-27%
Coding	14	-	-	-	-	34	48%	37-58%	-	-	52	52%	42-63%
Picture Compl	12	18	-	-	-	8	38%	27-47%	6	-	56	62%	53-73%
Block Design	21	2	-	43	-	-	66%	59-72%	8	-	26	34%	28-41%
Picture Arrang	10	13	-	1	-	11	35%	23-46%	3	-	62	65%	54-77%
Object Assembly	2	11	-	21	-	18	52%	42-60%	6	-	42	48%	40-57%
Simple RT	23	-	-	-	26	8	57%	48-64%	-	8	35	43%	36-52%
Choice RT	21	-	-	-	15	9	45%	36-54%	-	35	20	55%	46-64%
STM RT	28	-	-	-	3	5	36%	28-45%	-	31	33	64%	55-72%
Name Ident	20	-	-	-	5	-	25%	17-33%	-	60	15	75%	67-83%
Category Ident	17	-	-	-	-	5	22%	13-31%	-	53	25	78%	69-87%

DISCUSSION

On test occasion I the mean phenotypic correlation between the RTs and the Raven was -.24, and within the typically observed range. The phenotypic correlation among the RTs was .68. The covariances between the RTs and Raven was represented by three phenotypic factors, including a General factor, a Reaction Time factor (which was loaded just by Simple RT and Choice RT) and Specific factors. There was no evidence for the existence of a second (complex) Reaction Time factor, which suggests that there is no common variance among the complex RTs other than the part they share with the Raven. The genetic analyses showed the Reaction Time factor to be significant for only the unique environmental matrix,

but, in contrast, with loadings of the complex RTs. Shared family influences were not significant. The nonsignificant loading of the Raven on the General *E* factor implied that the correlation between the Raven and the RTs was exclusively mediated by the loading on the General *A* factor. Heritabilities of the RTs were substantial, ranging from 50% to 58%. The heritability of the Simple RT was as high as that of the Raven test (58%).

The mean correlation of the RTs with the WAIS subtests was lower compared to that with the Raven on test occasion I. The covariance among these variables was accounted for by five phenotypic factors and Specific factors. The five factors included a General, an IQ (loaded by all WAIS subtests), a Verbal, a Performance and a Reaction Time factor. Different from test occasion I, the Reaction Time factor was loaded by all but the Simple RT, with higher loadings for the Name and Category Identification RTs. In the genetic analyses, this five-factor model with Specifics was fitted to the *A*, *C* and *E* matrix. Just like in test occasion I, common environmental influences were not significant. All five factors were significant for the *A* matrix, while the unique environmental influences were accounted for by a General, a Reaction Time and Specific Factors. Just like in test occasion I, the RT loadings on the General *E* factor were all nonsignificant, meaning that the observed phenotypic correlation is entirely determined by loadings on the General genetic factor. Thus, there is no evidence that practice or training effects for these RTs (occasion I and II) influence the IQ-RT relationship. Although the degree of correlated genetic influences for these RTs may differ, for all RTs the General *A*, instead of the General *E*, was the mediating factor with IQ, independent of their particular complexity level. These conclusions are, of course, limited to the RT measures used. There was no evidence for differential genetic and environmental mediation of the SIP-IQ relationship for Verbal and nonverbal abilities. Also, no difference was observed in the genetic correlation between the RTs and the Verbal or Performance subtests. On test occasion II variations in heritabilities of the RTs cannot be related to the extent to which the measures tap an underlying Phenotypic General Speed factor (Vernon, 1989), nor to the extent to which they tap the General genetic factor. However, heritability estimates of the RTs seem to be systemized according to the extent to which they load on the genetic Reaction Time factor (A_{RT}): higher heritabilities were observed for RTs with higher loadings on the A_{RT}.

Phenotypic results on both test occasions showed the existence of a General factor, a Reaction Time factor and Specific factors. For test occasion II, three additional (IQ, Verbal and Performance) factors were observed for the WAIS subtests. Genetic factor analyses yielded different genetic and environmental factor

patterns. Phenotypic factor patterns may not be mirrored in both genetic and environmental components of variance, which is shown by the present results. For test occasion I the observed phenotypic Reaction Time factor proved to be constituted by environmental influences, whereas for test occasion II the Reaction Time factor was constituted by genetic as well as by environmental influences. The phenotypic relationship among tests comprising the Verbal and Performance scales of the WAIS is reflected in the genetic covariance among these variables, whereas the same environmental influences appear to be operating across all WAIS subtests.

On test occasion II, heritabilities for all but the Simple RT are lower compared to those of test occasion I. In the longitudinal genetic analysis of the RTs of test occasion I and II, lower heritabilities for test occasion II are observed as well. For Choice RT and Name Identification RT, for which sex differences were observed, heritability estimates for males dropped on test occasion II, whereas for females the heritability estimates increased slightly. There seems to be a trend of significant new genetic effects (specific to test occasion II) for the Simple RTs, whereas these specific genetic effects are less significant (for STM RT) or not significant at all for the more complex RTs.

Although genetic analyses of elementary cognitive tasks or RTs have been conducted on quite different sets of tasks, the pattern of results suggests that the observed heritabilities in RT tasks in adolescence and adults may be higher than those observed in children (Petrill *et al.*, 1995, 1996). Common environmental influences seemed to play an important role in the performance of RTs in children. In that respect heritabilities of RTs on test occasion II (at age 17.5) were not expected to be any lower than on test occasion I. This was not the case for most of the RTs. The heritabilities for the RTs in test occasion I were considerable, with the highest estimate for the Simple RT, which was as high as the heritability for the Raven (58%). Although common environmental influences were not significant at both ages, the heritabilities for most of the RTs at test occasion II were lower than those for test occasion I. Significantly different heritability estimates were observed only for Name Identification and Category Identification, which are reflected by the totally non-overlapping confidence intervals (CI) from test occasion I and II. For Simple RT, heritability at age 17.5 was almost equal to that at age 16 and so were the CIs.

It is unclear whether the significant decline in heritability was induced by the modifications of the RT task battery. At test occasion II, subjects were rewarded for each correct response and feedback was supplied on each reaction time that was slower than an established target reaction time value for a specific task. These

modifications may have induced other response strategies, which may have caused the differences in heritability of the RTs compared to test occasion I. Mean reaction times on all 5 tasks were significantly faster at test occasion II, but the percentages of correctly made trials were (except for the simple RT) significantly lower. Thus, it seems that more mistakes were made as a consequence of the fact that subjects were speeded up by these target values.

More complex RT tasks are expected to correlate more highly with intelligence because they impose increasing information processing demands and thus more closely approximate cognitive operations needed by intelligence subtest performance. Elementary cognitive tasks which more closely resemble intelligence tests are supposed to show higher correlations with intelligence test scores and are supposed to exhibit higher heritabilities. The correlation between the Raven and the Simple RT in test occasion I was not significantly different from the correlation with the STM RT, which is supposed to measure more complex cognitive information processing. This is also reflected by the fact that loadings of RTs on A_G are almost equally high. In contrast, on test occasion II the STM RT did show the highest correlation with the WAIS subtests, on average, as a consequence of its highest loading on A_G.

In accordance with the findings of Ho *et al.* (1988) and Baker et al. (1991) in adult and adolescent samples, the observed phenotypic correlations on both test occasions were entirely determined by common underlying genetic influences. Genetic variation which leads to faster RTs are associated with genetic variation determining higher scores on intelligence test. These findings were indicated by the significant (negative) loadings of all RTs on the General genetic factor and suggest that these speed variables might be an important component of general intelligence which is based on some common biological basis. The common biological basis for the speed measures and intelligence was hypothesized to tap neural speed and efficiency.

In all genetic studies (except the Petrill *et al.*, 1996 study) which have examined the relation between cognitive speed of processing and scores on psychometric ability tests, some phenotypic structure was assumed and calculated factor scores were entered in the multivariate genetic analyses. This study demonstrates the possibility of fitting meaningful phenotypic models to the covariance among a set of psychometric tests and RTs. In order to decompose the phenotypic structure into genetic and environmental components of variance, multivariate genetic analyses were performed on all variables and factor patterns were specified and tested separately for the genetic and environmental matrices.

6

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7

Appendix A

Chapter 2 dealt with the relationship between the Raven and PNCV of test occasion I, chapter 3 with the WAIS Full-Scale IQ score and PNCV of test occasion II. The relationships between Reaction Times and Raven (test occasion I) and Reaction Times and WAIS subtests (test occasion II) are discussed in chapter 5.

In addition to these results, this appendix provides the phenotypic correlations between Reaction Times and onset PNCV of test occasion I and II. Also reported are the correlations between the WAIS subtests and onset PNCV and the correlations between WAIS Verbal, Performance and Full-Scale IQ and Reaction Times of test occasion II.

Test Occasion I

Phenotypic analysis
Input Matrix:
Covariance matrix of the whole sample (N = 276) (Table 7.1).

