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Individual differences in P300 amplitude: a genetic study in adolescent twins

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Abstract

Using quantitative genetic research designs, we decomposed phenotypic variance in P300 parameters into genetic and environmental components. The twin method was used to carry out this decomposition. Event related potentials (ERPs) were measured during a visual oddball paradigm in a sample of 213 adolescent twin pairs. The presence of male and female same-sex and opposite-sex twins in the sample enabled us to study sex differences in the contributions of genetic and environmental effects to P300 parameters. For targets and nontargets, half of the variance in the P300 amplitude is attributable to factors shared by the family members. However, it remains unclear whether this resemblance is attributable to shared environmental or genetic influences. The same factors (genetic or shared environmental) were found to contribute to the individual differences in males and females. The contributions do, however, differ across gender. Multivariate genetic analyses investigated the covariance among various brain areas to determine whether the covariance between two or more leads is attributable to the same genetic and/or the same environmental factors. The covariance of the P300 amplitude measured at different locations was attributable both to unshared environmental and to shared factors. Again it was not possible to show that the shared factors where either genetic or shared environmental. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

Observed, or phenotypic, variance in P300 amplitude is known to be large (Sklare and Lynn, 1984; Polich, 1986). Using quantitative genetic research designs, the relative contributions of genetic and environmental influences to this phenotypic variance can be estimated. The P300 is attributed an increasingly important role as an indicator variable of a variety of complex behaviors (Begeleiter et al., 1984; Friedman et al., 1986; Polich et al., 1994), whose sources of phenotypic variance is largely unknown. An example of such a variable is alcoholism—in members of alcoholic families, a smaller P300 amplitude is usually observed (Begeleiter et al., 1984). As such, the P300 can serve as a quantitative, psychophysiological marker of a given phenotype. Depending on the nature of the phenotype, such markers can be used to identify individuals who are at risk (Iacono, 1985; Friedman, 1988). The quantitative genetic analysis of a marker will increase the understanding of the role of genetic and environmental influences on the associated phenotype.

The P300 is well suited as a phenotypic marker as it is associated with a variety of disorders and is characterized by large, individual differences. The P300 is viewed as a cognitive event related potential (ERP). Variation in P300 parameters are attributed to individual differences in capacity with which attentional resources are allocated during the updating of the working memory (Donchin and Coles, 1988; Polich and Kok, 1995). Behavioral disorders with a cognitive component are known to be associated with a deviant P300 amplitude. Such disorders include autism (Courchesne, 1987), schizophrenia (Friedman et al., 1986) and alcoholism (for a review, see Polich et al., 1994).

Although it has been shown that the P300 is influenced by genetic factors (Van Beijsterveldt and Boomsma, 1994), some questions remain unanswered. The size of the relative contributions of genetic and environmental factors to individual differences in P300 parameters is unclear. In addition, the contribution of these factors to the phenotypic covariation of P300 parameters between brain regions has yet to be addressed. Finally, the issue of gender differences in the sources of individual differences in P300 parameters has yet to be investigated. The aim of the present study is to address these questions.

1.1. Quantitative genetics

The object of the present quantitative genetic analysis is to estimate the contributions of genetic and environmental factors to phenotypic individual differences in P300 parameters. The emphasis is on individual differences within a homogeneous sample. In most psychophysiological research, in contrast, the emphasis is on the estimation of the phenotypic variance components that are due to specific experimental manipulations, or on the analysis of mean differences between populations of subjects.

To estimate the genetic contribution to individual differences in the P300 amplitude, one requires subjects who are characterized by known degrees of genetic and environmental relatedness. The twin method is based on the comparison of

