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# Genetic Contributions to Anatomical, Behavioral, and Neurophysiological Indices of Cognition

*Daniëlle Posthuma, Eco J. C. de Geus, and Dorret I. Boomsma*

The large genetic contribution to individual differences in cognitive abilities is well established (Bouchard & McGue, 1981; Plomin, Owen, & McGuffin, 1994). From childhood to early adulthood, the relative impact of genetic factors on cognitive abilities increases (Boomsma & van Baal, 1998; Cherny & Cardon, 1994) and becomes even higher from middle adulthood (Posthuma, de Geus, & Boomsma, 2001; Posthuma, Neale, Boomsma, & de Geus, 2001) to late adulthood (Plomin, Pedersen, Lichtenstein, & McClearn, 1994). Data from four large twin studies from the Dutch Twin Registry (see Table 9.1; Figure 9.1), which are partly longitudinal and partly cross-sectional, reflect this increasing heritability of cognitive abilities with age (Bartels, Rietveld, van Baal, & Boomsma, in press; Boomsma & van Baal, 1998; Posthuma, de Geus, et al., 2001; Rietveld, Dolan, van Baal, & Boomsma, in press; Rijdsdijk & Boomsma, 1997; Rijdsdijk, Boomsma, & Vernon, 1995). Shared environmental influences play a role only before adolescence and are of relatively low importance between ages 7 and 16. This pattern of the relative impact of genetic and environmental influences on cognitive abilities corresponds to that found in many other countries (Plomin, Chipuer, & Neiderhiser, 1994; Plomin, DeFries, & McClearn, 1990).

In spite of the overwhelming evidence for the existence of "genes for cognition," actual identification of such genes is limited to neurological mutations with rather severe cognitive effects (e.g., Pick's disease, X-linked mental retardation, and Huntington's disease), as reviewed by Flint (1999). Like the many rare diseases and disorders listed in online *Mendelian Inheritance in Man* (OMIM; McKusick, 1998), these genetic defects of cognition are largely Mendelian in nature. True polygenes (or quantitative trait locis; QTLs) that influence the normal range of cognitive ability have yet to be identified. One route to finding these genes is a better appreciation of individual differences in the anatomy and function of the main organ of information processing, the brain.

**Table 9.1.** Twin Correlations for Full Scale IQ in Dutch Twins (and Their Siblings) for Ages 5 to 50 Years

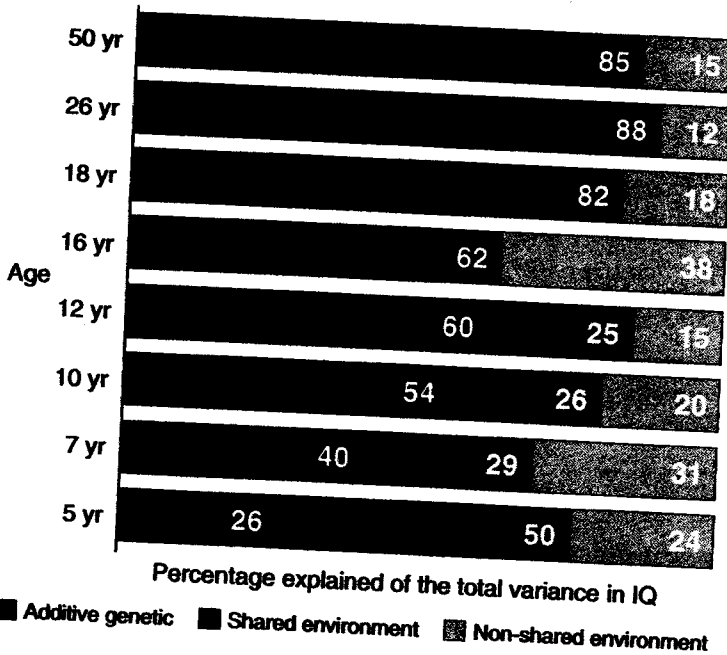
Age	MZF	DZF	MZM	DZM	DOS	MZ	DZ	Test
5 years	.77	.72	.75	.56	.61	.77	.62	RAKIT
<i>N</i>	46	37	42	43	39	88	119	
7 years	.74	.59	.61	.40	.53	.68	.50	RAKIT
<i>N</i>	41	34	37	41	38	78	113	
10 years	.83	.47	.75	.66	.47	.82	.50	RAKIT
<i>N</i>	43	37	38	41	37	81	115	
12 years	.85	.66	.85	.58	.31	.85	.54	WISC
<i>N</i>	43	37	36	39	35	79	111	
16 years	.50	.35	.77	.24	.42	.66	.39	RAVEN
<i>N</i>	46	36	37	31	44	83	111	
18 years	.84	.44	.86	.19	.24	.85	.30	WAIS
<i>N</i>	46	36	37	31	44	83	111	
26 years	.87	.36	.88	.64	.45	.88	.45	WAIS-3R
<i>N</i>	29	97	25	76	110	54	283	
50 years	.85	.52	.85	.27	.42	.85	.42	WAIS-3R
<i>N</i>	26	85	22	62	95	48	242	