Maximum-likelihood estimates of the phenotypic correlations between PNCV and Reaction Times are reported in Table 7.2. There were no significant correlations between Reaction Times and PNCV.

Test Occasion II

Phenotypic analysis
Input Matrix:
Covariance matrix of the whole sample (N = 326) (Table 7.3)

Maximum-likelihood estimates of the phenotypic correlations between Verbal IQ, Performance IQ, Full-Scale IQ and Reaction Times and PNCV are shown in Table 7.4. All correlations between PNCV and Reaction Times were nonsignificant.

Table 7.5 gives the correlations between PNCV and the WAIS subtest. Only the correlations between PNCV and Coding and PNCV and Object Assembly were significant.

Tables of appendix A: **Page**

Table 7.1

Test Occasion I: Covariance matrix of Reaction Times, Raven and peripheral nerve conduction velocity. Number of individuals = 276

	SRT	CRT	STM	NI	CI	Raven	PNCV
SRT	41.02						
CRT	32.78	49.93					
STM	57.06	80.32					
NI	33.68	46.91	67.18				
CI	36.02	53.94	68.10	127.16			
Raven	-8.29	-6.80	-11.80	-18.30	31.54		
PNCV	-3.04	-5.86	-7.77	-12.19	-4.13	68.62	

SRT = Simple Reaction Time, CRT = Choice Reaction Time, STM = Short Term Memory RT, NI = Name Identification, CI = Category Identification, PNCV = Peripheral Nerve Conduction Velocity.

Table 7.2

Test Occasion I: Maximum-likelihood estimates of phenotypic correlations between peripheral nerve conduction and Reaction Times and Raven. Number of individuals = 276.

	SRT	CRT	STM	NI	CI	Raven
PNCV	-.06	-.10	-.06	-.06	-.13	-.09

SRT = Simple Reaction Time, CRT = Choice Reaction Time, STM = Short Term Memory RT, NI = Name Identification, CI = Category Identification, PNCV = Peripheral Nerve Conduction Velocity. All correlation are non-significant.

Table 7.3

Test Occasion II: Covariance matrix of WAIS Verbal IQ, Performance IQ and Full-Scale IQ, Reaction Times and peripheral nerve conduction velocity. Number of individuals = 326.

	VIQ	PIQ	FIQ	SRT	CRT	STM	NI	CI	PNCV
VIQ	140.60								
PIQ	79.94	133.29							
FSIQ	125.48	113.23	132.62						
SRT	-219.26	-164.23	-217.54	4860.40					
CRT	-91.79	-110.39	-111.18	1738.20	2048.40				
STM	-268.69	-218.40	-276.21	2475.20	2061.50	5284.90			
NI	-140.87	-121.93	-148.65	1605.10	1527.30	2246.80	2068.90		
CI	-183.60	-165.24	-194.69	1514.30	1570.60	2645.30	2003.70	3660.40	
PNCV	6.06	7.54	7.54	12.19	5.50	8.66	1.56	-7.07	12.09

VIQ = Verbal IQ, PIQ = Performal IQ, FSIQ = Full-Scale IQ, SRT = Simple Reaction Time, CRT = Choice Reaction Time, STM = Short Term Memory RT, NI = Name Identification, CI = Category Identification, PNCV = Peripheral Nerve Conduction Velocity.

Table 7.4

Test Occasion II: Maximum-likelihood estimates of phenotypic correlations among WAIS Verbal, Performance and Full-Scale IQ, Reaction Times and peripheral nerve conduction velocity. Number of individuals = 326.

	VIQ	PIQ	FSIQ	SRT	CRT	STM	NI	CI	PNCV
VIQ	1								
PIQ	.58	1							
FSIQ	.92	.85	1						
SRT	-.27	-.20	-.27	1					
CRT	-.17	-.21	-.21	.55	1				
STM	-.31	-.26	-.33	.49	.63	1			
NI	-.26	-.23	-.28	.51	.74	.68	1		
CI	-.26	-.24	-.28	.36	.57	.60	.73	1	
PNCV	.15	.19	.19	$.05^{ns}$	$.04^{ns}$	$.03^{ns}$	$.01^{ns}$	$-.03^{ns}$	1

VIQ = Verbal IQ, PIQ = Performal IQ, FSIQ = Full-Scale IQ, SRT = Simple Reaction Time, CRT = Choice Reaction Time, STM = Short Term Memory RT, NI = Name Identification, CI = Category Identification, PNCV = Peripheral Nerve Conduction Velocity. ^{ns} = non-significant correlations.

Table 7.5

Test Occasion II: Maximum-likelihood estimates of phenotypic correlations between peripheral nerve conduction velocity and WAIS subtests. Number of individuals = 326.

	INF	COM	ARI	SIM	DS	VOC	CODE	PC	BLK	PA	OA
PNCV	$.07^{ns}$	$.13^{ns}$	$.06^{ns}$	$.10^{ns}$	$-.00^{ns}$	$.13^{ns}$	.20	$.08^{ns}$	$.06^{ns}$	$.03^{ns}$	.18

INF = Information, COM = Comprehension, ARI = Arithmetic, SIM = Similarities, DS = Digit Symbol, VOC = Vocabulary, CODE = Coding, PC = Picture Completion, BLK = Block Design, PA = Picture Arrangement, OA = Object Assembly. PNCV = Peripheral Nerve Conduction Velocity. ^{ns} = non-significant correlations.

8

Summary and discussion

The existence of reliable and stable individual differences in performance on psychometric intelligence tests or IQ, is beyond any doubt. Theories on the structure of intelligence give little information about underlying processes that may cause these individual differences (Brody, 1992). The search for biological determinants of intelligence that might explain differences in cognitive functioning has long been the subject of experimental psychology and can be divided into two main approaches. One explores the relation between general intelligence and the speed of execution of elementary cognitive tasks (reaction time tasks), based on ideas that can be traced back to Galton (1883). Another approach is to study individual differences in intellectual abilities in relation to physiological measures.

The existence of biological determinants underlying cognitive functioning gains much evidence from results of behavior genetic research, which has shown that genetic factors account for 50-60% of the phenotypic variance in psychometric intelligence (Bouchard & McGue, 1981). Beyond showing evidence for some genetic determination of phenotypes, quantitative genetic methods can also reveal the nature of the relationship between phenotypes. The correlation between phenotypes may be entirely environmental in origin or may be caused by underlying common genetic influences. Genetic analyses, thus, are of importance when interpreting the correlations between biological and behavioral variables.

Biological determinants of cognitive functioning may be translated into neurophysiological and biochemical processes in the central nervous system. Among a great number of biological variables, peripheral and central nerve conduction have been investigated in the search for biological determinants underlying the individual differences in psychometric intelligence. Reed (1984) hypothesized that, as far as individual differences in IQ are genetically determined, they can be attributed to genetic variability in the structure and amount of 'transmission proteins', which determine information processing rates and, consequently, intelligence. This is called the 'neural efficiency model of intelligence'. The established relationship between intelligence and Reaction Times on elementary cognitive tasks (a behavio-

ral manifestation of this neural efficiency) may provide additional evidence for this model (Vernon, 1993).

In the present study the relative contributions of genetic and environmental factors to the relation between peripheral nerve conduction velocity, reaction times and IQ was investigated. These characteristics were measured longitudinally in a group of 213 twin pairs. At the first test occasion the mean age was 16 years and at the second, 17.5 years.

In this general discussion, first, results are summarized of the phenotypic and genetic factor structures underlying the individual differences in WAIS subtest scores (test occasion II). This kind of genetic analysis on the WAIS subtest scores was only rarely conducted. Also, the results of the genetic association between the WAIS subtests and the Raven are discussed. Next the nature of the RT - IQ relationship and the longitudinal analysis results of RTs on test occasion I and II are discussed. In the next section special attention is drawn to the results on the genetic architecture of peripheral nerve conduction in humans. Finally, the results of the PNCV - IQ relationship of test occasion I and II (chapters 3 and 4) are summarized and a theory is suggested to account for the apparently contradictory findings of test occasion I and II.

Multivariate analysis of the WAIS subtests and the Raven

The factor structure underlying individual differences in WAIS subtest scores was explored by means of multivariate genetic analyses. The associations among the subtests were decomposed into parts due to genetic and environmental influences. Additive genetic and non-shared environmental influences accounted for the phenotypic covariance, whereas shared family background did not. The matrix of genetic correlations suggested a General factor, a Verbal factor, a Performance factor and Specific factors. The matrix of environmental correlations among subtests did not bear any evidence for a separate Verbal and Performance factor, the covariance structure indicated a General factor and Specific factors. Thus the regular subdivision of the WAIS (Wechsler, 1955) into a Verbal and Performance scale reflects genetic rather than environmental covariance between the subtests.