monozygotic (MZ) and dizygotic (DZ) twins (Boomsma and Gabrielli, 1985). MZ twins are genetically identical to each other while DZ twin share on average 50% of their genetic material. If genetic influences contribute to the phenotypic individual differences in P300 parameters, the MZ correlation will be greater than the DZ correlation. The difference in these correlations can be used to obtain an estimate of the heritability of the P300 parameters. Subsequently, one can obtain estimates of shared environmental influences by considering the residual resemblance between the twins when genetic influences have been taken into account. Here, one assumes that the shared environmental influences are the same for MZ and DZ twins (Plomin et al., 1990). Traditionally, heritability estimates based on twin data were obtained by doubling the difference between MZ and DZ correlations (Falconer, 1981). At present model fitting procedures are the standard way of estimating genetic and environmental influences (Jinks and Fulker, 1970; Eaves et al., 1978; Boomsma and Molenaar, 1986). These procedures enable one to specify models for multivariate, multi-group (e.g. males and females) data. In addition competing models can be compared on the basis of statistical (goodness-of-fit) criteria. In the present paper, the model fitting approach is used to analyse individual differences in P300 parameters.

1.2. P300 and twin studies

Former studies (Surwillo, 1980; Polich and Burns, 1987; Rogers and Deary, 1991) have demonstrated that the individual differences in P300 parameters are influenced by genetic factors (for a review, see Van Beijsterveldt and Boomsma, 1994). However, there is little agreement concerning the extent to which genetic factors contribute to the phenotypic variance in the P300 amplitude. In the study of Surwillo (1980), MZ twins display a greater resemblance than DZ twins in the latency of P300. The samples in the study were however quite small: six DZ and six MZ twin pairs. Polich and Burns (1987) also found a larger resemblance in the P300 amplitude and latency in a sample of 10 MZ twins compared to unrelated subjects. To investigate the possibility that the resemblance in the P300 amplitude and latency is due to shared environmental experiences, the experiment was repeated with DZ twins (Rogers and Deary, 1991). MZ twins displayed a larger resemblance than DZ twin pairs in the P300 latency, but not in P300 amplitude. Resemblance of the P300 amplitude has been demonstrated amongst family members (Eischen and Polich, 1994). Family studies, however, cannot distinguish between resemblance due to shared environment and resemblance that is due to genetic influences. Generally it is difficult to draw firm conclusions on the basis of these studies because of the small sample sizes. Three recent twin based studies of the P300 have employed larger samples (O'Connor et al., 1994; Katsanis et al., 1997; Van Baal et al., in press). These studies also employed the model fitting approach to estimate genetic and environmental components of variance. O'Connor et al. (1994) report a small genetic influence on P300 latency, but a substantial genetic influence on the P300 amplitude in the caudal leads (heritability $\approx 60\%$). Somewhat higher heritabilities ($\approx 80\%$) for P300 amplitude were reported by

Katsanis et al. (1997). They examined the heritability of the P300 waveform in 30 MZ and 34 DZ young (17–18 year-old) male twin pairs. These two studies did not address the question of gender differences in the variance of P300 parameters. In the study of Van Baal et al., in press both male and female twin pairs were included. P300 parameters were measured in 400 young children at ages 5 and 7, to determine the stability of the genetic and environmental influences. It was found that at both ages the heritability was low for the P300 amplitude associated with the targets (0–19%) and high in response to the nontargets (36–86%). The heritability did not differ across the sexes.

1.3. Present study

The present study is a part of a longitudinal study, in which the genetic and environmental influence on brain maturation are investigated in sample of 213 adolescents twin pairs. Because some sex differences have been observed in the P300 (Johnson, 1989; Polich et al., 1990; Segalowitz and Barnes, 1993), this study included female and male same-sex twin pairs and opposite-sex twins to investigate sex differences in genetic and environmental influences. Multivariate analyses of a multi-lead recordings were carried out to investigate the contributions of genetic and environmental factors to the phenotypic covariation of P300 parameters at different locations.

2. Methods

2.1. Subjects

A sample of 213 adolescents twins (mean age = 16.18, S.D. = 0.55) participated in the study. Addresses of twin pairs were obtained from participants in a large questionnaire study on health-related behavior (Boomsma et al., 1994). Subjects were invited by letter to participate in the experiment. As a reward for their participation the subjects received a present and costs incurred travelling to the laboratory were reimbursed.