*Note.* For the adult twins, the ages 26 ( $SD = 4.19$ ) and 50 ( $SD = 7.51$ ) are average ages (as opposed to the other age groups in which all subjects are of the same age). Additional siblings are modeled as similar to DZ twins (i.e., sharing on average 50% of genes and 100% shared environment) at ages 26 and 50 years. MZF = monozygotic female; DZF = dizygotic female; MZM = monozygotic male; DZM = dizygotic male; DOS = dizygotic opposite sex; RAKIT = Revisie Amsterdamsse Kinder Intelligentie Test; WISC = Wechsler Intelligence Scale for Children; RAVEN = Raven's Advanced Progressive Matrices; WAIS = Wechsler Adult Intelligence Scale; WAIS-3R = WAIS 3rd edition, Revised.

### Anatomical Measures of Cognitive Ability

An obvious source of individual differences in cognitive abilities is the size of the brain. Since the second half of the 19th century, positive relations between head size and intelligence have been observed. Correlations generally range around 0.20 (Jensen, 1994; Posthuma, Neale, et al., 2001) but can be as high as 0.44 (van Valen, 1974). Head size is usually measured with a measuring tape as circumference of the head. A more accurate measure of the size of the brain can be obtained through magnetic resonance imaging (MRI).

Willerman, Schultz, Rutledge, and Bigler (1991) correlated brain size as measured through MRI with IQ (measured with the revised Wechsler Adult Intelligence Scale, WAIS-R; Wechsler, 1981) in a sample of 40 unrelated participants. They found a correlation of 0.51, which was higher in men (0.65) than in women (0.35). In a follow-up study, Willerman,



**Figure 9.1.** Decomposition of the variance in Full Scale IQ into additive genetic variance, shared environmental variance, and nonshared environmental variance, at different ages. Studies are specified in Table 9.1. Significance of additive genetic influences is .03 at age 5; of shared environmental influences it is .06 at age 7, .09 at age 10, and .08 at age 12.

Schultz, Rutledge and Bigler (1992) suggested that, in men, a relatively larger left hemisphere better predicted verbal IQ than it predicted performance IQ, whereas in women the opposite was true. Since then, several studies have provided confirmative evidence that brain volume and IQ correlate around 0.40 (e.g., Andreasen et al., 1993; Egan et al., 1994; Raz et al., 1993; Storfer, 1999; Wickett, Vernon, & Lee, 2000).

In a large MRI study including 111 twin pairs and 34 additional siblings, the heritability of volumes of several brain structures was investigated (Baaré et al., 2001; Posthuma et al., 2000). Heritability estimates for intracranial volume, total brain volume, gray-matter volume, white-matter volume, and cerebellar volume were all between 80% and 90%. Genetic intercorrelations between these measures were all very high, indicating that a largely overlapping set of genes is responsible for individual differences in each of these measures.

To our knowledge, only two multivariate genetic studies have been conducted to investigate whether the relation between IQ and brain volumes is mediated through a common genetic pathway or through a common environmental pathway (see Table 9.2). The first study, often cited although only published as an abstract so far (Wickett, Vernon, & Lee, 1997), was based on MRI and IQ data from 68 adult men from 34 sibships and compared within-family correlations with between-family correlations

**Table 9.2.** Overview of Multivariate Genetic Studies Relating Neurophysiological

Study	Subjects	(Neuro-) physiological measure	Cognitive measure	Design
<b>Brain size/volume</b> Pennington et al. (2000)	Concordant or discordant for reading disorder/control 25/9 MZ 23/9 DZ	Brain volumes measured with magnetic resonance imaging	WISC WAIS-3R	Correlational study
Wickett, Vernon, and Lee (1997)	68 adult males (34 sibships)	Total brain volume measured with magnetic resonance imaging	MAB Trail Making Test Factor Referenced Tests	Correlation within families compared with correlation between families
<b>Reaction times/speeded responses</b> Luciano, Wright, et al. (2001)	166 MZ 190 DZ	Choice reaction time task	MAB	Multivariate genetic model fitting, including unreliability correction
Neubauer et al. (2000)	169 MZ 131 DZ	Sternberg's memory scanning; Posner's letter matching	RAVEN Leistungs Pruf System	Multivariate genetic model fitting
Finkel and Pedersen (2000)	45 MZA 67 MZT 94 DZA 86 DZT	Oral version of Digit Symbol and Figure Identification subtest (perceptual speed)	Cognitive factor constructed from 11 cognitive measures (including WAIS, Thurstone's Picture Memory, Card Rotations)	Multivariate genetic model fitting
Rijsdijk, Vernon, and Boomsma (1998)	82 MZ 109 DZ age 16	Donder's simple/two choice reaction time; Sternberg's Memory Scanning; Posner's Letter Matching	RAVEN	Multivariate genetic model fitting
Rijsdijk et al. (1998)	74 MZ 100 DZ age 18	Donder's simple/two choice reaction time; Sternberg's Memory Scanning; Posner's Letter Matching	WAIS	Multivariate genetic model fitting