Association among WAIS subtests showed the significance of a General intelligence factor (*g*) which was more dominant in the genetic matrix. The construct *g* refers to the positive manifold, the presence of positive intercorrelations among diverse tests of cognitive abilities. The General genetic factor was predominantly tapped by the verbal subtests. In addition to the genetic General and Group factors,

Specific factors were observed, accounting for the unique characteristics of each subtest, not shared by the other subtests. Multivariate genetic analyses, thus, can help solve the question about the nature of *g* (Jensen, 1993). The establishment of a genetic basis of *g* supports the notion of a biological basis of *g*.

A special feature of chapter 2 was the inclusion of the Raven (Raven, 1958) in the multivariate analyses. The Raven is a nonverbal test of reasoning and does not rely heavily on acquired knowledge. The association with the WAIS and other tests of mental abilities is expected to be the result of loadings on a General factor of intelligence *g*. With a multivariate genetic model it was possible to address the question whether this association is mediated by the General genetic factor or General environmental factor. The covariance of the WAIS subtests and the Raven was solely accounted for by the General genetic factor.

The finding of nonsignificant common environmental (family background) influences of the present study fits the idea that non-shared family environment becomes more important once children start their formal education (Scarr & McCartney, 1983, Thompson, 1993, Boomsma, 1993). Adoption studies indicate that younger children, regardless of genetic relatedness, resemble each other intellectually because of similar rearing environment. Adolescents are able escape the influences of the family by actively selecting their own environment and, therefore, resemblance will exists only if they share genetic background (Scarr & Weinberg, 1983).

Intelligence Quotient in the Dutch population

In the present study, individual differences in WAIS Full-Scale IQ score were shown to be highly heritable. The heritability estimate of 82% is higher than values reported for adult IQ (70%) as measured in reared apart MZ twins (Bouchard *et al.*, 1990) and higher than meta-analyses results of 50% to 60% (Bouchard & McGue, 1981). This difference remains even when the lower bound of the 95% confidence interval of our estimate is considered (75%). The upper bound was estimated to be 87%. The question is how this high heritability estimate in the Dutch population can be explained. When cultural influences on a phenotype are important and relatively homogeneous, environmental variance decreases and heritability will increase (Bouchard *et al.*, 1990). Tambs *et al.* (1984, 1986) argued that the high genetic variance for WAIS IQ observed in Norwegian twins could be a results of the rather egalitarian Norwegian society. Higher genetic variance was particulary observed in younger generations (Sundet *et al.*, 1981), which probably is an effect of developing social homogeneity. This was also demonstra-

ted by the fact that, compared to the US population, a smaller proportion of Norwegians was doing extremely poor on the test. A possible explanation for the high heritability for individual differences in IQ in Norway and The Netherlands could be that genetic and environmental influences upon intelligence are correlated. Genotype-environmental correlation refers to the fact that the environments which individuals experience may not be random, but are caused by their genes and the genes of their parents. It is possible that these higher heritability estimates are caused by the fact that social equality creates optimal educational conditions for all individuals and an equal chance to choose among a variety of secondary schools and educational institutions. Therefore, selection or choice of schools and length of education may be (actively) influenced by genotypes of individuals (rather than e.g social economical status of the parents) and, thus, a balanced, random sample of adolescents is likely to exhibit large genetic influences on IQ. This is called active genotype-environmental correlation.

Despite the higher heritability estimate for IQ in our study, the common finding of higher shared-family environmental influences on IQ in children compared to adolescence and adults, is also observed in the Dutch population (Boomsma & Van Baal, in press). This could be an effect of the rather uniform elementary school education which does not permit a large influence of (genotypically driven) choices of parents or children.

The action of specific mechanisms by which differences in genotypes in human behavior are expressed in phenotypic differences are still unclear. It is hypothesized that genetic influences may work indirectly by determining the effective psychological environment of the developing child (Scarr & McCartney, 1983). This is called passive genotype-environmental correlation or cultural transmission. Another explanation for the high heritability for individual differences in IQ a population could be that genetic differences might affect psychological differences indirectly, by influencing the effective environment of the developing child. An example is when higher than averaged ability children, in addition to the inherited genes, also benefit a more enriched environment of books and education etc. from there parents. Positive genotype-environmental correlations will increase estimates of all the genetic components of variance in phenotypes (Neale & Cardon, 1992). The genotype-environmental correlation declines from infancy to adolescence and the importance of the active genetic-environmental correlation (e.g. selection of schools and experiences) increases and exhibit stronger effects (Scarr & McCartney, 1983).

One way to disentangle genetic and environmental influences is by studying reared apart MZ and DZ twins. In studies of reared apart MZ twins, 70% of the

variance in IQ was found to be associated genetic variation. On other psychological traits reared apart MZ twins were as similar as MZ twins reared together. Correlated placement (if the adoptive homes were selected to be similar in trait-relevant features) did not seem to be the cause of psychological similarity. Social economic status effects on IQ in adoption studies have been found in children but not in adults. Another way to estimate the effects of genotype-environmental correlation (cultural transmission) can be accomplished by including parents' data in the twin model. However, no evidence for possible cultural transmission was found in parents and their children in a series of studies conducted in the Colorado Adoption Project (e.g. DeFries, Plomin, & LaBuda, 1987).

An earlier large Dutch study on hereditary and environmental influences upon intelligence was conducted by Vroon, de Leeuw and Meester (1986). Vroon *et al.* analyzed IQ as measured by the Raven Progressive Matrices and measures of educational and professional level in a sample of 2,847 fathers and sons, both recruited for military service in the Netherlands between 1945 and 1982. A father-son IQ correlation of .34 was reported. From a path analytic model in which educational level and IQ of the father predicted IQ of the son, it was concluded that only 3% of the variation in son's IQ was explained by these variables. Neither hereditary nor SES of the father was found to be responsible for IQ of the child. However, the path analytic model used by Vroon *et al.* failed to correctly specify the genetic relationship between parent and child. The observed correlation of .34 reported by Vroon *et al.* was in agreement with the DZ correlation for the Raven score of the present study (r = .39, for 111 twin pairs). This correlation also was in close agreement with the meta-analyzed father-son weighted correlation of .38, based on 2,843 pairings (Bouchard & McGue, 1981), and, thus, was not specific to the Raven test. In a paper by Rowe and Hay (1988) the method and conclusions of the Vroon *et al.* study were criticised. Data from nuclear families, especially when taking into account only one relation, are not sufficient to disentangle genetic and environmental influences since parents and children share both genes and environment. Fathers' educational level was seen as an environmental variable, but this variable can also contain genetic components. Contemporary behavior genetics uses more sophisticated methods and has gone beyond examining parent-child relationships to infer heritability estimates of behavioral traits.

From large studies conducted in the Netherlands it was concluded that IQ does not seem to predict occupational success. The concept 'Emotional Intelligence' (EQ), which is much more difficult to measure, was introduced to stress the importance of psychological stability and social skills in social economic achievement. IQ was claimed to account for just 20% of success in life. The other

factors important for predicting success in life vary from 'SES' to 'happiness'. Results indicated that high IQ university students were not socially more successful at middle age, compared to less skilled students (.

The relation between IQ and speed-of-information-processing

A theoretical explanation for the relationship between Reaction Times and IQ was given by the neural efficiency model (Jensen, 1982; Vernon 1993), in terms of three characteristics of Short Term Memory or 'working memory' in which basic cognitive operations are carried out. One of these is the limited storage capacity (of approximately seven units of information) for which not much variation is seen between individuals. The second is the rapid decay of information in absence of continuous rehearsal and the third is the trade-off between the amount of stored information units and the amount of information that can be processed at the same time. A fourth property is proposed as a solution for the limiting characteristics: the speed-off-information-processing. Because variation among individuals in the three other properties is limited, it is reasonable to assume that most variation will be observed in speed-of-information-processing. Individuals differ in the speed with which basic cognitive operations can be executed, a property that is related to individual differences in intellectual functioning.

On test occasion I, substantial heritabilities were observed for the Reaction Times (50% to 60%). The mean phenotypic correlation between the RTs and Raven test score was -.24 and was exclusively mediated by genetic influences. On test Occasion II, lower heritabilities were observed for the Reaction Times (32% on average). The mean correlation with the WAIS subtests (-.18), lower compared to test occasion I, was again solely determined by common underlying genetic factors. This RT-IQ relation, therefore, does not seem to be based on correlated environmental factors like training or practice effects on some kinds of test characteristic. The RT-IQ relationship was independent of the nature of the test (verbal or performance). In contrast to what was assumed by Vernon (1989), heritability estimates were observed not to depend on the extent to which they tap either a phenotypic General Speed factor and a General genetic factor. As loadings on the General genetic factor were more or less equal for all RT tasks on test occasion II, RT heritability estimates were more a function of the loadings on the genetic Reaction Time factor. Specific genetic influences were low for all RT tasks on both test occasions.

Longitudinal analysis of Reaction Times

Genetic and environmental influences, which were expressed at test occasion I and also effective at test occasion II, were significant for all RT tasks. There seemed to be a trend of significant new genetic effects specific to test occasion II for the simple RTs, whereas these specific genetic effects were less significant or not significant for the more complex RTs.