The subjects were divided into five groups by sex and zygosity: 38 monozygotic males (MZM), 37 dizygotic males (DZM), 52 monozygotic females (MZF), 38 dizygotic females (DZF) and 48 twins of opposite sex (DOS). For 114 same-sex twin pairs, zygosity was determined by blood or DNA typing. For the other same-sex twins the zygosity was determined on the basis of a questionnaire that was completed by the mother. The questionnaire contains items relating to physical similarity of face, eye, hair and skin color and the frequency with which family members and strangers confused the twins. In 17 twin pairs, zygosity was determined on the basis of the questionnaire that they completed themselves. Agreement between zygosity based on this questionnaire and zygosity based on blood group polymorphism was 95%.

2.2. Procedure and stimuli

The measurement session lasted for 3.5 h and took place in the morning or afternoon. Subjects visited the laboratory on the same day as their co-twin and were tested during the same part of the day. The session consisted of four tests: (i) measurement of the EEG/ERP; (ii) measurement of nerve conduction velocity (NCV); (iii) reaction time tests; and (iv) an IQ test (Rijsdijk and Boomsma, 1997). After arriving, subjects were given a short explanation of the experimental procedure. One member of the twin pair started with the ERP measurement and the other member with the measurement of NCV. After the EEG and EOG electrodes were put in place, the subject lay down on a bed in an electrically shielded and sound proof cabin. The instructions were displayed on a black and white monitor that was attached to the ceiling. EEG was measured during four experimental conditions in a fixed order: auditive habituation task, visual oddball task, background-EEG in rest with eyes open and finally with eyes closed. In the present paper the results for the visual oddball task are presented.

This visual oddball task consisted of two types of stimuli, infrequent stimuli (targets, $n = 25$) and frequent stimuli (nontargets, $n = 100$). The stimuli were white line drawings of cats and dogs (Snodgrass and Vanderwart, 1980), which were presented against a black background on a high resolution video monitor. The subjects were instructed to silently count the infrequent stimuli. After the task they were asked how many infrequent stimuli they had counted. The duration of a stimulus was 100 ms and the time between them varied quasi randomly from 1.5 to 2 s (mean = 1.75 s). Buildup time was < 20 ms. During the interstimulus interval (ISI) a central square was shown on the video monitor. To reduce eye movements subjects were instructed to fixate on this central square.

2.3. EEG-recording

Tin electrodes mounted in an electro cap were used to measure EEG and EOG activity. Recordings were made at the scalp locations F7, Fz, F8, C3, Cz, C4, P3, Pz, P4, O1, O2, T3, T4 and T6 according the 10-20 system (Jasper, 1958). Linked earlobes were used as references according to the method described in Pivik et al. (1993). Two separate preamplifiers with high input impedance were connected briefly to each of the reference electrodes and their output linked electrically. With the reference electrodes linked this way, the effects of possible imbalances in electrode impedance introduced by the electrical double layers are prevented. The electrode impedance for EEG and EOG was < 5 Kohm. Tin electrodes were placed at the canthus of each eye to record horizontal movements. To detect vertical movement, EOG was recorded from intra- and supra-orbital electrodes, in line with the pupil of the left eye. A ground electrode was attached to FPz. For both EEG and EOG, ECI (electro-gel) EEG paste was used.

All EEG- and EOG-signals were displayed and recorded by a 18-channel Nihon Kohden electroencephalograph (type EEG-4414A1K). The high pass filter was set to 0.03 Hz and the low pass filter was 35 Hz. Signals were sent to a 12-bit

analog-digital converter and computer-stored for off-line processing. During the ERP recording sampling rate of the AD-converter was set to 100 Hz.

Preprocessing of the EEG consisted of automatic removal of single trials with gross shifts in EEG amplitude and clipping. Single-trial eye movements were removed by means of a dynamic regression routine in the frequency domain (Brillinger, 1975). EOG was subtracted from the EEG by computing frequency dependent regression components with the EOG as the predictor and the EEG as criterion.

Subsequently, the EEG-signal was inspected for EEG-artifacts by moving a 'window' step by step along the trial. Within each window, consisting of 10 measurement points, the mean and S.D. was calculated. Trials with values larger than 2.5 times the S.D. from the mean were removed. Only the remaining trials (minimum 20 trials) were used for subsequent data-analysis.