## Indices of Brain Structure/Function to Measures of Cognitive Abilities

Heritability of (neuro-) physiological measure	Heritability of cognitive measure	Phenotypic correlation	Contribution of common genetic factors
MZ correlations (.78-.98) > DZ correlations (.32-.65) in both samples	Not reported	Reading disorder/ healthy sample 0.42/0.31	Genetic correlation 0.48 (both samples combined)
Not reported	Not reported	Correlation IQ-brain volume within families 0.24; between families 0.50	Suggestive of genetic mediation
79%-90%	89%	-0.31 to -0.56	Genotypic correlations -0.45 to -0.70
11%-61%	39%-81%	-0.08 to -0.50 (More difficult tasks → higher correlation)	65% of phenotypic correlation due to common genes
56%	Cognitive factor 61% (not age corrected) 85% (age corrected)	0.66	70% of genetic variance in cognitive factor was due to genes shared with perceptual; speed; 61% of phenotypic correlation due to genetic mediation
40%-58%	58%	Around -0.20	Genetic correlations around -0.40
22%-57%	33%-74%	-0.14 to -0.28	Genetic correlations -0.46 and -0.42

*Table 9.2 continues on next page*

Table 9.2. *Continued*

Study	Subjects	(Neuro-) physiological measure	Cognitive measure	Design
Baker, Vernon, and Ho (1991)	50 MZ 32 SS DZ ages 15-57	Battery of eight different reaction time tasks	MAB	Multivariate genetic model fitting
Ho, Baker, and Decker (1988)	30 MZ 30 SS DZ ages 8-18	Rapid Automatic Naming tests; Colorado Perceptual Speed test	WISC-R WAIS-R	Multivariate genetic model fitting, using IQ score and composite scores of reaction time tests
Inspection time Luciano, Smith, et al. (2001)	184 MZ 206 DZ age 16 years	Inspection time (pi-paradigm)	MAB	Multivariate genetic model fitting
Posthuma, de Geus, and Boomsma (2001)	Cross-sectional, mean age 26/50: 47/44 MZ 253/192 DZ and sib pairs	Inspection time (pi-paradigm)	WAIS-3R	Multivariate genetic model fitting
Peripheral nerve conduction velocity Rijsdijk and Boomsma (1997)	83 MZ 111 DZ age 18	Peripheral nerve conduction velocity	WAIS	Multivariate genetic model fitting
Rijsdijk, Boomsma, and Vernon (1995)	89 MZ 122 DZ age 16	Peripheral nerve conduction velocity	RAVEN	Multivariate genetic model fitting
EEG alpha peak frequency Posthuma, Neale, Boomsma, and de Geus (2001)	Cross-sectional, mean age 26/50: 47/44 MZ 253/192 DZ and sib pairs	Individual alpha peak during resting condition	WAIS-3R dimensions (verbal comprehension, working memory, processing speed, perceptual organization)	Multivariate genetic model fitting
EEG coherence van Baal, Boomsma, and de Geus (2001)	Longitudinal measurement (age 5/age 7) 71/77 MZ 96/105 DZ	Theta coherence (frontal, long, posterior)	RAKIT-VIQ/PIQ	Multivariate genetic model fitting

*Note.* MZ = monozygotic twins; DZ = dizygotic twins; MZA = MZ raised apart; MZT = MZ raised together; DZA = DZ raised apart; DZT = DZ raised together; SS = same sex; WISC = Wechsler Intelligence Scale for Children; WAIS = Wechsler Adult Intelligence Scale;

Heritability of (neuro-) physiological measure	Heritability of cognitive measure	Phenotypic correlation	Contribution of common genetic factors
45%	68%–85%	–0.59	Genetic correlations –0.92––1.00
49%–52%	78%	0.37–0.42	70%–100% of the phenotypic correlation is due to common genetic factors
36%	VIQ 81% PIQ 73%	–0.26 with VIQ –0.35 with PIQ	Genetic correlations –0.47 with VIQ –0.65 with PIQ
46%	VIQ 85% PIQ 69%	–0.19 with VIQ –0.27 with PIQ	Genetic correlations –0.31 with VIQ –0.47 with PIQ
66%	81%	0.15	Genetic correlation 0.20
77%	65%	No correlation	
71% age 26 83% age 50	66% to 83%	No correlation	
Age 5/7 frontal 55%/ 42% long 70%/81% posterior 57%/71%	Age 5/7 VIQ 56%/14% PIQ 63%/64%	Frontal and VIQ: –0.13/–0.13 (age 5/7) Frontal and PIQ: –0.10 (age 7) Long and PIQ: 0.07 (age 7)	Genetic correlations (accounted for 100% of the phenotypic correlation); Frontal and VIQ age 5 –0.16 age 7 –0.26

