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Genetic Analysis of Peripheral Nerve Conduction Velocity in Twins

F. V. Rijsdijk,^{1,3} D. I. Boomsma,¹ and P. A. Vernon²

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We studied variation in peripheral nerve conduction velocity (PNCV) and intelligence in a group of 16-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 0.65 for Raven IQ score and 0.77 for PNCV. However, there was no significant phenotypic correlation between IQ score and PNCV.

KEY WORDS: Peripheral nerve conduction velocity; IQ; heritability; twins.

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 such as the electroencephalogram (Courchesne, 1978), regional cerebral blood flow (Phelps *et al.*, 1982; Risberg, 1986), and cortical glucose metabolism (Chase *et al.*, 1984), nerve conduction velocity (NCV) has been investigated as a potential biological determinant of intelligence. Nerve conduction velocity is the speed with which electrical impulses are transmitted along nerve fibers and across synapses.

Peripheral NCV (PNCV) is a well-established, extensively studied neurological trait in humans for diagnosing neuromuscular and neurological diseases (Desmedt, 1980; Oh, 1984). 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 0.1 to 0.2; broad-sense heritabilities of 0.2 to 0.3). Tail NCV also correlated with certain behaviors such as open-field activity and defecation (Hegmann, 1979). Reed (1988) found a significant narrow-sense heritability in mouse tail NCV, 0.23. He suggested that in large natural populations of mammals, including humans, the heritability of NCV 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 heterogeneous-strain mice, for example, has a heritability of 0.21 ± 0.05 , which is much smaller than the heritability of around 0.8 in humans. According to Reed, a heritability of 0.5 or more for NCV in humans may be a reasonable estimate.

Three components of nerve action potentials can be distinguished. Onset NCV and peak NCV measure the conduction speed in the fast-conducting (large-diameter) nerve axons and the average-conducting (average-diameter) nerve axons, respectively, while end NCV involves slow-conducting (small-diameter) axons (Ma and Liveson, 1983; Oh, 1984). Onset NCV is commonly used in

¹ Department of Psychonomics, Vrije Universiteit, Amsterdam, The Netherlands. Fax: (31) 20 44 48832. e-mail: Rijsdijk@psy.vu.ne.

² Department of Psychology, University of Western Ontario, London, Ontario, Canada.

³ To whom correspondence should be addressed.

studies examining the relation between IQ and PNCV, because it reflects conduction of the fast nerve fibers. A high IQ is suggested to be a consequence of a 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 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 and 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 speed of information processing and thereby contribute to higher IQ test scores (Vernon, 1993, Reed, 1984).

Recently, Vernon and Mori (1992) reported correlations of 0.43 and 0.46 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 NCV 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 NCV 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 16-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 participated earlier 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 takes part in a longitudinal EEG and ERP study in which genetic and environmental influences on brain development are examined. This NCV 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 (one DZM, one MZF, and one 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 of correctly classified zygosity of the questionnaire compared with blood group polymorphism was 88%.

Intelligence Test

The Raven Standard Progressive Matrices Test (Raven, 1983) was administered without a time limit. The IQ score was 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 NCV 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

NCVs 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 soundproof cabin. Orthodromic electrical stimulation of the median nerve was accomplished using an ELTRON G-F 437 (Enraf Nonius) stimulator. The stimulator, two surface electrodes, provided positive, 0.05-ms-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 effective only if the arm temperature was 33 deg 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 ms. The preamplifier 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 terminal. Recording and reference electrodes were standard EEG silver-chloride 9-mm disk 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 center-to-center distance of 30 mm (anode

most proximal). A recording electrode (most distal) and a reference electrode were applied in the elbow (30-mm center-to-center distance) together with a ground electrode connected to the preamplifier. Impedances between electrodes were below 5 K Ω .

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

NCV Computation

From the two APs three 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 the wrist–elbow distance in millimeters (center-to-center 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 NCV (ONCV), peak NCV (PNCV), and end NCV (ENCV) for the nerve segment.

Statistical Analyses

The effect of sex on mean IQ and NCV measures was assessed by likelihood-ratio chi-square tests using the computer program LISREL7 (Jöreskog and Sörbom, 1988). These tests were used to compare the fit of a model that constrained parameter estimates for mean IQ and NCVs 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 five sex $\times$ 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

Fig. 1. (A) ONSET NCV distribution. The X axis is the nerve conduction velocity (m/s). (B) Raven IQ score distribution. The X axis is the number of correct items.

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 chi-square tests. The overall chi-square tests the agreement between the observed and the predicted variances and covariances in the five groups. A large chi-square (and a low probability) indicates a poor fit, while a small chi-square (accompanied by a high p value) indicates that the data are consistent with the model. Submodels were compared by hierarchic chi-square tests, in which the chi-square 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 df for the reduced model (Neale and Cardon, 1992).