For each subject, condition (target and nontarget) and lead (C3, Cz, C4, P3, Pz, P4, O1 and O2), the average ERPs were computed relative to the mean amplitude of a 100 ms prestimulus baseline period. Before averaging, latency variability was removed using a filter (Woody, 1967). This involved the following iterative procedure. First, the averaged waveform was computed and served as a template. The template was moved across each single trial in 10 ms lags in the range 200–700 ms after the stimulus onset. At each lag the correlation between the signal and template was computed. The time series was shifted until the cross-correlation between the time series and the template was maximal. After all trials were shifted in this manner, the average waveform was recomputed and used again as a template in a repetition of the procedure. The procedure was repeated until no significant shift of the time series occurred. After obtaining the Woody-filtered averaged ERPs, maximum amplitude and latency were automatically scored in a window from 300–600 ms relative to the 100 ms prestimulus level. This computer-assisted scoring of the P300 amplitude was checked by outlier identification followed by visual inspection of the ERP simultaneously in all leads.

2.4. Data analysis of means and variances

The assumption that the means and variances are the same for MZ and DZ twins and for birth order (first or second twin) was tested by hierarchical χ^2-tests. First, a fully saturated model was fitted to the data, in which variances, covariances and means were estimated in all five groups (MZM, DZM, MZF, DZF, DOS). Second, mean values and variances were constrained to be equal for oldest and youngest of a twin pair and for MZ and DZ twin pairs. The fit of this model was compared to the saturated model. Third, the means of the males and females were constrained to be equal across sexes, the fit of this model was compared with the fit of the previous model. Model comparisons were carried out by means of the likelihood ratio test (see below).

2.5. Genetic analyses

To estimate the influence of genetic and environmental factors, genetic covariance structure modeling was employed (Neale and Cardon, 1992). The aim of this modeling is the decomposition of the observed variance into additive genetic covariance (Va); due to the additive effect of alleles at multiple loci, shared (common) environmental variance (Vc), due to environmental influences shared by twins reared in the same family and unique, specific environmental variance (Ve), which are effects not shared between family members. The specific environmental variance, Ve, will include variance due to measurement error. The observed variance of the phenotype (Vp) is the sum of these three components of variance:

$$\mathrm{Vp} = \mathrm{Va} + \mathrm{Vc} + \mathrm{Ve}$$

Sometimes the variance components are standardized by dividing them by the total variance. Using this approach the heritability coefficient, h^2, is calculated as Va/Vp. Environmental coefficients, c^2 and e^2 are calculated likewise.

In the case of a multivariate phenotype, the symbols Vp, Va, Vc and Ve represent the phenotypic, additive genetic, shared environmental and unshared environmental covariance matrices, respectively. In the genetic covariance structure modeling of MZ and DZ twin, a sequence of models are tested to find out which model provides the best description of the observed data (Neale and Cardon, 1992). Let Σmz denote the observed (sample) covariance matrix of the MZ twins (Σdz is defined similarly). We partition the sample covariance matrices as follows:

$$\Sigma\mathrm{mz} = \begin{bmatrix} \Sigma\mathrm{mz}1,1 & \Sigma\mathrm{mz}1,2 \\ \Sigma\mathrm{mz}2,1 & \Sigma\mathrm{mz}2,2 \end{bmatrix}$$

$$\Sigma\mathrm{dz} = \begin{bmatrix} \Sigma\mathrm{dz}1,1 & \Sigma\mathrm{dz}1,2 \\ \Sigma\mathrm{dz}2,1 & \Sigma\mathrm{dz}2,2 \end{bmatrix}$$

where Σmz1,1 is the covariance matrix of the first member of the twinpair, Σmz1,2 is the twin 1–twin 2 covariance matrix, Σmz1,2 equals $\Sigma\mathrm{mz}2,1^{t}$ (^{t} denotes transposition), etc. Using the computer program Mx (Neale, 1994), we employed maximum likelihood (ml) estimation to fit a sequence of models to these covariance matrices. Mx provides maximum likelihood estimates of the parameters in the model and an overall χ^2 goodness-of-fit index. The χ^2 goodness-of-fit index can be evaluated against the degrees of freedom (df) associated with the model. The number of df equals the total number of observed statistics (the non-redundant elements in the symmetric matrices Σmz and Σdz) minus the number of estimated parameters. In specifying the model, we make use of a priori information relating to the genetic relatedness of the twins to identify the parameters in the model. For instance, we may fit a model incorporating additive genetic, shared environmental and unshared environmental covariance matrices. We would then specify:

$$\Sigma\mathrm{mz} = \begin{bmatrix} \mathrm{Va} + \mathrm{Vc} + \mathrm{Ve} & \mathrm{Va} + \mathrm{Vc} \\ \mathrm{Va} + \mathrm{Vc} & \mathrm{Va} + \mathrm{Vc} + \mathrm{Ve} \end{bmatrix}$$

$$\Sigma dz = \begin{bmatrix} Va + Vc + Ve & 0.5\ Va + Vc \\ 0.5\ Va + Vc & Va + Vc + Ve \end{bmatrix}$$

The additive genetic (co)variance component Va is weighed by 0.5 in the dz sample, because dz twin share 50% of their additive genetic effects. The shared environmental effect contribute equally to within the twin member covariance matrix (Σdz11, Σmz11, Σdz22, Σdz22) and the twin 1–twin 2 covariance matrix, because these influences are shared by the twin members regardless of their zygosity. We assume there that the shared environmental effects are identical for DZ and MZ twin. Empirical studies suggest that this assumption is tenable (Plomin et al., 1990). In addition to this model, we can fit more parsimonious models. The most parsimonious model includes only unshared environmental effects:

$$\Sigma mz = \begin{bmatrix} Ve & 0 \\ 0 & Ve \end{bmatrix}$$

$$\Sigma dz = \begin{bmatrix} Ve & 0 \\ 0 & Ve \end{bmatrix}$$

In all, we fit models incorporating the following covariance matrices: {Va, Vc, Ve}, {Va, Ve}, {Vc, Ve) and {Ve}. Certain models, such as {Vc}, {Vg} or {Va, Vc} are not fit because they are theoretically implausible (e.g. the absence of Ve would imply the absence of error variance).

In comparing competing models, we again make use of the likelihood ratio test. The models {Va, Ve}, {Vc, Ve} and {Ve} are nested under the model {Va, Vc, Ve}. The difference in χ^2 between the nested models is itself χ^2 distributed with the number of df equalling the difference in the number of df between the models. For example, the hypothesis that Vc equals zero involves fitting the model {Va, Vc, Ve} and the model {Va, Ve}, subtracting the obtained df and the χ^2 and evaluating the observed difference in χ^2 against the difference in the number of df. If the χ^2 exceeds some predetermined value (associated with a certain probability, alpha), the hypothesis that Vc equals zero is rejected. In addition to testing for the presence of variance components, we exploit the presence of male DZ and MZ twin (MZM, DZM) and female DZ and MZ twins (MZF, DZF), to investigate whether there are gender differences in the contribution of genetic and environmental sources to the within group (i.e. gender) phenotypic covariance matrix. The presence of DOS twins enables one to test the hypothesis that the same genetic influences are present in females and males, or qualitative differences in genetic influences (i.e. different genes). This important hypothesis can be investigated by testing whether the genetic correlation between the DOS twins deviates significantly from its theoretical value of 0.5. In the event of qualitative genetic differences the DOS genetic correlation is expected to be < 0.5 (Reynolds and Hewitt, 1995). Hypotheses relating to gender are again tested by means of the hierarchical likelihood ratio test.

In Mx, we employ the following parameterisation of each covariance matrix V: $V = \mathbf{LL}^t$, where **L** is the triangular, or Cholesky decomposition of the covariance matrix **L** (all supra-diagonal elements in **L** are zero). This parameterisation has the computational advantage that the matrix $\mathbf{LL}^t$ is (semi-)positive definite (Neale and Cardon, 1992).

The data of 8 leads (C3, Cz, C4, P3, Pz, P4, O1 and O2) were summarized into 16 × 16 (8 leads × 2 twin members) covariance matrices. For each of the five groups (MZM, DZM, MZF, DZF, DOS), the covariance matrix was calculated using the program PRELIS (Jöreskog and Sörbom, 1986).