WAIS–3R = WAIS 3rd Edition, Revised; MAB = Multidimensional Aptitude Battery; RAVEN = Raven's Advanced Progressive Matrices; RAKIT = Revisie Amsterdamse Kinder Intelligentie Test; VIQ = verbal IQ; PIQ = performance IQ.



of brain volume and IQ. A within-family correlation of 0.24 and a between-family correlation of 0.50 were reported, suggesting that some, but not all, of the phenotypic correlation between brain volume and IQ is due to a common underlying set of genes.

The second study (Pennington et al., 2000) specifically addressed the relation of reading disorder with brain volume but also included measures of IQ (Wechsler Intelligence Scale for Children [WISC; Wechsler, 1974] and the 3rd edition of the WAIS-R [WAIS-3R] scores [Wechsler, 1981]). In this study, both a reading disorder sample (25 monozygotic [MZ], 23 dizygotic [DZ]) and a non-reading disorder sample (9 MZ, 9 DZ) were included. The MZ and DZ correlations in the reading disorder sample and the non-reading disorder sample were comparable and suggested high heritability of brain volume (90%), which is in line with the larger study of Baaré et al. (2001). Phenotypic correlations between cerebral brain volume and IQ were 0.31 in the non-reading disorder sample and 0.42 in the reading disorder sample. The genetic correlation, as calculated from the cross-twin correlations, was 0.48 in the combined sample. This indicates that about half of the genetic influences on either cerebral brain volume or IQ is due to genetic factors influencing both. Put differently, 80% of the phenotypic correlation is explained by genetic mediation.

### Functional Measures of Cognitive Ability

Structural brain volumes seem to provide a first important point of entry to the genetic sources of individual differences in cognitive abilities. Most differences in cognitive ability, however, will arise from functional aspects of the brain. Several behavioral and neurophysiological indices of brain function have repeatedly been shown to be influenced by the cognitive demands of the tasks in which they are elicited. For example, increasing the information-processing load of a task results in prolonged reaction times within the same subject (Hick, 1952). The same holds for evoked brain potentials elicited in a working-memory task; increasing working-memory load results in a longer latency of the evoked brain potentials (McEvoy, Smith, & Gevins, 1998). These and many other clear links between cognition and behavioral or neurophysiological measures in cognitive neuroscience largely are based on within-subject observations. What is causing *within*-person variability does not necessarily also cause variability *between* people. To detect genetic sources of individual variation in cognitive abilities, behavioral and neurophysiological indices of information processing are needed that are associated with differences in cognitive abilities between people. Below we give an overview of our current armament of such "endophenotypes" of cognitive ability, where we restrict ourselves to discussing only those measures for which the bivariate genetic architecture with measures of psychometric intelligence has already been investigated.

## Behavioral Measures of Speed of Information Processing

Galton (1883) was the first to propose that reaction time is correlated with general intelligence and may be used as a measure of it. His observations and the results of empirical studies afterward led to the general belief in the speed-of-processing theory of intelligence: The faster the accomplishment of basic cognitive operations, the more intelligent a person will be (Eysenck, 1986; Vernon, 1987). Since then, reaction times consistently have been negatively related to intelligence (e.g., Deary, Der, & Ford, 2001; Vernon, 1987); that is, a shorter reaction time corresponds to a higher IQ. Correlations with IQ generally range between  $-0.20$  and  $-0.40$  but can be as high as  $-0.60$  (Fry & Hale, 1996). Higher correlations between reaction times and IQ usually are found when more complex reaction time tasks are used, although this effect is not unequivocally confirmed in empirical studies (Mackintosh, 1986).

Results from twin studies suggest heritabilities for reaction time of the same magnitude as those for IQ. McGue and Bouchard (1989) observed heritabilities of 54% and 58% for basic and spatial speed factors in a sample of MZ ( $N = 49$ ) and DZ ( $N = 25$ ) twins reared apart. For a general speed factor based on eight complex reaction time tests, Vernon (1989) found a heritability of 49% in 50 MZ and 52 DZ twins. In the same study, it was also found that reaction time tests requiring more complex mental operations show higher heritabilities. A bivariate analysis of these data with IQ in 50 MZ and 32 same-sex DZ pairs (15 to 57 years) was reported by Baker, Vernon, and Ho (1991). Phenotypic correlations of verbal and performance IQ with general speed were both  $-0.59$  and were entirely mediated by genetic factors. Genetic correlations were estimated at  $-0.92$  and  $-1.00$ . This is in line with results from an earlier study in which phenotypic correlations between reaction time (measured as the total number of correct responses on a timed task; see Table 9.2) and IQ ranged between 0.37 and 0.42, from which 70%–100% was attributed to genetic factors influencing both reaction time and IQ (Ho, Baker, & Decker, 1988).