RESULTS

Figure 1 shows the distribution of the raw scores for ONCV and Raven IQ. The raw scores for ONCV showed acceptable symmetry (skewness, 0.344; kurtosis, 0.053) (Fig. 1A). The Raven IQ distribution (Fig. 1B) was negatively skewed (skewness, -0.977 ; kurtosis, 1.66), and a quadratic transformation was used to obtain a more symmetric distribution (skewness, -0.485 ; kurtosis, 0.273).

Height, temperature, age (Oh, 1984; Stetson *et al.*, 1992), and physical exercise level (Reed, 1993) are possible confounders of NCV. Arm temperature was controlled for and showed no correlation with NCV. The NCV measures also showed no correlation with age and physical exercise level for males and females. All three NCV measures were correlated with height in males (0.20, 0.21, and 0.27; $p < .05$) but not in females.

In Table I the means and standard deviations for Raven IQ, the NCV measures, and height are presented. There are no differences between males and females for the Raven score, peak NCV, end NCV measures, and SML. Males and females dif-

ferred for onset NCV [$\chi^2(1) = 10.87$] and height [$\chi^2(1) = 135.85$].

The NCV means of 63.8 m/s (onset NCV) and 49.7 m/s (peak NCV) for the total population ($n = 312$) agree with values reported in the literature for adults (age, 20–60): 64.5 ± 4.28 and 55.99 ± 3.30 , respectively (Oh, 1984). ONCV showed high correlations with the other two NCV measures: 0.88 ($p < 0.001$) with peak NCV and 0.71 ($p < 0.001$) with end NCV. For onset NCV a test-retest reliability of 0.80 was found in a group of 13 university students, measured 2 weeks apart.

No significant correlations between the NCVs and the Raven IQ were seen in males or females. The correlation between Raven IQ and supramaximal level was also nonsignificant. Removing subjects with a Raven score less than 40 correct items did not improve the correlations between the NCVs and the Raven IQ.

The twin correlations for Raven IQ, NCV measures, and height are given in Table II, showing higher MZ than DZ correlations for all measures. The pattern of the male twin correlations (high MZ and low DZ correlations) for Raven IQ 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 deterioration in fit and the reduced AE no-sex-differences model gave the most parsimonious explanation of the data ($\chi^2 = 23.93$, $df = 13$, $p = .032$). Heritability for Raven IQ was 65% ($V_A = 20.02$, $V_E = 10.95$).

The height-NCV relationship was examined by a Cholesky triangular decomposition, with height entered as the first variable and the NCV phenotypes as the second variable. Figure 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 NCV and A_s and E_s are the genetic and environmental influences specific to NCV. The effects of A_c and E_c on height are represented in the parameters h_c and e_c and the effects of A_c and E_c on NCV in h'_c and e'_c . In Table III 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

Table I. Lisrel Estimates of Means and Standard Deviations for Raven IQ, Nerve Conduction Velocity Measures, and Height^a

	Males		Females		Sex differences χ^2 (df = 1)
	M	SD	M	SD	
Raven IQ	49.3	6.4	49.3	5.6	.37
NCV (m/s) Onset	62.3	7.7	65.2	8.3	10.87*
Peak	49.9	6.0	49.9	5.2	.55
End	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*

^a Raven IQ, number of correct items; SML, supramaximal level. For NCV, SML, and height, 129 males and 183 females. For Raven IQ, 196 males and 224 females.

* $\chi^2(1) > 3.841$ implies a significant difference between males and females.

Table II. Twin Correlations for Raven IQ, Nerve Conduction Velocities, and Height^a

	Raven IQ	Onset NCV	Peak NCV	End NCV	Height
MZM	0.76*	0.72*	0.75*	0.73*	0.98*
DZM	0.22	0.15	0.14	0.14	0.37*
MZF	0.52*	0.74*	0.68*	0.70*	0.88*
DZF	0.31*	0.46*	0.40*	0.43*	0.17
DOS	0.50*	0.17	0.12	-0.05	0.58*

^a For Raven IQ, 38 MZM, 36 DZM, 51 MZF, 37 DZF, and 48 DOS twin pairs. For NCV measures and height, 25 MZM, 20 DZM, 42 MZF, 30 DZF, and 39 DOS twin pairs.

* $p < .05$.

