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Genetic analysis of IQ, processing speed and stimulus-response incongruency effects

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Abstract

Psychometric IQ (WAIS-III), onset and peak latency of the lateralized readiness potential (LRP), decision time, and accuracy were assessed during an Eriksen Flanker task in a young (149 families) and in an older (122 families) cohort of twins and their siblings. Stimulus-response incongruency effects were found on all measures of processing speed and accuracy. The effects on the percentages of wrong button presses and too slow (>1000 ms) responses were larger in the older than in the younger age cohort. Significant heritability was found for processing speed (33–48%), accuracy (41%), and stimulus-response incongruency effects (3–32%). Verbal and performance IQ correlated significantly with stimulus-response incongruency effects on accuracy (-0.22 to -0.39), and this correlation was completely mediated by an underlying set of common genes. It is concluded that measures of the ability to perform well under conditions of stimulus-response incongruency are viable endophenotypes of cognitive ability.

Keywords: Intelligence; Endophenotype; Lateralized readiness potential (LRP); Heritability; Genetic correlation

1. Introduction

The presence of genetic influences on cognitive ability is well established (e.g. Bouchard and McGue, 1981; Plomin et al., 2001). Little is known, however, about the pathways that lie between genes and cognitive ability. Two strategies may be

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employed to identify these pathways. The first, bottom-up strategy starts with the sequence of known genes, identifies the gene product, establishes the function of the gene product at the cellular level, its possible role in neuronal networks and ultimately its effects on cognition. A second, top-down strategy focuses on individual variability in cognitive ability. It consecutively traces individual differences in cognitive ability back to differences in brain function, to the neurophysiological substrates determining brain function, to the cellular pathways underlying this neurophysiology, to the proteins involved in these cellular pathways, and finally to the genes coding for these proteins.

In the top-down strategy, cognitive psychophysiological experimentation plays a crucial role by indexing the first important element in this approach; individual differences in brain function. Measures of brain function that correlate with cognitive ability through shared genetic factors are called "endophenotypes" (de Geus and Boomsma, 2002). A rapidly increasing number of potential endophenotypes have already been tested for crucial properties of heritability and (genetic) covariation with cognitive ability (for a review see Posthuma et al., 2002). A specific class of these endophenotypes came from the theoretical framework of the neural speed theory of intelligence (Eysenck, 1986; Vernon, 1987, 1993). Within this framework, many studies have looked at the heritability of reaction times and their correlation with measures of intelligence (e.g. Baker et al., 1991; Ho et al., 1988; Finkel and Pedersen, 2000; Luciano et al., 2001; Neubauer and Knorr, 1997; Rijsdijk et al., 1998). Reaction times are moderately to highly heritable (40–80%) and correlate around −0.20 to −0.40 with measures of intelligence. This association is largely (70–100%) explained by common underlying genetic factors that influence both reaction times and intelligence.

Reaction time in a typical choice reaction time task reflects the final outcome of a multi-stage process of stimulus detection, stimulus evaluation, response selection, response activation, and response initiation. Processing speed of each of these stages can be indexed separately, and tested for heritable individual differences and their relevance to intelligence. For instance, we previously showed that 46% of the individual differences in the speed of early stimulus detection (as measured by inspection time), can be ascribed to genetic differences among subjects (Posthuma et al., 2001b). Moreover, the correlation between this early step and IQ was shown to be completely mediated through a common genetic pathway (Posthuma et al., 2001b). Besides early stimulus detection and reaction times, a number of studies have looked at P3 latency as a measure of the speed of stimulus evaluation. van Beijsterveldt and van Baal (2002) reported a "meta"-heritability across these studies of 51%. Also, a number of studies have reported correlations of P3 latencies with IQ, although not systematically (for a review see Wright et al., 2002). To date there have been virtually no investigations of individual differences in the speed of other stages of information processing.

A potential measure of another aspect of processing speed is the lateralized readiness potential (LRP). The LRP is mathematically derived from the Bereitschaftspotential or Readiness Potential (RP; Kornhuber and Deecke 1965). The onset of the LRP is considered to reflect the output of the response selection stage (Coles,

1989; Eimer, 1998) and its peak latency is thought to additionally reflect central motor processes that take place after response selection has taken place, i.e. response activation (Falkenstein et al., 1994). Actual response initiation can be measured by EMG onset or alternatively as the release of a home button (decision time). In this paper, we examined the heritability of the latency of (pre-) motor selective response activation using the onset and peak latency of the LRP. The heritability of the speed of response initiation was examined using decision time. Since large individual differences in speed–accuracy trade off may exist, even under standardized instructions, we also assess the heritability of accuracy. To test their viability as endophenotypes of cognitive ability, we examined the phenotypic and genetic correlation of processing speed and accuracy with psychometric IQ.

The LRP was obtained during an Eriksen flanker task (Eriksen and Eriksen, 1974). We tested processing speed during the performance of the *congruent* trials because these are comparable to the two-choice reaction time tasks used in many studies testing the neural speed of intelligence hypothesis. In addition, the Eriksen flanker task can be used to specifically test the effects of stimulus-response incongruency. Stimulus-response incongruency in this task generally induces slowing and loss of accuracy (Botvinick et al., 1999; Cohen et al., 1992; Kramer et al., 1994). This may reflect impairment of selective attentional control over the local inhibitory circuits in the perceptual or premotor cortices (Cohen et al., 1992; Servan-Schreiber, 1990; Spencer and Coles, 1999) or of top-down inhibitory control of frontal executive areas (e.g. Kramer et al., 1994; West, 1996). The concepts of selective attention as well as inhibitory control are included in almost all theories of higher cognitive function (Anderson and Spellman, 1995; Baddeley, 1986; Dempster, 1991, 1992; Fuster, 1997 West, 1996). Therefore, we examined the heritability of stimulus-response incongruency effects and explored their phenotypic and genetic correlation to IQ.

All assessments were made in a large sample of twin pairs and their singleton siblings. Twin families had been recruited from two separate age cohorts: 149 families with a mean age of 26 (SD 4.2) and 122 families with a mean age of 50 (SD 7.5). A randomly drawn sample of one subject per family was used to explore the effects of age and sex on stimulus-response incongruency effects on the onset and peak latency of the LRP, decision time and the number of too slow and incorrect responses. Structural equation modelling on the complete sample of genetically related subjects (twins and additional siblings) was used to examine whether individual differences in processing speed during trials with congruent stimulus-response mapping are influenced by genetic factors. Following this, the heritability was tested for stimulus-response incongruency effects using the contrast between stimulus-response congruent and stimulus-response incongruent trials. For all Eriksen flanker task derived measures we then computed the phenotypic correlation with psychometric IQ. In the main multivariate analyses, these phenotypic correlations were decomposed into a genetic and environmental part to test (1) whether common underlying genetic or environmental factors influence processing speed, accuracy and intelligence and (2) whether common underlying genetic or

environmental factors influence stimulus-response incongruency effects and intelligence.