More recently, Rijdsdijk, Vernon, and Boomsma (1998) conducted a multivariate genetic analysis on reaction time data and IQ data, using 213 twin pairs measured at ages 16 and 18. Heritabilities were reported for age 16 of 58%, 57%, and 58% for simple reaction time, choice reaction time, and IQ (the Raven Advanced Progressive Matrices Test; Raven, 1958), respectively. Phenotypic correlations of simple reaction time and choice reaction time with IQ were  $-0.21$  and  $-0.22$ , respectively, and were completely mediated by common genetic factors. Virtually the same picture was shown at age 18, where the same reaction time battery was correlated with IQ as measured with the WAIS (see Table 9.2).

Finkel and Pedersen (2000) investigated the underlying covariance structure of measures of speed and measures of cognition in a sample of 292 reared-together and reared-apart MZ and DZ twins (ages 40–84 years). Speed was measured by oral versions of the Digit Symbol and Picture Identification subtests of the WAIS. A cognitive factor was constructed based on several standard IQ tests. The phenotypic correlation between

the speed factor and the cognitive factor was 0.66, of which 61% was due to correlated genetic factors between the two. Also, Finkel and Pedersen reported that 70% of the genetic variance in the cognitive factor was shared with the speed factor.

Neubauer et al. (2000) reported heritability estimates of reaction time data and IQ (Raven) ranging from 11% to 61% and 39% to 81%, respectively. Phenotypic correlations between reaction time data and IQ (Raven, 1958) data were between  $-0.08$  and  $-0.50$ , in which higher correlations with IQ were found for more complex reaction time tasks. Common genetic influences on reaction time and IQ accounted for 65% of the observed phenotypic correlation.

Evidence for a genetic mediation between reaction time and IQ also emerged from a recent large twin study by Luciano, Wright, et al. (2001). Using reaction time data and IQ data from 166 MZ pairs and 190 DZ pairs, Luciano, Wright, et al. (2001) reported high heritabilities for both reaction time (79%–90%) and IQ (89%), with phenotypic correlations between  $-0.31$  and  $-0.56$  and genotypic correlations between  $-0.45$  and  $-0.70$ . In other words, common genetic influences explained at least 70% of the observed phenotypic correlation between reaction times and IQ.

In summary, nongenetic studies have shown a consistent and stable relation between reaction time and IQ; interindividual variance in reaction time explains about 10%–30% of IQ test variance. This has been confirmed by results from genetic studies, which additionally showed that between 65% and 100% of this covariance is explained by a common underlying genetic mechanism.

Inspection time is a measure of central nervous system (CNS) processing and is defined as the minimum display time a subject needs for making an accurate perceptual discrimination on an obvious stimulus. It is distinct from reaction time because there is no need to make the discrimination quickly; all that is required is an accurate response. Visual inspection time can easily be measured in a computerized version of the  $\Pi$ -paradigm in which participants are asked to decide which leg of the  $\Pi$ -figure is longest. Visual inspection time is generally thought to reflect speed of apprehension or perceptual speed. A meta-analysis conducted by Kranzler and Jensen (1989) on almost all studies until 1989 investigating the relation between inspection time and intelligence indicated that inspection time and IQ correlate around  $-0.50$ : The less time a person needs to make an accurate decision on an obvious stimulus, the higher his or her IQ. The overall consensus on the relation between inspection time and IQ is given by Deary and Stough (1996): Inspection time accounts for approximately 20% of intelligence test variance.

Recently, two large twin studies have investigated whether the relation between inspection time and IQ is mediated by shared genetic factors or by shared environmental factors (Luciano, Smith, et al., 2001; Posthuma, de Geus, et al., 2001). These two studies were also the first to report on the heritability of inspection time *per se*. Using 184 MZ pairs and 206 DZ pairs age 16, Luciano, Smith, et al. (2001) reported a heritability estimate of inspection time of 36% and of IQ measures between 73% and

81%. Posthuma, de Geus, et al. (2001) reported a slightly higher heritability estimate of inspection time (46%) and similar heritability estimates of IQ measures (WAIS-3R) ranging from 69% to 85%. The latter sample consisted of 102 MZ pairs and 525 DZ/sibpairs belonging to two age cohorts (mean ages = 26 and 50 years;  $SD = 4.2$  and  $7.5$ , respectively).