Fig. 2. Cholesky triangular decomposition for height with NCV. A_c and E_c reflect the genetic and environmental influences common to height and NCV. A_s and E_s reflect the genetic and environmental influences specific for NCV.

model was tested which constrained the total genetic and environmental variance in NCV to be equal for males and females and allowed the variation in height to vary across gender. Thus, for NCV $[(h'_c)^2 + (e'_c)^2]_{\text{males}} = [(h'_c)^2 + (e'_c)^2]_{\text{females}}$ and

Table III. Bivariate Genetic Model Fitting of Height with Nerve Conduction Velocities

Model	df	Onset NCV		Peak NCV		End NCV	
		χ^2	<i>p</i>	χ^2	<i>p</i>	χ^2	<i>p</i>
<i>ADE</i> sex-diffs NCV & height	32	30.94	.52	33.66	.39	40.24	.15
<i>ADE</i> males <i>AE</i> females	35	32.16	.62	34.69	.48	40.24	.25
<i>AE</i> sex-diffs NCV & height	38	34.79	.62	38.82	.43	46.90	.15
<i>AE</i> sex-diffs height	40	36.89 ^a	.61	40.25 ^a	.46	48.86 ^a	.16

^a Best-fitting model; for all three NCV measures the best-fitting model included a constraint for keeping the total genetic and environmental variance for NCV equal for males and females, while for height, variances were allowed to vary across gender.

$[(e'_c)^2 + (e_s)^2]_{\text{males}} = [(e'_c)^2 + (e_s)^2]_{\text{females}}$, implying no sex differences in heritability for NCV. This model showed the best fit for onset, peak NCV, and end NCV. In Table IV the parameter estimates for the best fitting models are presented. The covariation of height with the NCV phenotypes was genetically mediated in females and influenced by *A* and *E* in males. However, the overall covariation of height and NCV was small. The heritabilities for onset NCV, peak NCV, and end NCV before controlling for height were 76, 68, and 64%, respectively, and after controlling for height, 76, 70, and 66% for females and 76, 74, and 70% for males, respectively. Heritabilities for height were 86% for females and 96% for males.

DISCUSSION

This study is the first to determine the heritability of peripheral NCV in humans. As Reed (1988) predicted, a large heritability of 0.77 was found for onset NCV, which would make NCV an interesting quantitative genetic trait that could potentially explain genetic differences on human intelligence.

The test-retest correlation of 0.80 for onset NCV ($n = 13$) implies a reliability index of 0.64 (r^2). The onset NCV heritability of 0.76, therefore, suggests nearly all reliable variation in NCV to be heritable.

For Raven IQ 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; Vernon, 1993).

However, no significant correlation between peripheral NCV and IQ was found in our sample. The mean NCVs are in agreement with the values reported in the literature (Oh, 1984) for the same nerve segment and technique, but our standard deviations for both males and females were higher (7.7 and 8.3 vs 4.3 and 6.0 and 5.2 vs 3.3 for onset and peak NCV, 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 NCV 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 NCV with IQ level. We, however, found no correlation between physical activity level and NCVs.

Our results contrast sharply with those observed in two samples by Vernon and Mori (1992). They found correlations between PNCV and IQ of 0.43 ($n = 85$) and 0.46 ($n = 88$). In our study, arm temperature was experimentally controlled and supramaximal stimulation was used to measure NCV just as in the studies by Vernon and Mori. A possible explanation for the lack of correlation between NCV and IQ, therefore, is the use of the Raven IQ test. This lack of correlation is consistent with results of Jensen and Reed (1991), who found

Table IV. Genetic and Environmental Specific and Common Effects of the Bivariate Model of Height with Nerve Conduction Velocities^a

	Genetic & environmental specific effects for NCV				Genetic & environmental common effects for NCV				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
ONCV	7.112	3.991	6.970	3.925	0.705	0.0	1.579	0.721	4.958	2.007	7.832	1.587
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
ENCV	3.766	2.682	3.735	2.415	0.725	0.0	0.872	1.168	4.954	2.016	7.800	1.586

^a Total genetic variance for NCV measures equal for males and females: $[(h_s)^2 + (h'_c)^2]_{\text{males}} = [(h_s)^2 + (h'_c)^2]_{\text{females}}$. Total environmental variance equal for males and females: $[(e_s)^2 + (e'_c)^2]_{\text{males}} = [(e_s)^2 + (e'_c)^2]_{\text{females}}$.

no correlation between median nerve arm NCV 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 and PNCV.

The correlations of 0.43 and 0.46 between NCV 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 [0.91 for full-scale IQ (Jackson, 1984)]. The correlation of the Raven Advanced Progressive Matrices with the WAIS full-scale IQ is 0.72 (Vernon, 1983) and is even lower with verbal IQ and performance IQ (0.57 and 0.69, respectively). The fact that Raven IQ and WAIS IQ have only around 50% of their variance in common may account for the absence of a phenotypic correlation between Raven IQ score and NCV [though see Wickett and 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 NCV study in which the WAIS is administered. The results from this study will resolve the issue of whether the use of the Raven IQ test is an explanation for the failure to confirm the positive correlation between peripheral conduction velocity and IQ level.

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