On the second visit, subjects were rewarded for each correct response, but were also speeded up by feedback on their response time and were encouraged to be faster than an established target reaction time value. This may have caused different response strategies, for example faster responding with a bigger chance of operating the wrong key. Evidence for this effect was shown by the lower mean reaction times (faster responses) and a higher percentage of errors on all tasks. The 'environmental' pressures on test occasion II (as a consequence of the modified administration procedure) could have increased the unique environmental variance observable in the individual differences in reaction times. This may be an explanation of the significant decrease in heritabilities for the RTs (except Simple RT) on test occasion II.

The relation between IQ and peripheral nerve conduction velocity

Test Occasion I

No significant correlation between PNCV and Raven test score was observed at test occasion I (mean age, 16 years). Heritability estimates for Raven and PNCV were 65% and 76%. Reed (1993), observed increased brain nerve conduction and PNCV in mice as a result of environmental enrichment and physical exercise. He suggested that physical exercise level might increase PNCV and therefore should be taken into account when studying the relationship between IQ and PNCV. Physical activity scores from questionnaire data on sports participation did not correlate with PNCV in our sample.

The experimental conditions of accessing PNCV were in close agreement with the Vernon and Mori (1992) studies, which observed substantial correlations between PNCV and IQ. Temperature, the main confounder of PNCV, was experimentally controlled for and supramaximal nerve stimulation was applied. Supramaximal stimulation ensures stimulation of all (slow and fast) fibres in the nerve bundle (chapter 3). The other PNCV - IQ studies which failed to replicate the results of Vernon & Mori (Reed & Jensen, 1991 and Barrett *et al.*, 1990) had also administered the Raven. An IQ test that more resembled the MAB (employed

in the Vernon & Mori studies) was suggested to replicate the positive correlation between PNCV and IQ.

Test Occasion II

A low but significant correlation was observed between WAIS Full-Scale IQ score and PNCV (r = .16). Heritability estimates for WAIS IQ and PNCV were 81% and 66%, respectively. The Raven score of test occasion I also showed a low but significant correlation with the PNCV of test occasion II. This correlation was almost as high as the correlation between the WAIS and PNCV of test occasion II, suggesting that the lack of correlation between IQ and PNCV of the first measurement was not due to the use of the Raven.

PNCV heritability estimates on both test occasion were high but the test-retest correlation between PNCVs of test occasion I and II turned out to be very low, although no changes were made in experimental procedures. Lack of PNCV stability caused by statistical artifacts as non-binormality were ruled out (chapter 4). The question, then, was what other factors could have caused this observed instability of the PNCV measure. One possible factor causing this instability, could have been an unreliable PNCV acquisition procedure. However, the twin correlation patterns of both occasions suggest otherwise. Measurement errors and technical pitfalls (causing unreliable acquisition) would have been evenly distributed among all subjects and all groups. The high MZ correlation (on both test occasions) suggests that the lack of test-retest correlation was not caused by measurement error and the relatively low DZ correlations suggest that the high MZ correlations are not a result of correlated measurement errors. Additional evidence for the reliability of the PNCV acquisition procedure is provided by the high split-half correlation for the 3 latencies (obtained from two nerve action potentials) for both test occasion I and II.

It was speculated that the lack of correlation between PNCV at age 16 and age 18 could be explained by ongoing maturation in this age interval. We therefore investigated what is known about maturation in human peripheral nerves in this age interval. Also, from the longitudinal PNCV measures difference scores between occasion I and occasion II were computed for all subjects and similarity of this difference score between MZ and DZ twins was explored.

Maturation of peripheral nerve conduction in humans

There are only a few clinical maturation studies on PNCV reporting data of sensory and mixed nerve conduction velocity in infants and children. In a study by Gamstorp and Shelburne (1965), median and ulnar sensory PNCV (digit-wrist) was studied in 72 normal children, aged 2 weeks to 15.5 years. The nerve conduction velocity of young infants was roughly 50% of the adult value. A rapid increase during the first few years was followed by small changes through later childhood and adolescence. The changes were interpreted as a functional expression of increasing thickness and myelination of the nerve fibres.

In a second study by Cruz Martinez *et al.* (1978), normal values of sensory PNCV in distal and proximal segments of median, ulnar and sural nerves were determined in 76 normal subjects from newborns to children of 14 years of age. From infancy to age 14, sensory (digit-wrist) and mixed PNCV (wrist-elbow) can be considered an index of maturation of the sensory peripheral nerve fibres. At about 3 months of age the values were below 50% of adult values. PNCV develops in logarithmic function with age: PNCV increases about a 100% during the first year of life and it continues to increase with a progressively slower rate. In young adults normal sensory values are reached earlier in lower than in upper limbs, and also earlier in proximal (wrist-elbow) than in distal (digit-wrist) segments in the upper limbs. This is an indication that myelination starts proximally. Maximum sensory PNCV from the proximal segment is higher than in the distal segment. This difference increases with maturation of the peripheral nerve fibres. There are indications that maturation in sensory fibres is slower than in motor fibres.

Oh (1993) summarized the results of PNCV maturation studies as follows: The changes in PNCV are most profound in the first few years of life. PNCV in all fibres is about 50% of the normal adult values in the full-term newborn baby, reaching about 75% of the adult value at 1 year of age, and about 100% at 4-6 years of age. Peripheral nerve conduction is suggested to increase in a logarithmic function and is likely due to: (1) the increase in the number of large fibres between birth and 8 years of age, when the number is the same as in adult nerves, and (2) the complete myelination of nerve fibres by 5 years of age. No further increase in PNCV between age 6 and 16 was noted (Oh, 1993). In adults PNCV decrease with age, possibly caused by an increased loss of large fibres or segmental demyelination after age twenty. For mixed nerve conduction, the rates of decrease are 4.0 m/sec in the median nerve per decade.

The main disadvantages of these PNCV maturation studies are the use of rather small samples with a broad age range to establish normative values. It is possible that subtle changes in PNCV were left undetected by the design of these

studies. On the basis of our own results, we propose that PNCV might still undergo maturation processes between age 16 and 18.

The maturation hypothesis of the relation between PNCV and IQ

To investigate the hypothesis that differences in maturation may have caused the low test-retest correlations, difference scores in PNCV were computed (measure assessed on occasion II - measure assessed on occasion I). PNCV did not increase or decrease systematically, there were positive and negative difference scores. Positive difference scores can be an indication that PNCV is still increasing and has not yet reached the highest value, whereas negative scores might reflect a phase beyond this point in which PNCV is decreasing.

Strikingly, the MZ correlations for this difference score were very high as opposed to the relative low DZ scores. These results indicated that the causes for the changes in PNCV in the age interval 16 - 17.5 years were more alike for MZ twin pairs compared to DZ pairs. These causes could be ongoing maturation processes controlled by genetic influences. A reasonable assumption would be that, with respect to PNCV development, individual growth curves show the same morphology but slightly different slopes, indicating individual differences in speed of maturation. Figure 8.1 shows a hypothetical PNCV growth curve for 3 individuals. In the next step we may assume that these maturation processes (biologically determined) might be more alike in MZ twins compared to DZ twins. Genetic analyses of the difference scores revealed this measure to be highly heritable (86%). This means that PNCV value at age 18 is better predicted by the rise or fall in PNCV of the co-twin than the own score at age 16.

It is possible that the variance in IQ determined by PNCV is only fully observable when PNCV has reached its peak value as a consequence of new genetic effects. This additional genetic variance in PNCV could be responsible for the additional genetic variance in IQ and is supported by the increase of IQ heritability in adults (Bouchard, 1993).