Luciano, Smith, et al. (2001) reported a correlation between inspection time and performance IQ of  $-0.35$  and between inspection time and verbal IQ of  $-0.26$ . Posthuma, de Geus, et al. (2001) reported slightly lower correlations:  $-0.27$  and  $-0.19$ , respectively. Both studies unanimously found that the phenotypic correlations between inspection time and performance IQ/verbal IQ were completely mediated by common genetic factors. This meant that in the study by Luciano et al. the genetic correlation between inspection time and performance IQ was  $-0.65$  and between inspection time and verbal IQ was  $-0.47$ . In the study by Posthuma et al., the genetic correlations were  $-0.47$  and  $-0.31$ , respectively. Thus, the genes shared with inspection time are, across studies, estimated to explain between 10% and 42% of the total genetic variance in IQ.

Peripheral nerve conduction velocity (PNCV) is a measure of the speed with which action potentials travel the length of the axons in the peripheral nervous system; a high PNCV corresponds to faster conduction. The relation of PNCV with IQ does not go undebated; in some studies no relation was found (Barret, Daum, & Eysenck, 1990; Reed & Jensen, 1992; Rijdsdijk et al., 1995) or a positive relation was found only in men (Tan, 1996; Wickett & Vernon, 1994). The general agreement, however, is that PNCV relates positively to measures of intelligence (Vernon & Mori, 1992), thereby providing evidence for the speed-of-information processing theory of intelligence (Eysenck, 1986; Vernon, 1987).

The first and only study reporting on genetic influences on PNCV was a large longitudinal study conducted by Rijdsdijk and colleagues (Rijdsdijk & Boomsma, 1997; Rijdsdijk et al., 1995). Rijdsdijk and colleagues determined PNCV for the wrist-elbow segment of the median nerve of the right arm for 213 sixteen-year-old twin pairs. By using structural equation, they estimated modeling heritability at 76% for PNCV at age 16 and 66% at age 18. At age 16, no correlation between PNCV and IQ scores as measured with the Raven test was found. However, at age 18, IQ (as measured with the WAIS) correlated .15 with PNCV, and this correlation was entirely mediated by common genetic factors (Rijdsdijk & Boomsma, 1997).

### **Electrophysiological Measures of Speed of Information Processing**

Electrophysiological indices of speed of information processing are considered to be a more direct measure of the speed of brain functioning than behavioral measures. Several noninvasive techniques, such as functional MRI, positron emission tomography, and electroencephalography (EEG), have repeatedly shown that quantitative differences in brain functioning are related to differences in cognitive functioning (Fabiani, Gratton, &

Coles, 2000; Reiman, Lane, Petten, & van Bandettini, 2000). Despite the vast amount of brain imaging studies investigating the brain during the execution of distinct cognitive operations (Gazzaniga, 2000), very little have done so using a genetic design. The only indices of which the relation with cognitive functioning have been investigated in a genetic design are two measures derived from the EEG: coherence and alpha peak frequency.

EEG recording is a noninvasive technique to measure electrical activity of the brain. EEG activity can be analyzed according to the frequency spectrum that is obtained when a Fourier transformation is performed on an EEG time series. Generally, five frequencies are distinguished in the EEG power spectrum: delta (0.5–4 cycles per second), theta (4–8 cycles per second), alpha (8–13 cycles per second), beta (13–30 cycles per second), and gamma (>30 cycles per second). Since the 1990s, the underlying biological mechanisms of the different frequencies, especially the alpha and beta rhythms, are well understood and have been described in the literature (Lopes da Silva, 1991; Steriade, Gloor, Llinás, Lopes da Silva, & Mesulam, 1990).

The dominant frequency in an adult human EEG spectrum lies in the alpha range, around 10 cycles per second. The alpha peak frequency has been related to cognitive abilities in general and to (working) memory in particular. Lebedev (1990, 1994) proposed a functional role for the human alpha peak frequency in stating that “cyclical oscillations in an alpha rhythm determine the capacity and speed of working memory. The higher the frequency the greater the capacity and the speed of memory” (p. 254; 1994). In addition, Klimesch (1997) argued that thalamo-cortical feedback loops oscillating within the alpha frequency range allow searching and identification of encoded information. He speculated that faster oscillating feedback loops would correspond to faster access to encoded information. These theories are supported by the results of some recent studies. Klimesch found that the alpha peak frequency of good working-memory performers lies about 1 Hz higher than that of bad working-memory performers. Anokhin and Vogel (1996) reported a correlation of 0.35 between alpha peak frequency and verbal abilities. In addition, Klimesch (1999) found that, within the same subject, alpha peak frequencies increase with increasing cognitive load of the task in which they are measured.