2. Methodology

2.1. Subjects

Subjects were recruited from the Netherlands Twin Register (Boomsma, 1998) as part of a large ongoing project on the genetics of cognition and adult brain function (Posthuma et al., 2001a,b; Wright et al., 2001). Adult twins and their non-twin siblings were asked to participate in a testing protocol lasting 4.5 hrs. In one half of the protocol, psychometric intelligence, inspection time and decision time were assessed, in the other half electroencephalographic activity (EEG) was measured. The EEG registration consisted of a resting EEG measurement (Posthuma et al., 2001a), an oddball task (van Beijsterveldt et al., 2001), a spatiovisual working memory task (Hansell et al., 2001) and the Flanker task (Eriksen and Eriksen, 1974). The order of these tasks within the EEG session was fixed. The order of the two halves of the protocol was randomized across family members. In the present paper only data from the IQ test and from the Eriksen Flanker Task are reported.

Six hundred and eighty-eight family members from 271 extended twin families had participated in the study by December 2000. Participating families consisted of one to eight siblings (including twins). On average 2.5 subjects per family participated. In a young adult cohort 171 males and 210 females participated, in an older cohort this was 135 males and 172 females. The young cohort included 54 MZ pairs, 73 DZ pairs, 18 single twins and 109 additional siblings. The older cohort included 48 MZ pairs, 58 DZ pairs, 15 single twins, and 80 additional siblings.

2.2. Intelligence testing

IQ was measured with the Dutch version of the Wechsler Adult Intelligence Scale (WAIS-III, 1997). Standardization norms for this version are currently being determined and at this point we can report unstandardized raw IQ scores only. All analyses, however, will explicitly model effects of sex and age on the raw IQ scores. Performance IQ was calculated as the mean score of three subtests (picture completion, block design, matrix reasoning) and verbal IQ was based on the mean score on four subtests (information, similarities, vocabulary, arithmetic).

2.3. Flanker task procedure

Subjects were in a supine position facing a monitor at 80 cm distance, in a dimly lit sound attenuated, and electrically shielded chamber. Two boxes with an upper and a lower button were placed left and right in front of the subject. A single randomized sequence of 120 trials was generated and used for all subjects. A trial was started when the subject simultaneously pressed the left and right lower buttons. Subjects

always used the index fingers. The trials started with a tone (1 KHz, 100 ms) and a simultaneously presented fixation dot in the centre of the monitor. After 1000 ms, the stimulus array was presented for 100 ms (see Fig. 1). Stimuli consisted of a horizontal stimulus array comprising five arrowheads. Left and right arrowheads occurred with equal probability. Likewise, the flanking arrowheads were as often congruent as incongruent with the target arrow. This resulted in four conditions each containing 30 trials: left congruent ($<<<<<$), right congruent ($>>>>>$), left incongruent ($>><>>$), and right incongruent ($<<><<$).

Subjects were instructed to respond with the left hand if the central arrowhead pointed to the left, and with the right hand if the central arrowhead pointed to the right. Responding meant releasing the lower "home" button and pushing the upper "response" buttons. They were asked to respond as fast and accurately as possible and to ignore the flanking arrowheads. Visual feedback ("right", "wrong" or "too slow", and total current points) was presented 1000 ms after the onset of the stimulus array, and lasted 1500 ms. They gained 1 point for each correct response and lost 5 points for wrong button presses or too-slow responses. Wrong button presses incorporated all premature responses, wrong home button releases, and wrong response button presses. Responses were too slow when they exceeded the maximum response time of 1000 ms. Trials were separated by an inter trial interval of 1500 ms after which the next trial started as soon as both home buttons had been pressed.

Home button release time and time of response button pressing were stored for all trials as well as the number of too-slow responses (>1000 ms) and wrong button presses. Performance measures were decision time, the number of incorrect and the number of too-slow responses. These measures were all averaged over left and right hand trials. Decision time was computed as the time interval between stimulus onset and home button release. Too-slow responses and wrong button presses were counted and converted to a percentage, because in a small number of subjects, timing information on a few of the 120 trials was lost. Before recording, all subjects received 30 practice trials.

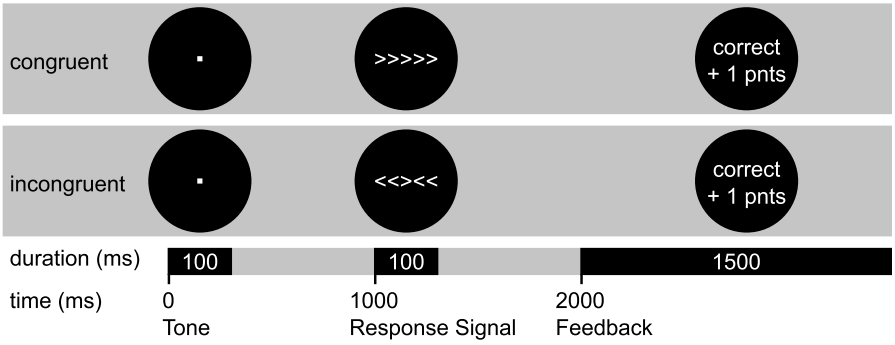

Fig. 1. Temporal structure of the LRP task.

2.4. EEG recording and LRP computation

The EEG was recorded with 19 Ag/AgCl electrodes mounted in an electrocap. Signal registration was conducted using an AD amplifier developed by Twente Medical Systems (Enschede, The Netherlands). Signals were continuously represented online on a Nec multisync 17'' computer screen using POLY 5.0 software (POLY, 1999) and stored for offline processing. Standard 10–20 positions were F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2 (Jasper, 1958). Additionally F1 and F2 were placed halfway between F3 and Fz, and between Fz and F4, respectively. Positions C3 and C4 are located above the right and left motor cortices, respectively, and are used in this analysis.

Software-linked earlobes (A1 and A2) served as reference. The vertical electrooculogram (EOG) was recorded bipolarly between two Ag/AgCl electrodes, affixed 1 cm below the right eye and 1 cm above the eyebrow of the right eye. The horizontal EOG was recorded bipolarly between two Ag/AgCl electrodes affixed 1 cm left from the left eye and 1 cm right from the right eye. An Ag/AgCl electrode placed on the forehead was used as a ground electrode. Impedances of all EEG electrodes were kept below 3 kΩ, and impedances of the EOG electrodes were kept below 10 kΩ. The EEG was amplified (0.05–30 Hz), digitized at 250 Hz and stored for offline processing.