For intelligence there seems to be an increase in heritability from infancy to childhood and a decrease in common environmental influences during adolescence (Thompson, 1993). As children become older and enter schools and other social institutions, the effects of common (parental) environment decrease and the effects of genetic factors may, thus, increase. Longitudinal twin and family studies may reveal the age-dependent changes in the relative contributions of genetic and environmental effects to individual differences in IQ. A longitudinal study from adolescence to early adulthood was conducted in a sample of Swedish male twins

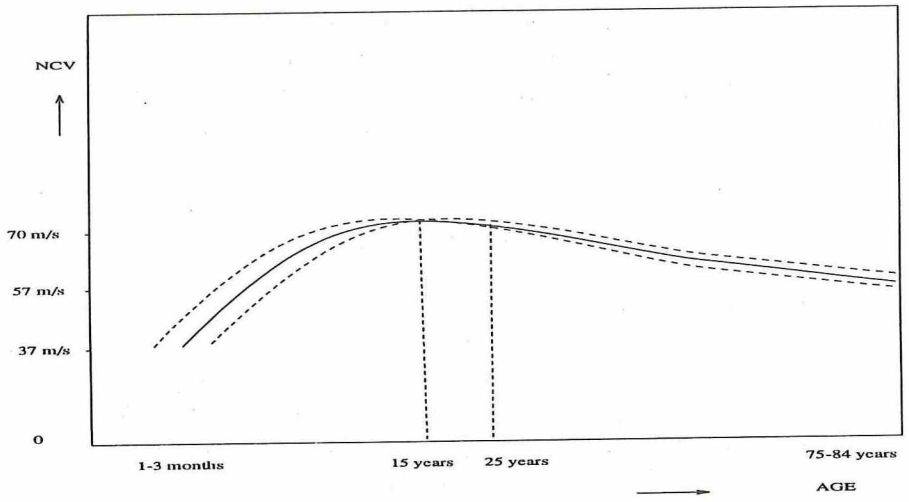

Figure 8.1
Hypothetical PNCV growth curves for three individuals. All three show the same morphology, but slightly different slopes, indicating individual differences in speed of PNCV maturation.

between 12 to 18 years of age (Fishbein, 1979). Verbal ability and inductive reasoning skills were examined. No longitudinal analyses were conducted, but correlations for verbal ability were reported to increase slightly from .70 to .78 for MZ twins and decreased from .60 to .50 for DZ twins. For inductive reasoning tests, correlations increased for both MZ and DZ twins, from .59 to .78 and from .46 to .56, respectively. Heritability, thus, for males seems to increase from around 20 to 40%.

Another way to derive heritability changes in IQ is by cross-sectional studies. In a meta-analysis on age and development of IQ based on 103 studies published between 1967 and 1985, a tendency of greater decrease in DZ compared to MZ twin correlations and, consequently, an increase in heritabilities is noticed (McCartney *et al.*, 1990). Analysis of adoption data from the Colorado Adoption Project indicates that genetic influence on IQ increases steadily between infancy and middle childhood (Fulker *et al.*, 1988). Although little adult twin IQ data are available, MZ correlations appear to peak at about 16-20 years (Bouchard, 1993).

Thus, the increase in heritability of IQ in adolescence and adults, may provide some evidence for additional genetic variance in IQ as a result of NCV maturation that probably results from increasing thickness and myelination of the nerve fibres not only centrally, but observable in the periphery as well. There are theories

suggesting that higher intelligence might be associated with higher central conduction speed. Miller (1994) proposed that this association could by related to central myelination. The observed positive correlation between brain size (as measured by Magnetic Resonance Imaging) and IQ (e.g. Wicket *et al.*, 1994, Willerman *et al.*, 1991, Schultz *et al.*, 1993) also supports the myelin hypothesis. Thicker myelin sheathed nerves are faster, more accurate in signal processing and might therefore be associated with faster information processing and higher scores on IQ tests (Miller, 1994).

This myelin hypothesis is supported by recent studies on age-related changes in cognitive functioning. The long-standing believe that cognitive changes in the normal healthy elderly were caused by widespread neuron death is challenged by recent findings based on more sophisticated neural imaging techniques (Wickelgren, 1996). The higher densities observed in young brain tissue compared to old tissue (interpreted as cell loss) could have been an effect from commonly used methods for preparing brain tissue for microscopy study in which young cortical tissue simply shrank more than old tissue. New studies indicate no age-related differences in cell number and some imaging studies indicate that age-related brain shrinkage is almost exclusively due to loss of white matter, probably caused by shrinkage of myelin.

Recent studies in monkeys suggest that a breakdown of myelin may account for the cognitive changes in aging. No age-related differences in the volume of the animals' grey matter were observed. It was theorized that myelin breakdown slows neural conduction along an axon and may influence problem solving speed (Peters, 1996). This theory is in congruence with the observation that PNCV decreases with age, as a possible cause of an increased loss of large fibres and segmental demyelination after age twenty.

Final remarks

Traits that are influenced by multiple factors (like variation in intelligence) are unlikely to show large correlations with a single causal factor. Consistently replicable small significant correlations between psychometric and biological variables may be of theoretical importance. This is especially true when these correlations are shown to be genetically determined. Genetic analyses by means of twin studies, thus, may play an essential role in the theoretical interpretation of the relationships of biological and behavioral variables (Jensen & Sinha, 1993). The small genetically mediated correlation in our study between PNCV and IQ

contributes to theoretical knowledge in terms of the 'neural efficiency' model. The fact that this relationship was not observed at the first test occasion was explained by ongoing maturation processes in PNCV between age 16 and 18. So, the correlation between PNCV and IQ, as initially reported by Vernon and Mori (1992) has been replicated and this correlation is indeed genetically mediated.

In accordance with other studies (Ho, Baker & Decker, 1988; Baker, Vernon & Ho, 1991) the moderate correlations between Reaction Times and IQ, were entirely mediated by genetic influences. There was no relationship between PNCV and Reaction Times, which both seem to be independent correlates of human intelligence. This observation, to some extent, agrees with the suggestion of Vernon and Mori (1992). They found both RT and PNCV contributing to the prediction of IQ in two studies (multiple R's = .53 and .57) and hypothesized that the relationship between IQ and speed-of-information-processing was, at least in part, a function of each one's correlation with PNCV. However, the partial RT - IQ correlations remained significant after PNCV was controlled for. Vernon and Mori concluded that intelligence and speed-of-information-processing may be thought of as two types of related cognitive abilities (e.g. verbal and quantitative abilities), which are both correlated with PNCV, but their relationship is not attributable to PNCV.

The next question that rises is of what interest (theoretically or practically) the observed correlation between PNCV and IQ can be? Multivariate genetic analyses of cognitive abilities suggest a substantial overlap of genetic influences and imply a common set of genes associated with these traits (Plomin, Owen & McGuffin, 1994). Molecular techniques are now applied to identify multiple loci affecting normal variation in psychometric abilities. The first allelic association studies to identify quantitative trait loci (QTL) associated with intelligence have been conducted (Plomin *et al.*, 1994, Plomin *et al.*, 1995) using markers related to genes which are likely relevant to neural functioning. Two of the three initially identified markers of the Plomin *et al.*, 1994 study (alcohol dehydrogenase 5 and the beta polypeptide of nerve growth factor) yielded results in the same direction but were not significant in the replication sample (Plomin *et al.*, 1995). This was possibly due to limited statistical power. The third marker (EST00083) of mitochondrial origin was also significant in the replication sample and the technique was described in Skuder *et al.* (1995).

Recently, the specific hypothesis of the hierarchical genetic structure of cognitive abilities (as suggested by multivariate quantitative genetic research) was supported by means of QTL analyses. In cognitive abilities the genetic effects are largely general, but some genetic effects are specific to certain abilities. Four

markers were identified which showed similar predicting effects across the ability scales (Verbal, Spatial, Perceptual Speed and Memory), suggesting that they are related to general cognitive ability (*g*). These associations became negligible when the effects of *g* (WISC-R IQ score) were removed. Three other markers continued to be significantly associated with specific cognitive ability scales after the effects of *g* were removed (Petrill *et al.*, in press). QTL research concerning cognitive disabilities did yield promising findings in the context of reading disabilities. A QTL on chromosome 6 was identified to be associated with dyslexia (Cardon *et al.*, 1994). Recently, this result was replicated in a study by Grigorenko *et al.* (1996) in which word segmentation (a basic process involved in reading) was linked to markers on chromosome 6, whereas single word reading (presumably a higher-order process) was linked to markers on chromosome 15. These findings may in the future contribute to early diagnosis and intervention.

QTL studies with regard to PNCV have not yet been carried out. A well established genetic correlation between PNCV and IQ could, from a speculative point of view, make PNCV an additional (relatively easy obtainable) measure to (physiologically) select extreme phenotypes and investigate linkage to markers associated with genes which are thought to be important for myelination and neural functioning. In this way a more particular set of genes (markers) may be identified which can increase the power to detect QTLs for cognitive abilities.

9

Samenvatting

Er is weinig twijfel over het feit dat er individuele verschillen bestaan in de prestatie op intelligentietests. Bestaande theorieën over de structuur van intelligentie zijn niet in staat de onderliggende processen te verklaren die deze individuele verschillen veroorzaken. In de experimentele psychologie is men reeds vele decennia op zoek naar mogelijke biologische determinanten die individuele verschillen in intelligentiescores zouden kunnen verklaren. Deze zoektocht is ruwweg onder te verdelen in twee onderzoekstradities. De ene traditie begon reeds in de vorige eeuw met de studies van Galton (1883) en onderzoekt het verband tussen intelligentiescores en de snelheid waarmee elementaire cognitieve taken (reactietijdtaken) worden uitgevoerd. De andere traditie richt zich op het verband tussen individuele verschillen in intelligentiescores en fysiologische (biologische) maten.