Results from a few small twin studies have suggested that alpha peak frequency is influenced by genetic factors (Christian et al., 1996), and it has also been speculated that its relation with IQ is due to a genetic basis (e.g., Vogel, 2000, p. 117). In only one multivariate genetic study, however, the nature of the relation between alpha peak frequency and cognitive abilities is formally investigated. Including 102 MZ pairs and 525 DZ/sib pairs from two age cohorts ( $M = 26$  and 50 years;  $SD = 4.2$  and 7.5, respectively), Posthuma, Neale, et al. (2001) found that alpha peak frequency is highly heritable. In young adults ( $M = 26$  years;  $SD = 4.2$  years), heritability was estimated at 71%; in older adults ( $M = 50$  years;  $SD = 7.5$  years), heritability was somewhat higher at 83%. Heritabilities for the WAIS-3R dimensions ranged from 66% to 83%. Surprisingly, no correlation was found between alpha peak frequency and IQ (WAIS-3R), thereby

dismissing alpha peak frequency as a valuable endophenotype for specific cognitive abilities as measured with the WAIS-3R. However, alpha peak frequency may still be of importance for cognitive functioning, especially for memory functioning. Although working memory is an important aspect of IQ (Engle, Tuholski, Laughlin, & Conway, 1999; Kyllonen & Christal, 1990; Necka, 1992), it also is suggested that it comprises more than psychometric IQ as measured with the WAIS dimensions. A genetic relation between alpha peak frequency and specific aspects of (working) memory has not been investigated yet.

A second measure that can be extracted from the Fourier-transformed EEG is the degree of connectivity between certain brain areas. It is sometimes speculated that efficient interconnectivity of the brain relates positively to IQ. Studies relating coherence (a measure of connectivity of the brain) to IQ have indeed reported a relation between efficient connectivity (i.e., low coherence) and measures of intelligence (e.g., Anokhin, Lutzenberger, & Birbaumer, 1999; Jausovec & Jausovec, 2000; van Baal, Boomsma, & de Geus, 2001).

The amount of EEG coherence in the different frequency bands has previously been found to be under the influence of genetic factors (van Beijsterveldt & Boomsma, 1994). Van Beijsterveldt, Molenaar, de Geus, and Boomsma (1998) reported a mean heritability of 60% for coherence in 213 twin pairs age 16 years. A longitudinal study by van Baal et al. (2001) and van Baal, de Geus, and Boomsma (1998) included 70 MZ twin pairs and 97 DZ twin pairs who were measured at ages 5 and 7 years. In children, the dominant frequency is in the theta range. For frontal, long, and posterior theta interhemispheric coherence, heritabilities of 55%, 70%, and 57%, respectively, were reported at age 5. At age 7, these were 42%, 81%, and 71%, respectively. At age 5, frontal theta coherence and verbal IQ correlated  $-0.13$ , which was completely explained by common underlying genetic factors influencing both traits (van Baal et al., 2001). At age 7, significant correlations were found between frontal theta coherence and verbal IQ ( $-0.13$ ), frontal theta coherence and performance IQ ( $-0.10$ ), and long distance theta coherence and performance IQ ( $0.07$ ). Again, these correlations were entirely ascribed to correlated genetic influences (van Baal et al., 2001).

### **Candidate Genes Derive From Anatomical and Functional Measures of Cognitive Ability**

Summarizing the above discussion, we highlight the following:

- Brain size and IQ correlate around 0.40. About 80% of this correlation is due to common underlying genetic factors.
- Reaction times and IQ correlate in the range  $-0.20$  to  $-0.40$ , depending on task complexity. Of this correlation, 70% to 100% is due to common underlying genetic factors.

- Inspection time and IQ correlate in the range  $-0.20$  to  $-0.40$ . Of this correlation, 100% is due to common underlying genetic factors.
- Frontal theta coherence in children is correlated  $-0.13$  with IQ. Of this correlation, 100% is due to common underlying genetic factors.
- Alpha peak frequency does not correlate with IQ as measured with the WAIS-3R.

This suggests that genes important for brain size, reaction times, inspection time, and theta coherence may also be important for intelligence, which fits very well in the *myelination hypothesis* as formulated by Miller (1994). According to this hypothesis, generally, the relation between speed and intelligence can be explained if part of the interindividual variance in intelligence can be ascribed to interindividual variance in the degree of myelination of cortico-cortical connections. If true, this could explain why more intelligent brains show faster nerve conduction, faster reaction times, and faster inspection times. And, all other things equal, thicker myelin sheaths will result in larger brain volume, thus explaining the positive relation between brain size and IQ (Miller, 1994). Although it is unlikely that the myelination hypothesis explains all observed anatomical, behavioral, and physiological relations with cognitive functioning, it provides theoretical guidance in the choice of candidate genes for cognition: Genes important for myelination also may be important for cognition. Several such genes have been implicated from animal models, some of which are known to cause dysmyelination in humans as well. The *Plp* gene (Xq22.3), for example, codes for two membrane proteins important for myelination. Disruption of expression of the *Plp* gene in mice causes a disruption in the assembly of the myelin sheath, which leads to a profound reduction in conduction velocity of CNS axons (Boison & Stoffel, 1994; Griffiths, Montague, & Dickinson, 1995; Ikenaka & Kagawa, 1995; Lemke, 1993). Mutations in the same gene in humans are known to result in Pelizaeus-Merzbacher disease (PMD; e.g., Anderson et al., 1999; Griffiths et al., 1995; Woodward & Malcolm, 1999). PMD is a hypomyelination disease which, in its mildest form, may lead to optic atrophy and dementia. Other genes implicated to be important for myelination in knock-out mouse studies are the *cgt* gene (Stoffel & Bosio, 1997), the *MAG* gene (for reviews, see Bartsch, 1996; Fujita et al., 1998; Sheikh et al., 1999), and the *tn-r* gene (Weber et al., 1999).