LRPs were computed for correct trials only. Per trial, the epoch used for data analysis started 250 ms preceding stimulus array onset, and ended 1000 ms after onset of the stimulus array. The mean amplitude in the 250 ms preceding the stimulus array was defined as the baseline. Epochs were discarded from further analyses if values exceeded 200 μV on the vertical or horizontal EOG channels, or values exceeded 80 μV on the EEG channels. A three step subtraction method was performed to calculate the LRP waveforms. First, we subtracted the time series recorded from C4 from those recorded over C3 on each trial for the right hand responses. Second, we subtracted the time series recorded from C4 from those recorded over C3 on each trial for left hand responses. Third, the two difference waves for left and right hand responses were subtracted, which resulted in the LRP waveform. This method is also known as the double subtraction method:

$$\mathrm{LRP} = (\mathrm{C3} - \mathrm{C4})_{\mathrm{righthand}} - (\mathrm{C3} - \mathrm{C4})_{\mathrm{lefthand}}$$

Peak latency of the LRP was determined by searching the most negative value in the 350–900 ms post stimulus window. Onset of the LRP was calculated by a single-subject based regression procedure with one degree of freedom (Mordkoff and Gianaros, 2000). This method fits a linear regression to the LRP slope using the individually fixed LRP peak negativity. The intercept with the x-axis denotes LRP onset.

2.5. Statistical procedure

2.5.1. Effects of SEX and AGE COHORT on stimulus-response incongruency effects

As the total sample existed of genetically related subjects, a subset of unrelated subjects was obtained by randomly drawing one subject from each family. On this subset of genetically *un*related subjects, effects of sex and age cohort and their interactions with condition were tested using a repeated measurements MANOVA (GLM, SPSSwin v10.0, 1999). The within subjects factor was CONDITION (congruent, incongruent), and between subjects factors were SEX (female, male) and AGE COHORT (younger, older). Stimulus-response incongruency effects and modulation by age and sex are reflected in the CONDITION main effects, and the AGE COHORT × CONDITION and SEX × CONDITION interaction effects, respectively.

2.5.2. Phenotypic correlation of IQ with processing speed, accuracy and stimulus-response incongruency effects

In the subset of genetically *un*related subjects, Pearson correlations of verbal IQ and performance IQ with the onset and peak latency of the LRP, decision time, percentage too-slow responses or wrong button presses were calculated using SPSS 10.0. As the percentages of too-slow responses and wrong button presses were highly skewed both a log-transformation and a transformation to an ordinal scale were used. The transformation to the ordinal scale was done by regrouping the data into four categories: 0–5% slow, 5–10%, 10–15%, and more than 15%. Polyserial correlations with IQ were calculated using the software package PRELIS (version 2.12a; Jöreskog and Sörbom, 1996). The log-transformed and the ordinally transformed variables gave highly similar results. Only correlations obtained using the log-transform of the percentages too-slow responses and wrong button presses will be presented.

2.5.3. Estimating heritability of processing speed, accuracy, and stimulus-response incongruency effects

To estimate heritability of the processing speed we used onset and peak latency of the LRP and decision time in the *congruent condition*. To estimate heritability of accuracy we used the percentages too-slow responses or wrong button presses in the *congruent condition*. However, the data from the congruent condition were analyzed in a single analysis with the data from the incongruent condition to allow us to simultaneously estimate the heritability of the stimulus-response incongruency effects on speed and accuracy by using a linear combination of the two scores ($+1 \times \text{incongruent} + -1 \times \text{congruent}$) in the path model. The percentages of too-slow responses or wrong button presses had to be log transformed to obtain normality, so here a linear combination of the log-transformed variables in the congruent and incongruent condition would not work. Stimulus-response incongruency effects on accuracy, therefore, were obtained from a separate analysis on the log transform of the contrast between the two conditions.

Heritability was derived from structural equation modelling that estimates sources of (co-) variance in the observed measures due to additive genetic variation (A) or due to shared (C) and non-shared environmental (E) variation (Neale and Cardon, 1992). MZ twins share 100% of their genes, while DZ twins share on average 50% of their genes, as do singleton sibling pairs. Shared environment is per definition 100% shared by the twins of both MZ and DZ pairs, and will consist mainly of the family environment. Thus, the expectation for the covariance between two members of an MZ twin pair is A+C. The expectation for the covariance between two members of a DZ twin pair or between singleton sibling pairs is 1/2A+C. Non-shared environmental factors incorporate those factors in the environment that are not shared by siblings. The expectation for the variance is A+C+E.

Our extended twin design (i.e. consisting of twins and additional siblings) provides data characterized by families of variable size. Such 'incomplete' data can be analyzed in Mx (Neale, 1997) via full information maximum likelihood, which uses the observed data, and provides parameter estimates that make the observed data most likely. In order to obtain a measure of how well the specified model for means and covariances fits the observed values, the raw data option in Mx calculates the negative Log-Likelihood (−LL) of the raw data for each pedigree (Lange et al., 1976), as:

$$-\mathrm{LL} = -k\,\log(2\pi) + \log|\Sigma| + (y_i - \mu)'\,\Sigma^{-1}(y_i - \mu),$$

where k ($k = 1, \ldots, p$; p is the number of family members times the number of phenotypes) denotes the number of observed variables within a family (and can vary over families), Σ is the expected covariance matrix of family members with dimension p by p, y_i (for $i = 1, \ldots p$) is the vector of observed scores, μ is the column vector of the mean expected values of the variables for that pedigree, and $|\Sigma|$ and $\Sigma - 1$ are the determinant and inverse of matrix Σ, respectively.

Since the families are independent, their joint likelihood is the product of their individual likelihoods and the log of the joint likelihood is the sum of the log likelihoods per family. Thus, summing the negative likelihoods (−LLs) of all families gives the −LL of the model. In Mx the −LL of the model is doubled because twice the difference between two models (2{−LL full model−(−LL nested model)}) is—under certain regularity conditions—asymptotically distributed as χ^2. Thus, two nested models (a nested model includes fewer parameters and does not introduce new parameters compared to the model under which it is nested) which provide −2LLs, may be subtracted to provide a Δ(−2LL) which has a χ^2 distribution. A high χ^2 against a low gain of degrees of freedom (Δdf) denotes a worse fit of the second, more restrictive model relative to the first model.

When the model is written in terms of matrix algebra, generalization from the univariate case to a multivariate case becomes straightforward. Let matrices **A**, **C** and **E** be of dimensions $n \times n$, where n denotes the number of variables measured on each subject. Matrix **A** denotes the genetic component, matrix **C** denotes the shared environmental component, while matrix **E** denotes the non-shared environmental component. The diagonal elements of matrix **A** denote the genetic variances of the three variables. For example, element a_{11} is the genetic variation in the first variable.

The off-diagonal elements of matrix **A** represent the genetic covariance between variables. Analogously, the diagonal elements of matrices **C** and **E** denote the shared and non-shared environmental variances of the three variables, and the off-diagonal elements denote the covariances due to shared and non-shared environmental influences.

As matrices **A**, **C**, and **E** are covariance matrices, they are restricted to be positive definite. This is accomplished by calculating matrices **A**, **C**, and **E** as the product of a triangular matrix and its transpose. Thus, matrix **A** is calculated as $\mathbf{X}\times\mathbf{X}'$, where **X** is triangular and of dimensions 3×3 (for three variables). Analogously, matrix **C** is $\mathbf{Y}\times\mathbf{Y}'$, and matrix **E** is $\mathbf{Z}\times\mathbf{Z}'$. This is also known as a Cholesky factorization of matrices **A**, **C** and **E**.