Biologische determinanten van cognitief functioneren worden vaak gezocht in neurofysiologische en biochemische processen van het centraal zenuwstelsel. Naast een groot aantal andere fysiologische maten werd zenuwgeleidingssnelheid in het centrale en perifere zenuwstelsel onderzocht als potentiële biologische determinant van intelligentie (Reed & Jensen, 1989, 1991, 1993; Vernon & Mori, 1992). Zenuwgeleidingssnelheid is de snelheid waarmee elektrische impulsen worden doorgegeven in een zenuw (de zogenaamde nerve conduction velocity: NCV). Deze snelheid wordt onder andere bepaald door de dikte van de myelinescheden rondom de zenuwen. Perifere zenuwgeleiding (PNCV) is een basale fysiologische maat en is perifeer in verschillende zenuwen te bepalen met standaard neurologische meettechnieken (o.a. Oh, 1993). Reed (1984, 1988) heeft als eerste geopperd dat NCV-variatie, in de normale range, geassocieerd zou kunnen zijn met individuele verschillen in intelligentie en informatieverwerking en gedeeltelijk de genetische invloeden op intelligentie zou kunnen verklaren. Hij kwam tot deze hypothese op grond van enkele observaties in dieronderzoek. Genetisch onderzoek in dierpopulaties leverde redelijke erfelijkheidsmaten op (h^2 = 20-30%) voor PNCV in de staart van muizen (Hegmann *et al.*, 1973; Reed, 1983). Ook werd geobserveerd dat

PNCV-verschillen tussen selectielijnen van muizen geselecteerd op hoge en lage caudale PNCV samen hingen met gedragsverschillen tussen deze lijnen (Hegmann, 1979). Reed voorspelde een grotere erfelijkheid van PNCV (rond de 50%) bij de mens en suggereerde dat individuele verschillen in intelligentie bepaald zouden kunnen worden door genetische verschillen in de structuur en de hoeveelheid 'transmissie-proteïnen' die individuele verschillen in de snelheid en efficiency van informatieverwerking bepalen en op die manier het cognitief functioneren beïnvloeden. Dit wordt ook het 'neural efficiency model of intelligence' genoemd (Jensen, 1982; Vernon, 1983, 1985). De grote consensus die bestaat over het verband tussen reactietijden op elementaire cognitieve taken en intelligentiescores geeft additionele ondersteuning voor dit model (Vernon, 1993). Snellere reacties bij het oplossen van elementaire cognitieve taken (reactietijdtaken) worden immers verondersteld een snellere informatieverwerkingssnelheid te reflecteren.

Grotere efficiency van het zenuwstelsel zou ook in de perifere zenuwen meetbaar kunnen zijn en het verband tussen individuele verschillen in deze maat en individuele verschillen in intelligentie zou eenvoudig te onderzoeken zijn. Deze hypothese werd voor het eerst getoetst door Vernon en Mori (1992). In twee onafhankelijke onderzoeken werd een verband gevonden tussen perifere zenuwgeleidingssnelheid (gemeten in de arm), intelligentie en reactietijden op elementaire cognitieve taken. Op grond van dit onderzoek werd geconcludeerd dat een algemene 'neural efficiency factor' de belangrijkste biologische determinant is van individuele verschillen in psychometrische intelligentie.

Theorieën met als uitgang dat individuele verschillen in intelligentiescores gedeeltelijk verklaard kunnen worden door individuele verschillen in fysiologische maten, worden ondersteund door de overtuigende resultaten van gedragsgenetisch onderzoek naar intelligentie. Intelligentie is verreweg de meest uitvoerig onderzochte variabele in de gedragsgenetica en kennis over de genetische en omgevingsinvloeden op individuele verschillen in intelligentie is omvangrijk. Ongeveer 50-60% van de fenotypische variantie in psychometrische intelligentie wordt verklaard door genetische factoren (Bouchard *et al.*, 1990). Om de bijdrage van genetische en omgevingsinvloeden op een bepaalde eigenschap te bepalen worden gegevens van genetisch verwante personen, zoals tweelingen, gebruikt. De tweelingmethode vergelijkt de overeenkomst van een bepaalde eigenschap tussen monozygote (MZ) en dizygote (DZ) tweelingen om een schatting van de erfelijkheid te krijgen. MZ-tweelingen zijn 100% genetisch gelijk, terwijl DZ-tweelingen gemiddeld 50% genetisch verwant zijn, net zoals gewone broertjes en zusjes. Dit gegeven vormt de basis voor het opstel-

len van een model waarmee de variantie in een geobserveerde eigenschap uiteengelegd kan worden in een deel dat wordt verklaard door erfelijke factoren, een deel dat kan worden toegeschreven aan systematische effecten van een gedeelde (gezins)omgeving en een deel dat samenhangt met omgevingsfactoren die uniek zijn voor een individu. MZ-tweelingen zijn genetisch identiek en als ze in hetzelfde gezin zijn opgegroeid moeten verschillen tussen leden van een paar veroorzaakt worden door de unieke omgevingsfactoren. Bij DZ-tweelingen kunnen die verschillen zowel door de unieke omgeving als door erfelijke factoren verklaard worden. In tegenstelling tot de unieke omgeving, dragen gedeelde omgevingsinvloeden bij tot een grotere gelijkheid voor leden van zowel MZ- als DZ-paren. Gedeelde omgevingsinvloeden zorgen voor een grotere overeenkomst tussen individuen afkomstig uit een gezin en dus voor de verschillen die bestaan tussen leden van verschillende gezinnen. Een grotere overeenkomst tussen bijvoorbeeld intelligentiescores van MZ-tweelingen vergeleken met die van DZ-tweelingen, vormt een eerste indicatie dat erfelijke factoren een rol spelen. Als de overeenkomst tussen MZ- en DZ-tweelingen gelijk is, vormt dat een aanwijzing dat gemeenschappelijke omgevingsfactoren van belang zijn.

Behalve het onderzoeken van de mate waarin genetische en omgevingsfactoren individuele verschillen in gedrag of psychofysiologische eigenschappen beïnvloeden, kan ook worden onderzocht in welke mate het verband tussen twee eigenschappen wordt veroorzaakt door genetische en omgevingsfactoren (Martin & Eaves, 1977; Boomsma, Martin & Neale, 1989; Neale & Cardon, 1992). Twee eigenschappen kunnen correleren doordat ze beiden worden beïnvloed door dezelfde genetische factoren maar ook doordat alleen de omgevingsinvloeden correleren. Om een biologische maat te onderzoeken als potentiële determinant van intelligentie is het van belang na te gaan of de relatie voornamelijk door onderliggende gecorreleerde genetische invloeden wordt bepaald.

In dit proefschrift worden de resultaten beschreven van een onderzoek naar de genetische (co)variantie van intelligentie, reactiesnelheid en zenuwgeleidingssnelheid in een groep van 213 Nederlandse tweelingparen. Deze groep is tweemaal gemeten, eenmaal op zestien-jarige leeftijd en de tweede keer op achttien-jarige leeftijd. Deze groep tweelingen participeerde gelijktijdig ook in een EEG/ERP-onderzoek naar de genetische en omgevingsinvloeden op de ontwikkeling van de hersenen (Van Beijsterveldt *et al.*, 1996). Dit is het eerste onderzoek waarbij de genetische basis van zenuwgeleidingssnelheid werd onderzocht in de mens.

Multivariate analyse van de WAIS-subtests en de Raven

Een deel van dit proefschrift beschrijft de multivariate genetische analyses van de individuele verschillen in scores op de elf subtests van de Nederlandse versie van de WAIS (Wechsler Adult Intelligence Scale) afgenomen op achttien-jarige leeftijd en de score op de Raven-test (afgenomen op zestien-jarige leeftijd). Met dit soort analyses is het mogelijk de samenhang tussen de subtests uit te splitsen naar een deel veroorzaakt door gecorreleerde genetische en een deel veroorzaakt door gecorreleerde omgevingsfactoren. Gedeelde gezinsfactoren bleken geen rol te spelen in de geobserveerde fenotypische samenhang tussen de subtests. Genetische factoren en niet-gedeelde (unieke) omgevingsfactoren bleken de onderliggende factoren in deze samenhang. De genetische factoren konden worden onderverdeeld in een *algemene*, een *verbale*, een *performale* factor en *specifieke* factoren. De algemene factor representeert een soort (genetische) overlap van vaardigheden die belangrijk zijn voor het uitvoeren van alle subtests. De verbale factor geeft de overlap aan van subtests die te maken hebben met verbale (taal-) kennis, terwijl de performale factor het gemeenschappelijke deel verklaart van subtests die een beroep doen op onder andere ruimtelijk inzicht. De specifieke factoren verklaren een deel van de variantie in subtests die uniek is voor elke subtest en geen verband houdt met de rest. Voor de niet-gedeelde omgevingsfactoren bleek er geen evidentie voor een aparte verbale en performale factor. Slechts een algemene factor en specifieke factoren verklaarden deze omgevingscomponent. De gangbare opsplitsing van de WAIS in een verbale en performale schaal geeft dus eerder de genetische dan de omgevingscovariantie weer tussen de subtests.