Thus, genetic correlations between IQ scores and behavioral and neurophysiological indices of brain structure and function may provide a theoretical framework from which candidate genes from cognitive functioning may be proposed. A second advantage of finding good "endophenotypes" for cognitive functioning is that they are more "upstream," as Kosslyn and Plomin (2001) put it, and thus are likely to be influenced by a smaller number of genes. When such behavioral and electrophysiological endophenotypes are included in genome screens aimed at detecting QTLs important for cognition, they can boost the statistical power to detect these QTLs (Boomsma, Anokhin, & de Geus, 1997; de Geus & Boomsma, 2002; Leboyer et al., 1998).

A few examples of the usefulness of this approach are already available from the field of alcohol research. The P3 event-related potential (ERP) is generally believed to provide a sensitive electrophysiological index of the attentional and working-memory demands of a task (Donchin & Coles, 1988; Picton, 1992). Because disturbed information processing is a feature in alcoholism, a genetic association between the DRD2 gene, of which the A1 allele is more frequent in alcoholics as compared with non-alcoholics (Kono et al., 1997; Noble et al., 1998), and P3 latency was tested in a study that included 32 sons of active alcoholic fathers, 36 sons of recovering alcoholic fathers, and 30 sons of social drinker fathers (mean age of children = 12.5 years,  $SD = 0.1$  years; Noble, Berman, Ozkaragoz, & Ritchie, 1994). The frequency of the A1 allele of the DRD2 gene was highest in the group of sons of active alcoholic fathers, followed by the sons of recovering alcoholic fathers and sons of social drinker fathers, respectively. It is interesting to note that the A1 allele was also associated with prolonged P3 latency (42 ms). This result confirms the expected involvement of the dopaminergic system in cognitive functioning.

Williams et al. (1999) reported linkage on the chromosome 4 region near the class I alcohol dehydrogenase locus ADH3 for alcoholism and P3 amplitude. Several other loci influencing P3 amplitude have also been reported (Almasy et al., 2001; Begleiter et al., 1998). Another linkage result for EEG measures has been reported for a rare condition known as *low voltage EEG*, the near absence of an alpha rhythm (Anokhin et al., 1992; Steinlein, Anokhin, Yping, Schalt, & Vogel, 1992).

### Endophenotypes Galore

It should be kept in mind that this chapter only discusses behavioral and neurophysiological indices of which the *genetic* relation with cognitive abilities had already been investigated. There are many other behavioral or neurophysiological measures that correlate with IQ, and because some of these measures have been shown to be (highly) heritable, they may correlate with IQ through a common genetic pathway. Examples of such measures include glucose metabolism in the brain (Haier et al., 1988; Haier, Siegel, Tang, Abel, & Buchsbaum, 1992), ERPs (Gevins & Smith, 2000; Hansell et al., 2001; Wright et al., 2001), and brain wave complexity (Blinkhorn & Hendrickson, 1982). Especially the field of ERPs has provided a vast number of studies relating latency and amplitude of evoked brain potentials to cognitive ability (for reviews, see Deary & Caryl, 1997; Fabiani et al., 2000). Heritability estimates are generally moderate to high (van Beijsterveldt & Boomsma, 1994) and vary for specific ERP components. For example, the slow wave is a late, long-duration ERP component that has been shown to reflect working-memory processes (Ruchkin, Canoune, Johnson, & Ritter, 1995). Hansell et al. (2001) investigated the heritability of the slow wave elicited in a working-memory task for 391 adolescent twin pairs. Thirty percent of the total variance and around 50% of the reliable variance in the slow wave was due to genetic influences. In a



sample of 335 adolescent twin pairs and 48 siblings, Wright et al. (2001) estimated the heritabilities of the P3 amplitude and latency in the ranges 48%–61% and 44%–50%, respectively.

These neurophysiological indices of information processing that have already been shown to be related to cognitive functioning and also show moderate to high heritability present promising endophenotypes for cognition. Before measuring them in large samples and including them in actual DNA-based gene hunting, however, the bi- (or multi-) variate genetic architecture of these indices with measures of higher order cognitive abilities needs to be established.

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