2.5.4. Decomposition of phenotypic correlations with IQ into environmental and genetic correlation

A multivariate decomposition of covariances into genetic and environmental components was used for each measure that showed a significant phenotypic correlation with verbal or performance IQ. The decomposition of covariances into genetic and environmental components necessitates the use of a genetically informative design, such as the twin design. The variance is formally represented as

$$\mathbf{A}+\mathbf{C}+\mathbf{E}=\mathbf{X}\times\mathbf{X}'+\mathbf{Y}\times\mathbf{Y}'+\mathbf{Z}\times\mathbf{Z}'.$$

The covariance is formally represented as

$$\mathbf{A}+\mathbf{C}=\mathbf{X}\times\mathbf{X}'+\mathbf{Y}\times\mathbf{Y}' \text{ for MZ twins,}$$

$$0.5\times\mathbf{A}+\mathbf{C}=0.5\times\mathbf{X}\times\mathbf{X}'+\mathbf{Y}\times\mathbf{Y}' \text{ for DZtwins.}$$

The *genetic correlation* between variables i and j (r_{gij}) is derived as the genetic covariance (a_{ij}) between variables i and j divided by the square root of the product of the genetic variances of variables i (a_{ii}) and j (a_{jj});

$$r_{gij}=\frac{a_{ij}}{\sqrt{a_{ii}\times a_{jj}}}.$$

Analogously, the *shared* (r_{cij}) *and non-shared* (r_{eij}) *environmental correlation* between variables i and j are derived as the respective environmental covariances between variables i and j divided by the square root of the product of the respective environmental variances of variables i and j. The phenotypic correlation (r) is the sum of the product of the genetic correlation and the square roots of the genetic variances of the two phenotypes and the product of the environmental correlation and the square roots of the environmental variances of the two phenotypes.

$$r = r_{gij} \times \sqrt{\frac{a_{ii}}{(a_{ii} + c_{ii} + e_{ii})}} \sqrt{\frac{a_{jj}}{(a_{ii} + c_{ii} + e_{ii})}} + r_{cij} \times \sqrt{\frac{c_{ii}}{(a_{ii} + c_{ii} + e_{ii})}} \sqrt{\frac{c_{jj}}{(a_{ii} + c_{ii} + e_{ii})}} + r_{eij} \times \sqrt{\frac{e_{ii}}{(a_{ii} + c_{ii} + e_{ii})}} \sqrt{\frac{e_{jj}}{(a_{ii} + c_{ii} + e_{ii})}}.$$

r = genetic contribution + shared environmental contribution + non-shared environmental contribution.

3. Results

3.1. Effects of SEX and AGE COHORT on stimulus-response incongruency effects

Psychometric IQ scores were available for 688 subjects (271 families). Table 1 shows age and IQ for the random selection of unrelated individuals, one from each of these families. Analyses of sex and age cohort effects on verbal and performance IQ for this sample have been described elsewhere (Posthuma et al., 2001b). Briefly, it was found that males generally had higher IQ scores than females and younger subjects had higher IQ scores than older subjects.

Seventy eight subjects did not perform the Eriksen flanker task. For the remaining 610 subjects (250 families) data on the average decision time over correct trials and the percentage of trials with too-slow responses or wrong button presses are shown

Table 1
Age and IQ in the randomly selected group of unrelated subjects

		Age	Verbal IQ	Performance IQ
Young females	*N*	74	74	74
	Mean	26.02	28.24	23.64
	Sd	3.78	5.03	3.51
Young males	*N*	75	75	75
	Mean	25.96	29.23	24.34
	Sd	4.41	4.83	3.14
Older females	*N*	63	63	63
	Mean	51.11	26.04	19.40
	Sd	7.46	6.22	3.89
Older males	*N*	59	59	59
	Mean	50.59	29.33	20.62
	Sd	7.36	5.07	4.05

Table 2
Decision time, percentage wrong button presses and percentage responses 'too slow' in the randomly selected group of unrelated subjects

		Decision time (ms)		Percentage wrong button presses		Percentage 'too slow'	
		Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent
Young females	*N*	68	68	68	68	68	68
	Mean	456.99	552.66	0.20	3.31	2.52	8.52
	Sd	39.47	41.89	0.68	8.83	3.20	8.89
Young males	*N*	69	69	69	69	69	69
	Mean	467.34	562.91	0.23	2.05	3.07	9.00
	Sd	36.27	40.27	1.01	5.75	4.81	9.47
Older females	*N*	59	59	59	59	59	59
	Mean	499.66	586.08	2.38	6.78	8.50	22.12
	Sd	44.93	51.22	5.47	11.46	8.10	18.68
Older males	*N*	54	54	54	54	54	54
	Mean	497.60	589.26	0.74	5.94	7.26	17.71
	Sd	46.92	53.38	2.44	11.50	8.60	16.50

in Table 2. The expected effects of CONDITION were found for the percentage too-slow ($F(1, 246) = 188.98$, $P < 0.0001$), percentage wrong button presses ($F(1, 246) = 44.27$, $P < 0.0001$), and decision time ($F(1, 246) = 1872.92$, $P < 0.0001$): stimulus-response incongruency resulted in a prolonged decision time (+92.33 ms), more wrong button presses (3.63%) and more too-slow (9.00%) responses. No main or interaction effects were found involving SEX.

Significant effects of AGE COHORT were found for the percentage too-slow ($F(1, 246) = 46.67$, $P < 0.0001$), percentage wrong button presses ($F(1, 246) = 12.68$, $P < 0.0001$), and decision time ($F(1, 246) = 40.84$, $P < 0.0001$). Older subjects made more responses that were 'too-slow' (+8.12%), made more wrong button presses (+2.51), and had prolonged decision times (+33.17 ms) as compared to younger subjects. In addition, AGE COHORT significantly interacted with CONDITION for the percentage too slow ($F(1, 246) = 21.49$, $P < 0.0001$) responses and wrong button presses ($F(1, 246) = 4.56$, $P < 0.05$). Stimulus-response incongruency led to a larger percentage wrong button presses responses in the older cohort (4.80%) than in the younger cohort (2.47%). Likewise, it affected the percentage too-slow responses more in the older cohort (12.03%) than in the younger cohort (5.96%). In contrast, the AGE COHORT × CONDITION interaction failed to reach significance for decision time ($F(1, 246) = 2.38$, $P = 0.12$). Because the number of too-slow responses was higher in the older cohort, particularly during the incongruent condition, the lack of an interaction effect on decision time may have reflected the exclusion of the correct but slow trials. To explore this, we plot histograms of the reaction time (decision time+movement time) from all correct trials in the congruent and incongruent conditions for the two age cohorts in Fig. 2. In the incongruent condition of the older cohort it is evident that a number of correct trials are missing from the distribution because we classified reaction times above 1000 ms as too-slow. However, extrapolating from the normal curve this missing tail accounts for only about 3–5% of the responses. In reality, 20% of the trials were coded too slow. This means that 15–17% of the too-slow responses were not simply "correct but slow", but must have been drawn from another distribution.