De fenotypische associatie tussen subtests van intelligentietests duidt op het bestaan van een algemene intelligentiefactor *g*. Het construct *g* representeert de overlap die bestaat tussen verschillende cognitieve tests. Multivariate genetische analyses zijn belangrijk voor het onderzoeken van de aard van *g* (Jenssen, 1993). De algemene intelligentiefactor bleek in dit onderzoek voornamelijk uit genetische invloeden te bestaan, zoals bleek uit de grotere ladingen van de subtests op de algemene genetische factor vergeleken met de kleinere ladingen op de algemene niet-gedeelde omgevingsfactor. De associatie tussen de Raven (een non-verbale redeneertest) en de WAIS-subtests werd onderzocht door deze mee te nemen in de multivariate analyse. De lading van de Raven op de algemene omgevingsfactor bleek niet significant, die op de algemene genetische factor wel. Het verband tussen de Raven en de WAIS bleek daardoor uitsluitend bepaald te worden door gemeenschappelijke genetische factoren.

Intelligentie in de Nederlandse populatie

In dit onderzoek bleken individuele verschillen in de WAIS IQ-score sterk door erfelijke factoren bepaald te zijn (h^2 = 82%). Deze waarde is hoger dan die gewoonlijk in de literatuur gerapporteerd staan: 50% - 60%, verkregen uit meta-analyses en 70% gemeten in gescheiden opgegroeide MZ-tweelingen (Bouchard *et al.*, 1990). Een hogere erfelijkheid voor de WAIS IQ-score is ook gemeten in Noorse tweelingen (Tambs *et al.*, 1984, 1986) en werd toegeschreven aan de mogelijke gevolgen van de grote sociale gelijkheid in de Noorse samenleving. De hoge erfelijkheid voor IQ zou op verschillende manieren verklaard kunnen worden. Als culturele invloeden op een bepaald fenotype belangrijk en relatief homogeen zijn, dan zal de omgevingsvariantie dalen en zullen erfelijke invloeden stijgen. Een voorbeeld hiervan is de baseball-cultuur in de Verenigde Staten. Omdat de meeste Amerikaanse jongens gelijke mogelijkheden hebben zich te ontplooien in het baseball-spel, is het waarschijnlijk dat de erfelijkheid van baseball-talent bij jonge Amerikaanse mannen heel hoog is (Bouchard *et al.*, 1990).

Een tweede mogelijke verklaring voor de hoge erfelijkheid in individuele verschillen in IQ-scores is dat erfelijke en omgevingsinvloeden op IQ gecorreleerd zijn (de zogenaamde G × E correlatie). In dat geval zijn omgevingsfactoren die een persoon beïnvloeden niet willekeurig, maar bepaald door het genotype van de persoon zelf of door dat van de ouders. Scarr & McCartney (1983) differentiëren tussen twee vormen van genotypische beïnvloeding van de omgeving. De eerste is de indirecte (passieve) beïnvloeding van de omgeving van het kind, ook wel culturele transmissie genoemd. Een voorbeeld hiervan is als kinderen met hogere intellectuele gaven, naast de geërfde genen, ook profiteren van een intellectueel stimulerende omgeving die geschapen wordt door de ouders en dus ook weer gerelateerd is aan hun genotype. Zo'n positieve G × E correlatie leidt tot een overschatting van de genetische component in de variantie (Neale & Cardon, 1992). Culturele transmissie kan geschat worden door data van de ouders op te nemen in het model. Echter, een serie studies uit het Colorado Adoption Project leverde geen evidentie voor het bestaan van dit effect. De actieve vorm van de G × E correlatie speelt mogelijkerwijs een grotere rol bij adolescenten en volwassenen.

Een grotere sociale gelijkheid in een populatie biedt aan ieder individu gelijke mogelijkheden wat betreft educatie en intellectuele ontplooiing, waardoor het kiezen van een opleiding en het aantal jaren van scholing sterk (op actieve wijze) bepaald zou kunnen worden door de genetische aanleg van het individu zelf in plaats van door, bijvoorbeeld, de sociaal-economische status

van de ouders. In dat geval zal men, wat betreft individuele verschillen in IQ, een grotere rol van genetische invloeden observeren in een representatieve steekproef van volwassenen.

Ondanks de geobserveerde hogere erfelijkheid voor IQ in dit onderzoek, wordt (overeenstemmend met gegevens uit de literatuur) een grotere invloed van gedeeldeomgevingsinvloeden op IQ-scores bij jonge Nederlandse kinderen waargenomen (Boomsma & Van Baal, in press). Bij zeven-jarigen zijn deze gedeeldeomgevingsinvloeden al niet meer duidelijk aanwezig, waarschijnlijk als gevolg van het begin van de formele basisschooleducatie.

De relatie tussen reactiesnelheid en intelligentie

Individuele verschillen in de snelheid en efficiency van informatieverwerking (mogelijk bepaald door individuele verschillen in 'transmissie-proteïnen') beïnvloeden het cognitief functioneren. Informatieverwerkingssnelheid wordt doorgaans geoperationaliseerd in termen van reactietijden op elementaire cognitieve taken, en er bestaat grote consensus over het verband tussen reactietijden en intelligentiescores (correlaties tussen -.2 en -.3). Snellere reacties bij het oplossen van elementaire cognitieve taken worden immers verondersteld een snellere informatieverwerkingssnelheid te reflecteren. Een theoretische verklaring voor het verband tussen reactiesnelheid en IQ-scores werd gegeven met behulp van het 'neural efficiency model of intelligence' in termen van drie eigenschappen van het kortetermijngeheugen (Short Term Memory, STM). Die eigenschappen zijn: de beperkte opslagcapaciteit van informatieeenheden, het snelle verval van informatie als er geen herhaling plaats vindt en de 'trade-off' tussen de hoeveelheid opgeslagen informatie en de hoeveelheid die tegelijk verwerkt kan worden. Deze eigenschappen worden als limiterende factoren gezien die het informatieverwerkingssysteem zouden kunnen laten 'overlopen', ware het niet voor de vierde grootheid: de snelheid waarmee basale cognitieve operaties wordt uitgevoerd. Omdat er waarschijnlijk weinig variatie bestaat in de eerste drie eigenschappen van het kortetermijngeheugen, is het mogelijk dat mensen voornamelijk verschillen in de snelheid van uitvoer van basale cognitieve operaties. Er bestaan individuele verschillen in de snelheid waarmee basale cognitieve operaties uitgevoerd worden die gerelateerd zijn aan individuele verschillen in intellectueel functioneren.

Bij de eerste meting werden aanzienlijke erfelijkheidsmaten gemeten voor vijf reactietijdtaken (h^2 = 50 - 60%). De gemiddelde fenotypische correlatie met de Raven-testscore was (-.24). Bij de tweede meting waren de erfelijkheidsmaten lager (gemiddeld 32%). Dit zou misschien een effect kunnen zijn

van een wijziging in de afname-procedure van de tests, waarbij proefpersonen werden gestimuleerd sneller te reageren dan een gestelde streeftijd (grotere omgevingsdruk). De gemiddelde correlatie met de WAIS-subtests was ook lager (-.18). Echter, een belangrijke bevinding in het huidig onderzoek was de replicatie van resultaten van twee voorgaande genetische studies naar het reactiesnelheid-IQ verband (Ho, Baker & Decker, 1988; Baker, Vernon & Ho, 1991). Net als die twee studies wees in dit onderzoek de genetische covariantie-analyses uit dat het verband tussen snelheid van informatieverwerking en intelligentiescores (bij beide metingen) volledig door genetische factoren wordt bepaald. Dat wil zeggen dat de reactietijd-IQ-relatie dus niet het gevolg is van correlerende omgevingsfactoren (zoals praktische oefening en vaardigheid), die gemeenschappelijke aspecten van beide soorten tests beïnvloeden. De gemiddelde genetische correlatie tussen de reactietijden en de Raven-testscore was -.42 en tussen de reactietijden en de WAIS verbale/performale subtests, -.46 en -.42, respectievelijk. Het is aannemelijk dat een deel van individuele verschillen in de prestatie op intelligentietests wordt verklaard door individuele verschillen in de snelheid waarmee basale cognitieve operaties uitgevoerd kunnen worden. De reactietijd-IQ-relatie (bij de tweede meting) was ook niet afhankelijk van de aard van de tests (verbaal of performaal).

Vernon & Mori (1992) vonden een verband tussen reactietijden en perifere zenuwgeleidingssnelheid, maar concludeerden dat de reactietijd-IQ-relatie niet wordt veroorzaakt door individuele verschillen in perifere zenuwgeleidingssnelheid (PNCV), omdat deze relatie bleef bestaan nadat het effect van PNCV uitgepartialiseerd was in een regressieanalyse. Reactiesnelheid en IQ kunnen gezien worden als twee gerelateerde maten voor cognitief functioneren en hebben eerder een aparte relatie met PNCV (Vernon & Mori, 1992). In ons onderzoek is er bij beide metingen geen verband gevonden tussen PNCV en reactiesnelheid.