Two further measures of processing speed were derived from the LRP: onset and peak latency. We found that a number of subjects did not show a waveform resembling a readiness potential, which made computation of the LRP problematic. We then decided to select only subjects with a minimum of 30 correct trials (for the congruent as well as the incongruent condition) who had unambiguous LRP traces, even if this meant compromising statistical power of the genetic analyses in terms of lowered sample sizes.

A reliable onset of the LRP was available for 376 subjects in the congruent condition and 361 subjects in the incongruent condition. Peak latency of the LRP was available for 407 subjects in the congruent condition and 376 subjects in the incongruent condition. Fig. 3 shows the grand averages of the LRP waveforms in the congruent and incongruent conditions for the remaining participants in both age cohorts. The figure nicely demonstrates the stimulus-response incongruency effects on the onset and peak latency of the LRP. The positive dip before the onset of the negative shift in the incongruent condition reflects activation of the wrong response.

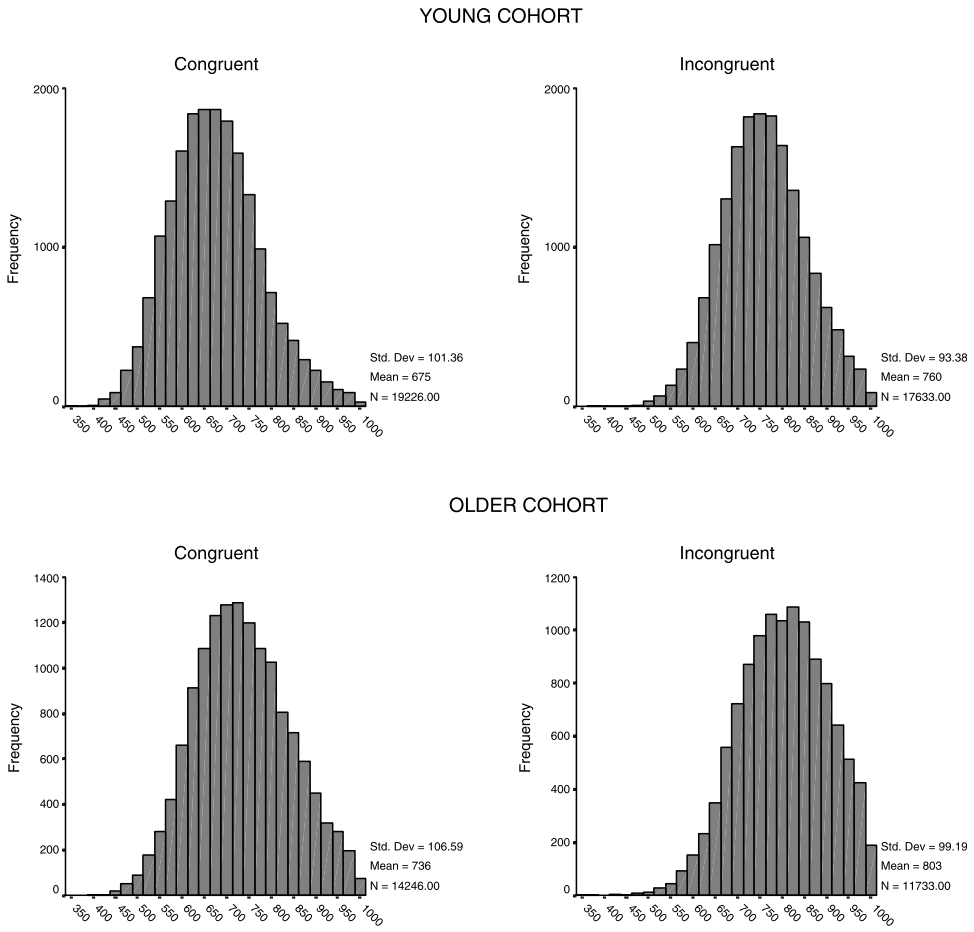

Fig. 2. Distribution of the single trial reaction times (decision time+movement time). Reaction time was recorded in correct trials only; trials with reaction times over 1000 ms were coded too slow.

The analyses of the effects of SEX and AGE COHORT were again performed on the subset of genetically unrelated subjects. LRP latencies of these subjects are shown in Table 3. For the onset ($F(1, 175) = 666.16$, $P < 0.0001$) and peak latency of the LRP ($F(1, 184) = 450.32$, $P < 0.0001$) significant effects of CONDITION were found. The presence of incompatible flankers resulted in a prolonged onset (+115.86 ms) and prolonged peak latency (+96.96 ms). The main effect of AGE COHORT was significant for the onset ($F(1, 175) = 6.07$, $P < 0.05$) and peak latency of the LRP ($F(1, 184) = 16.77$, $P < 0.0001$) and indicated that the onset (+13.55 ms) and the peak latency of the LRP (+32.60 ms) were slower in the older compared to the young cohort. There were no main effects of SEX, and no interactions of SEX with either AGE COHORT or CONDITION.

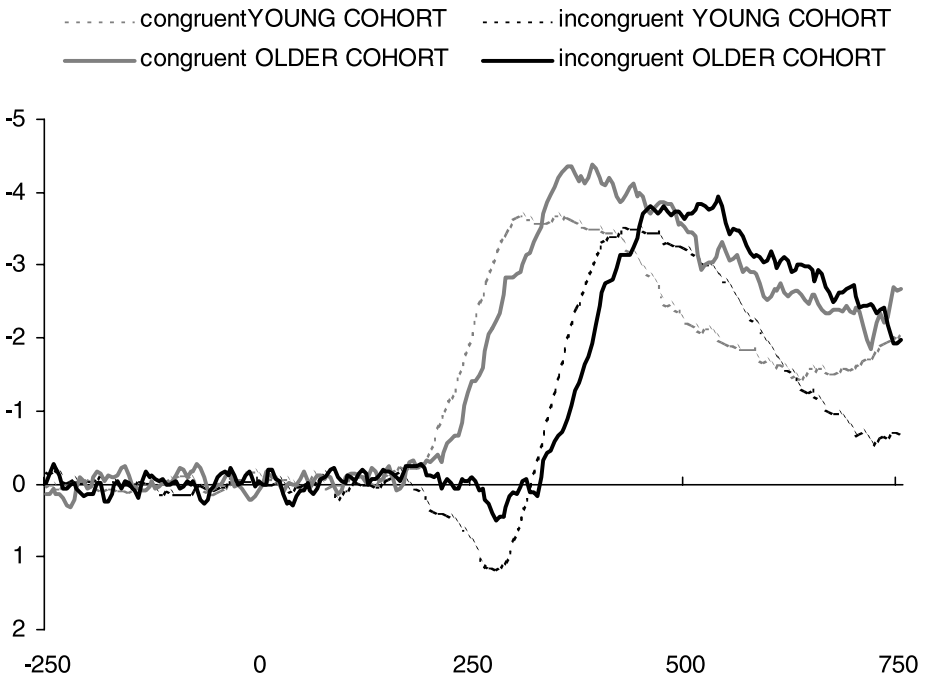

Fig. 3. Grand averages of the LRP.

3.2. Genetic analyses of processing speed and accuracy

The distribution of percentage wrong button presses and percentage too-slow responses was highly skewed. In view of the comparable effects of stimulus-response

Table 3
Onset and peak latency of the LRP in the randomly selected group of unrelated subjects

		Onset (ms)		Peak latency (ms)	
		Congruent	Incongruent	Congruent	Incongruent
Young females	*N*	50	50	55	55
	Mean	186.96	301.04	347.75	441.93
	Sd	49.61	52.39	62.04	56.01
Young males	*N*	57	57	60	60
	Mean	194.63	322.84	359.00	452.20
	Sd	39.55	45.94	65.83	53.47
Older females	*N*	35	35	36	36
	Mean	214.46	312.43	386.33	487.00
	Sd	51.93	49.48	41.73	56.18
Older males	*N*	37	37	37	37
	Mean	204.81	318.97	379.08	478.86
	Sd	42.38	39.84	82.28	69.02

incongruency effects and aging on both type of incorrect responses, we collapsed them into a single percentage for the genetic analyses. This percentage was still highly skewed, and analyses were run using both a threshold model and a log transform. The ordinal transformation and log-transformation gave highly similar results (data not shown) and below we report only on the log-transform of the percentage incorrect response. Maximum likelihood estimates of the twin correlations are given in Table 4. Virtually all MZ correlations are higher than DZ twin correlations. This suggests the presence of genetic influences on the variance in onset and peak latency of the LRP, decision time, percentage incorrect responses, and verbal and performance IQ.

Decomposing the variance in IQ measures by structural equation modelling into genetic, shared and non-shared environmental components confirmed our previous finding (see Posthuma et al., 2001b) that verbal and performance IQ are highly heritable (85 and 69%, respectively). No evidence was found for shared environmental influences. Although the final sample size for the LRP measures is significantly larger than any previous study on the LRP, and more than sufficient to estimate age and sex effects on the mean, it is still critically small for the separate detection of genetic influences and shared environmental influences (see e.g. Posthuma and Boomsma, 2000). We choose, therefore, to decompose the variance in genetic variance (A) and non-shared environmental variance (E; including measurement error) and not to include shared environmental variance in the model. Thus, although the factor A is modelled as additive genetic influences, it should be kept in mind that this factor may also contain shared environmental influences. Table 5 shows the fit statistics of the full AE model and the best reduced variance decomposition models in which different models were allowed for the young and older cohort in each of the two conditions.

The congruent condition was used to assess heritability of processing speed and accuracy. Under the most parsimonious models, genetic influences explained 43% of interindividual differences in the onset of the LRP in the young cohort and 46% of interindividual differences in the peak latency of the LRP in the older cohort (see Table 6). Genetic influences explained 33% of the variance in decision time in the young and 48% of the variance in the older cohort. In the older cohort, 41% of the variance in accuracy derived from genetic influences. No genetic influences on the percentage incorrect responses in the young cohort could be detected. This may not be surprising as in the young cohort very few incorrect responses were given in the congruent condition, keeping the interindividual variance very low.

3.3. Genetic analyses of the effects of stimulus-response incongruency

The contrast between the congruent and incongruent conditions was used to assess heritability of the effects of stimulus-response incongruency on processing speed and accuracy. Table 7 shows that individual differences in the effects of stimulus-response incongruency on onset and peak latency of the LRP were not due to genetic differences, with the exception of the onset of the LRP in the young cohort. However, individual differences in the effects of stimulus-response incongruency on

Table 4
Twin correlations

	Onset		Peak latency		Decision time		Percentage incorrect		IQ	
	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent	Congruent	Incongruent	VIQ	PIQ
Young cohort										
MZ	0.69 (16)	0.15 (18)	0.04 (23)	0.73 (20)	0.56 (46)	0.49 (46)	−0.24 (46)	0.30 (46)	0.84 (54)	0.70 (54)
DZ	0.24 (117)	−0.02 (119)	0.21 (136)	0.03 (129)	0.06 (241)	0.35 (239)	0.07 (241)	0.26 (241)	0.47 (283)	0.31 (283)
Older cohort										
MZ	0.35 (16)	0.44 (13)	0.41 (18)	0.16 (14)	0.50 (45)	0.33 (45)	0.39 (45)	0.38 (45)	0.84 (48)	0.70 (48)
DZ	−0.32 (68)	0.09 (54)	0.29 (81)	0.48 (47)	0.24 (185)	0.22 (183)	0.23 (185)	0.30 (185)	0.47 (242)	0.31 (242)

MZ = monozygotic twins; DZ = dizygotic twin and twin-sibling pairs. VIQ, PIQ = verbal and performance IQ. Between brackets: number of pairs.

Table 5
Fit statistics of the full AE and the best (reduced) variance decomposition models (**bold**)

	−2LL	df	χ^2	Δdf	*P*
ONSET					
Full AE-model	7852.73	721			
E-model, AE-model for congruents in young cohort	**7857.34**	**726**	**4.62**	**5**	**0.47**
PEAK LATENCY					
Full AE-model	8577.71	767			
E-model in young cohort, AE-model in older cohort	**8579.36**	**770**	**1.65**	**3**	**0.65**
DECISION TIME					
Full AE-model	**12 393.12**	**1200**			
% INCORRECT					
Full AE-model	12 322.22	1201			
AE-model, E-model for congruents in young cohort	**12 323.94**	**1202**	**1.72**	**1**	**0.19**

All models are bivariate models that include the congruent and incongruent conditions and a linear combination of these two conditions to derive estimates for the stimulus-response incongruency effects.

Table 6
Percentage of the variance in processing speed and accuracy explained by additive genetic variation (A) and non-shared environmental variation (E)

	YOUNG COHORT		OLDER COHORT	
	A	E	A	E
ONSET				
Full AE-model	48 (7–76)	52 (24–93)	3 (0–28)	97 (72–100)
E-model, AE-model for congruents in young cohort	**43 (3–73)**	**57 (27–97)**	**–**	**100**
PEAK LATENCY				
Full AE-model	2 (0–23)	98 (77–100)	46 (20–66)	54 (34–80)
E-model in young cohort, AE-model in older cohort	**–**	**100**	**46 (20–66)**	**54 (34–80)**
DECISION TIME				
Full AE-model	**33 (10–54)**	**67 (46–90)**	**48 (25–66)**	**52 (34–75)**
% INCORRECT				
Full AE-model	3 (0–23)	97 (77–100)	41 (20–58)	59 (42–80)
AE-model, E-model for congruents in young cohort	**–**	**100**	**41 (20–58)**	**59 (42–80)**

decision time and on the percentage incorrect responses (including too slow) were under significant genetic control. Under the most parsimonious models, genetic influences explained 25% of interindividual differences in decision time in the young cohort and 32% in the older cohort. Genetic influences explained 23% of the variance in percentage incorrect in the young and 29% in the older cohort.