De relatie tussen perifere zenuwgeleidingssnelheid en intelligentie

De resultaten van de eerste meting leverden geen bewijs voor een verband tussen perifere zenuwgeleidingssnelheid in de arm en intelligentie zoals gemeten met de Raven Standard Progressive Matrices Test. De Raven-test meet het 'logisch-redeneren'. De PNCV bleek, zoals voorspeld, een hoog-erfelijke maat (76%). De erfelijkheid voor de scores op de Raven-test was 65%. Er werd geopperd dat het gebruik van een test die algemene intelligentie meet (zoals gebruikt in het onderzoek van Vernon en Mori, 1992) beter het verband tussen IQ en PNCV tot uitdrukking zou kunnen brengen.

Bij de tweede meting (leeftijd 18) werd wel een significant verband gevonden tussen WAIS IQ en PNCV. Dit verband bleek puur door gemeenschappelijke genetische factoren bepaald te zijn. Echter, de overeenkomst tussen PNCV gemeten op 16- en 18-jarige leeftijd bleek heel laag. Dit was niet te verklaren door veranderingen in experimentele procedures. Gebrek aan stabiliteit van de PNCV-maat bleek ook niet veroorzaakt te zijn door statistische artefacten (als non-binormaliteit). Een onbetrouwbare meettechniek werd uitgesloten, omdat anders de huidige PNCV tweeling-correlaties (met name de hoge MZ-correlaties) niet geobserveerd zou zijn. Op beide leeftijden werd een hoge correlatie tussen de PNCV van leden van MZ-paren gemeten en een relatief kleinere correlatie tussen leden van DZ-paren. Als er sprake zou zijn van een onbetrouwbare meettechniek en apparatuur, zouden meetfouten gelijk verdeeld moeten zijn over alle proefpersonen. De lage DZ-correlatie geeft dus aan dat de grote overeenkomst tussen leden van MZ-paren niet het gevolg kan zijn van gecorreleerde meetfouten. Er werd vervolgens geopperd dat het gebrek aan overeenkomst tussen PNCV op 16- en 18-jarige leeftijd misschien het gevolg zou kunnen zijn van rijpingsprocessen die nog niet helemaal voltooid zijn. In de literatuur is over de maturatie van PNCV in dit specifieke leeftijdsinterval niets bekend. Veranderingen in PNCV worden verondersteld het gevolg te zijn van een toename in het aantal grote zenuwvezels en door de afgeronde myelinesatieprocessen. Aangenomen wordt dat PNCV van baby's ongeveer 50% van de volwassen waarde heeft, dat deze zeer snel toeneemt in de eerste levensjaren en dat dan de snelheid minder of nauwelijks toeneemt tijdens de late kinderjaren en de tienerjaren (Oh, 1993). Het nadeel van deze maturatiestudies is het gebruik van kleine groepen proefpersonen met een breed leeftijdsinterval waardoor eventuele subtiele veranderingen in PNCV tussen leeftijd 16 en 18 ongedetecteerd zouden kunnen blijven.

Bij nadere inspectie bleek de groep adolescente tweelingen opgesplitst te kunnen worden in personen met een positieve of negatieve PNCV-verschilscores (= PNCV(18 jaar) - PNCV(16 jaar)). Deze verschillen zijn uitgelegd in termen van rijpingsprocessen van de PNCV. Van de personen met een negatieve verschilscore werd verondersteld dat de maturatie van de PNCV reeds voltooid is en zelfs al aan het afnemen is, terwijl een positieve verschilscore zou inhouden dat de PNCV nog niet de hoogste waarde heeft bereikt. Verbluffend was het feit dat de overeenkomst voor PNCV-verschilscores tussen leden van MZ-paren heel groot bleek te zijn vergeleken met de overeenkomst in DZ-paren. De PNCV-score op 18-jarige leeftijd van een lid van een paar is dus een betere voorspeller van de verandering in PNCV van het andere lid, dan

zijn/haar eigen PNCV-score op 16-jarige leeftijd. Het is een redelijke gedachte dat er individuele verschillen in het verloop van het PNCV-rijpingsproces bestaan en dat individuele groeicurven van MZ-tweelingen een grotere overeenkomst vertonen vergeleken met die van DZ-tweelingen. Uit de genetische analyses van de PNCV-verschilscores bleek dat deze een hoog-erfelijke maat was (h^2 = 86%). Het is mogelijk dat het deel van de variantie in IQ dat bepaald wordt door PNCV pas te meten is als de PNCV uitgerijpt is en de hoogste waarde heeft bereikt. De gedachte dat door de voltooide rijping van PNCV een additionele genetische variantie wordt toegevoegd aan IQ, zou passen in de observatie dat de erfelijkheid van IQ nog toeneemt in adolescenten en jong-volwassenen (Bouchard, 1993). Additionele genetische variantie door PNCV zou het resultaat kunnen zijn van de toenemende dikte van myelinescheden rondom de zenuwvezels, niet alleen centraal, maar ook perifeer waarneembaar. Zenuwvezels met een dikkere myelineschede zijn sneller en accurater en kunnen daarom geassocieerd zijn met snellere informatieverwerking en hogere IQ-scores (Miller, 1994). Deze myeline-hypothese wordt ondersteund door recent onderzoek op het gebied van cognitieve verouderingsprocessen. Nieuwe neurale imagingtechnieken tonen aan dat de afname in hersenvolume bij ouderen eerder het gevolg is van een afname van myeline dan van het afsterven van neuronen (Wickelgren, 1996). Een afname in cognitief functioneren zou dus geassocieerd kunnen zijn met afname in dikte van myelinescheden op centraal niveau. Andere evidentie wordt geleverd door de observatie dat cognitieve veranderingen bij oudere apen gepaard blijken te gaan met afname in volume van de 'witte stof' (myelinescheden) en niet van het aantal neuronen (Peters, 1996).

Slotopmerkingen

De vraag is wat het belang is van een geobserveerde correlatie tussen PNCV en IQ. De grote overlap in genetische invloeden, betrokken bij tal van taken die verschillende aspecten van intelligentie meten, suggereert beïnvloeding van een gemeenschappelijke verzameling genen. Moleculair-biologische technieken worden nu toegepast voor het identificeren van de genen (zogenaamde QTL = Quantitative Trait Loci) die normale verschillen in IQ bepalen. Kandidaat-markers worden ingezet die gerelateerd zijn aan genen die belangrijk zijn voor het neuraal functioneren. Twee van de drie aanvankelijk geïdentificeerde markers uit de Plomin *et al.* (1994) studie (alcohol dehydrogenase-5 en de beta-polypeptide van de *nerve growth factor*) gaven in een replicatiestudie (Plomin *et al.*, 1995), hoewel niet significant, resultaten in gelijke richting. De

derde marker (EST00083) bleek wel significant in een replicatiestudie (Skuder, *et al.*, 1995).

Resultaten van recentelijk QTL-onderzoek ondersteunen de hypothese dat in de hiërarchische structuur van cognitieve vaardigheid de genetische effecten voornamelijk algemeen van aard zijn met additionele genetische factoren, specifiek voor bepaalde vaardigheden. Vier markers werden geïdentificeerd die geassocieerd waren met de verschillende vaardigheden (verbaal, ruimtelijk inzicht, perceptuele snelheid en geheugencapaciteit) wat er op wijst dat ze gerelateerd zijn aan algemene intelligentie *g*. Deze associaties verdwenen als de effecten van *g* (Full-Scale IQ-score op de WISC) werden verwijderd, echter, drie andere markers bleven significant geassocieerd met specifieke cognitieve vaardigheden (Petrill *et al.*, in press). Wat betreft cognitieve stoornissen is er een QTL gevonden op chromosoom 6 die geassocieerd is met dyslexie (leesstoornissen) (Cardon *et al.*, 1994). Onlangs is dit resultaat gerepliceerd voor één component van dyslexie, woord-segmentatie, die waarschijnlijk een basaal leesproces representeerd. Daarnaast werd ook een QTL geïdentificeerd op chromosoom 15 voor het het hoger leesproces, woord-lezen (Grigorenko *et al.*, 1996).

Er is tot nu toe nog geen QTL-onderzoek verricht op het gebied van perifere zenuwgeleidingssnelheid. Een betrouwbare (genetische) relatie tussen PNCV en IQ zou PNCV wellicht tot een interessante eigenschap maken voor QTL-onderzoek naar IQ. Door voor extreme fenotypische PNCV-waarden linkage te onderzoeken met markers, geassocieerd met genen waarvan verondersteld wordt dat ze bijdragen tot myelinevorming en neuraal functioneren, zou men misschien een kleinere, specifieke groep markers kunnen identificeren die het zoekproces naar QTLs voor intelligentie zouden kunnen versnellen.

Dankwoord

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