Table 7
Percentage of the variance in *stimulus-response incongruency effects* on processing speed and accuracy explained by additive genetic (A) and non-shared environmental variation (E)

	YOUNG COHORT		OLDER COHORT	
	A	E	A	E
ONSET				
Full AE-model	15 (0–49)	85 (51–100)	10 (0–45)	90 (55–100)
E-model, AE-model for congruents in young cohort	**26 (2–47)**	**74 (53–98)**	**–**	**100**
PEAK LATENCY				
Full AE-model	6 (0–28)	94 (72–100)	3 (0–35)	97 (65–100)
E-model in young cohort, AE-model in older cohort	**–**	**100**	**3 (0–35)**	**97 (65–100)**
DECISION TIME				
Full AE-model	**25 (6–44)**	**75 (56–94)**	**32 (3–69)**	**68 (31–97)**
% INCORRECT				
Full AE-model	**23 (6–40)**	**77 (60–94)**	**29 (5–12)**	**71 (48–95)**

3.4. Phenotypic correlations with verbal IQ and performance IQ

The phenotypic correlations (by age cohort) of onset and peak latency of the LRP and decision time with verbal and performance IQ are shown in Table 8. These correlations do not show a meaningful pattern for the young cohort, but suggest a significant relation between processing speed and IQ in the older cohort. However, in contrast to our expectation, this IQ/processing speed correlation was not reflected in the onset and peak latency of the LRP.

Table 9 shows the pattern of correlations of stimulus-response incongruency effects with verbal and performance IQ. Significant correlation was found with IQ for the effects on accuracy. Incongruency effects on the number of too slow and the number of wrong button presses were significantly larger in the subjects with lower IQ scores.

3.5. Decomposition of the phenotypic correlations into genetic and environmental correlations

Only the significant phenotypic correlations in Tables 8 and 9 were selected for decomposition into genetic and environmental components. The results of this decomposition are depicted in Table 10. The correlation of verbal and performance IQ with decision time in the older cohort was completely explained by an underlying set of genes. Dropping the environmental contributions to verbal IQ/decision time and performance IQ/decision time correlations did not cause a significant worsening of the fit of the model (VIQ $\chi^2_1 = 0.02$, $P = 0.88$; PIQ $\chi^2_1 = 0.001$, $P = 0.98$). The correlation of verbal and performance IQ with percentage incorrect in the congruent condition in the older cohort was also completely explained by an underlying set of

Table 8
Phenotypic correlation of verbal (VIQ) and performance (PIQ) with processing speed and accuracy

		Onset	Peak latency	Decision time	Wrong button presses	'Too slow'	Total incorrect
Young	VIQ	0.01	0.10	0.06	0.11	−0.04	−0.01
Cohort	PIQ	−0.02	0.04	0.09	0.00	−0.14	−0.13
Older	VIQ	0.13	0.06	−0.21*	−0.07	−0.25**	−0.23*
Cohort	PIQ	0.03	−0.16	−0.25**	−0.07	−0.24**	−0.23*

* Significant at the 0.05 level.
** Significant at the 0.01 level.

Table 9
Phenotypic correlation of verbal (VIQ) and performance IQ (PIQ) with stimulus-response incongruency effects

		Onset	Peak latency	Decision time	Wrong button presses	'Too slow'	Total incorrect
Young	VIQ	−0.07	−0.24**	0.01	−0.11	−0.24**	−0.22**
Cohort	PIQ	0.08	−0.10	−0.18*	−0.33**	−0.29**	−0.39**
Older	VIQ	0.01	−0.13	0.14	−0.28**	−0.29**	−0.36**
Cohort	PIQ	−0.06	−0.04	0.11	−0.29**	−0.32**	−0.39**

* Significant at the 0.05 level.
** Significant at the 0.01 level.

Table 10
Genetic correlation and genetic contribution to the significant phenotypic correlations with verbal (VIQ) and performance IQ (PIQ)

	VIQ		PIQ	
	Genetic correlation	Genetic contribution[a] (%)	Genetic correlation	Genetic contribution[a] (%)
Decision time (older)	−0.20 (−0.41 to −0.001)	100	−0.34 (−0.56 to −0.12)	100
Percentage incorrect (older)	−0.51 (−0.70 to −0.31)	100	−0.52 (−0.73 to −0.30)	100
Incongruency effects on the percentage incorrect (young)	−0.44 (−0.79 to −0.20)	100	−0.68 (−1.00 to −0.43)	100
Incongruency effects on the percentage incorrect (older)	−0.37 (−0.89 to −0.12)	100	−0.48 (−0.93 to −0.21)	100

[a] Genetic contribution = percentage of the phenotypic correlation explained by a genetic correlation.

genes. Dropping the environmental contributions from the model did not cause a significant worsening of the fit (VIQ $\chi^2_1 = 0.37$, $P = 0.54$; PIQ $\chi^2_1 = 0.01$, $P = 0.94$).

The correlation of verbal and performance IQ with stimulus-response incongruency effects on the percentage incorrect responses in both cohorts was completely explained by an underlying set of genes. Dropping the environmental contributions to these correlations for both cohorts did not cause a significant worsening of the fit of the model (VIQ;$\chi^2_2 = 1.20$, $P = 0.55$; PIQ:$\chi^2_2 = 2.80$, $P = 0.25$).

4. Discussion

This study examined the genetic contribution to interindividual variance in the speed of selective response activation, decision time and accuracy in the congruent condition of the Eriksen Flanker task. It also examined the genetic contribution to slowing and loss of accuracy induced by stimulus-response incongruency. It was specifically tested whether processing speed, accuracy and stimulus-response incongruency effects were genetically correlated with IQ. These analyses required a large sample of genetically related subjects, in our case twins and their singleton siblings. This large sample provided us with the opportunity to evaluate effects of age and sex on these measures for which most previous samples using the Flanker task had only low statistical power. Below, we review these age and sex effects and follow this with a discussion of phenotypic and genetic correlations with IQ.

As expected, the presence of incongruent flankers led to a significant increase in the onset (115.86 ms) and peak latency of the LRP (96.96 ms) and in decision time (92.33 ms), which is in line with previous findings on this task (e.g. Eriksen and

Eriksen, 1974; Botvinick et al., 1999; Casey, et al., 2000; Gratton et al., 1988; Kopp et al., 1996; Kramer et al., 1994). No evidence of sex differences was found on the performance of the Eriksen flanker task throughout. For age, the expected effects were found on all measures of processing speed. Subjects from the older age cohort (mean age 50) had an onset of the LRP that was on average 13.55 ms delayed compared to subjects in the younger age cohort (mean age 26). The peak latency of the LRP was delayed by an average of 32.60 ms in the older age cohort, and decision times were prolonged by 33.17 ms. At first sight, this cognitive slowing did not seem amplified by stimulus-response incongruency, since no evidence was found for an interaction of age-cohort and condition on decision time. This is consistent with findings from a previous study that looked at decision time during an Eriksen flanker task and compared means across a cohort of 32 young (mean age 20.6) subjects and a cohort of 30 older subjects (mean age 67.8) subjects (Kramer et al., 1994). They found significant differences in mean decision time between the two cohorts (i.e. the older subjects had a longer decision time) and significant prolongation of decision time in the incongruent condition compared to the congruent condition in both cohorts, but no interaction effects.

It should be noted, however, that our measures of processing speed were all computed over trials in which a correct response had to be given within 1000 ms. Slower trials were coded as 'too slow' and no mean decision time was recorded for these trials; instead the 'too slow' feedback was given instantaneously. This stern criterion was chosen to make sure that the subjects would remain motivated to respond as fast as possible. Fig. 2 suggests that at least part of the potentially correct trials in the incongruent condition in the older cohort fell in the 'too slow' category, which meant they were not used to compute average decision time, onset and peak latency of the LRP. We found a significantly larger stimulus-response incongruency effect on the percentage responses too slow in the older cohort: the presence of incongruent flanking stimuli induced 12.03% more too-slow responses than the congruent condition. This figure was only half (5.96%) in the young cohort. These findings do allow for possible amplification of cognitive slowing by stimulus-response incongruency in the older cohort. The failure of the age cohort by condition interaction on decision time to reach significance may have been due to removing these "correct but slow responses just after 1000 ms". However, three observations suggest that a substantial part of the too-slow responses were qualitatively different from such correct but slow responses. First, unless the distribution in Fig. 2 is extremely skewed to the right, only a few percent of the correct trials are missing—far less than the actual percentage of too-slow responses found. Secondly, in 74% of the too-slow responses the home button was never released. This means that even the decision time was larger than 1000 ms, almost double of what it is in the correct trials. In these trials subjects literally 'did not lift a finger'. Thirdly, the number of wrong button presses also showed evidence of stronger stimulus-response incongruency effects in the older than in the younger cohort. Stimulus-response incongruency, therefore, seems to do more harm than response slowing alone. A fair summary of our findings is that older subjects experience more interference by

incongruent flankers than younger subjects when they have to respond correctly within a fixed time frame.

The source of individual differences in the interference induced by stimulus-response incongruency is still unresolved. Larger interference may derive from impairments in local inhibitory connections in the motor or perceptual system (Cohen et al., 1992; Servan-Schreiber, 1990; Spencer and Coles, 1999) or from impairments in top-down inhibitory control signals generated by a supervisory attentional system (Kramer et al., 1994; West, 1996) or a conflict monitoring system (Botvinick et al., 2001).

Localisation of these impairments in cognitive control in the brain is still unresolved although the frontal cortex seems to play an important role (Botvinick et al., 1999; Dempster, 1991; Fuster, 1997; Hazeltine et al., 2000; MacDonald et al., 2000; Smith and Jonides, 1999; Ullsperger and von Cramon, 2001). For our purposes it suffices that processes of inhibitory control and attentional selection are highly plausible source of individual differences in cognitive ability. Although cognitive ability (or IQ) in itself is highly heritable, it is likely to be influenced by a number of genes of small effect. These genes are more easily uncovered by focussing on elementary aspects of cognition, such as processing speed or resistance to interference. The main goal of our study was to test Flanker task derived behavioural and electrophysiological measures of processing speed and resistance to interference as viable "endophenotypes" of cognitive ability. This endophenotype approach requires that the Flanker-task derived measures must be heritable and show evidence of genetic correlation to intelligence (de Geus and Boomsma, 2002).

Using the complete dataset of genetically related subjects, it was found that genetic effects accounted for over 40% of the variance in LRP-onset (young cohort) and LRP-peak amplitude (older cohort) in the congruent condition. Neither parameters, however, were systematically associated with verbal and performance IQ, and no genetic correlation could be found. This contrasted with our expectation that the more intelligent subjects would be fastest in their selective response activation. This expectation derived from the theoretical framework of the neural speed theory of intelligence (Eysenck, 1986; Vernon, 1987, 1993). Within this framework, previous studies have systematically found reaction time to be a heritable trait that is both genetically and phenotypically correlated with measures of intelligence (e.g. Baker et al., 1991; Finkel and Pedersen, 2000; Ho et al., 1988; Neubauer and Knorr, 1997; Rijsdijk et al., 1998; Luciano et al., 2001). In an earlier report on these same subjects we found that the speed of early stimulus detection (as measured by inspection time) was significantly correlated with IQ through a common genetic pathway (Posthuma et al., 2001b). We now extend these findings by showing a similar pattern for decision time in the older cohort, where a significant genetic correlation was found of decision time with verbal (-0.20) and performance IQ (-0.34).

It is unclear why the onset or peak latency of the LRP did not show the expected (genetic) correlation with IQ that we did find in these same subjects with the other processing speed measures (inspection time and decision time), and that others found with total reaction time (Finkel and Pedersen, 2000; Luciano et al., 2001). A first explanation is that the largest source of individual differences relevant to IQ may

simply be in the early perceptual stage of a response, in the stage between selective response activation and the actual response execution, or even in movement execution itself. A second more humble explanation may be the difference in the reliability of the methodologies to assess the various parameters. Reaction times can be recorded with a high level of fidelity, whereas the ERPs, almost by their nature, are highly noisy. Error variance is further increased by the use of a difference score, i.e. the subtraction of left and right EEG signals. Although LRP data are highly useful to compare groups, they may be less suitable to a pure individual differences design. Interestingly, the latency of another ERP, the P3 latency, also showed no evidence of a genetic correlation with IQ in a group of adolescent twins in who IQ and reaction time did derive from common genetic factors (Wright et al., 2002). Aware of the potential problems in the reliability of the LRP, we rigidly selected only those traces in which a clear readiness potential was visible, and used only subjects in which we could average 30 of such traces. As a consequence of this selection of highly reliable LRP traces, a substantial number of subjects were lost, eroding the power to detect low but reliable correlation with IQ.

In addition to processing speed, we also examined the effects of stimulus-response incongruency as a possible genetic correlate of IQ. Effects of stimulus-response incongruency on the LRP-derived measures did not classify as useful endophenotypes of verbal or performance IQ, and neither did the effects on decision time. In contrast, the effects of incongruent flankers on the percentage of incorrect responses were heritable in both age cohorts and correlated at a genetic level with psychometric IQ. In other words, the genetic factor underlying these stimulus-response incongruency effects also explained part of the variance in verbal and performance IQ. We conclude that the ability to perform correctly on a speeded choice reaction time task under conditions of response conflict is a viable endophenotype of cognitive ability.

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