The full multivariate genetic model {Va, Vc, Ve} included eight genetic factors, eight nonshared factors and eight shared environmental factors. Fig. 1 depicts the path diagram without the shared environmental influences. The latent factors, portrayed as circles, are represented by eight additive genetic factors and eight unique environment factors. The first set of factors load on all leads (C3, Cz, C4 and so on), the second set of factors loads all except the first lead (Cz, C4 and so on) and account for the rest of the variance, the third set of factors having nonzero loadings on all except the first two leads (C4, P3, Pz etc.). Note that this specification results in a matrix of factor loadings (between the latent factor and the observed variables), that displays the triangular pattern (**L**). The specification of shared environmental factors, which we have discarded in Fig. 1 to ease presentation, proceeds along the same lines.

3. Results

Data of nine twin pairs were discarded because one or both twins did not perform the counting task well and/or had bad signals. About 68% of the twins had exactly the right number of targets, 20% of the twins counted one target too many or too few. No significant differences in performance were found between oldest and youngest twins or between MZ and DZ twin pairs.

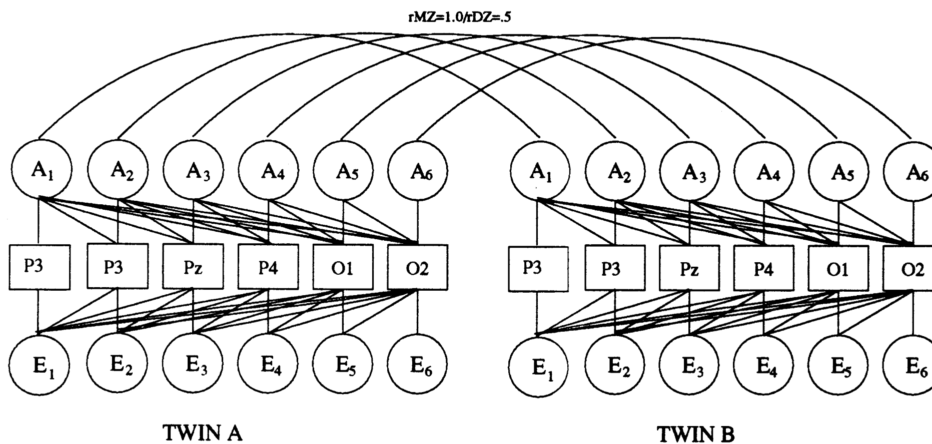

Fig. 1. Multivariate genetic path model. The squares represent the observed P300 amplitude on the central, parietal and occipital electrodepositions in the youngest (twin A) and oldest (twin B) twin. The circles 'A1'–'A8' represent the latent genetic factors, that each correlate 1 between the youngest and oldest MZ twin and 0.5 for DZ twins. The circles 'E1'–'E8' represent the latent nonshared environmental factors.

Table 1
Estimated means and variances of the P300 amplitude

Lead	Males		Females		MZ = DZ	Males = Females
	M	S.D.	M	S.D.	$\Delta\chi^{2\,a}$	$\Delta\chi^{2\,b}$
Targets						
c3	13.76	(4.41)	14.16	(4.44)	8.51	0.61
cz	17.20	(5.53)	18.18	(5.49)	11.48	2.41
c4	14.37	(4.43)	14.43	(4.90)	12.36	1.60
p3	16.70	(4.99)	17.58	(4.98)	16.92	2.05
pz	19.19	(5.55)	20.12	(5.63)	20.82	1.93
p4	17.06	(4.95)	17.93	(5.23)	23.76	2.36
O1	16.24	(6.14)	16.44	(5.44)	10.93	2.44
O2	15.81	(5.80)	15.97	(5.52)	16.77	1.86
Nontargets						
c3	10.03	(3.34)	10.25	(3.55)	10.77	4.71
cz	12.42	(4.08)	11.25	(4.70)	8.02	7.87*
c4	10.67	(3.55)	9.68	(3.41)	15.47	0.00
p3	12.84	(3.78)	11.94	(3.61)	11.24	4.34
pz	14.64	(4.65)	13.69	(4.20)	5.65	4.77
p4	13.27	(4.35)	12.44	(4.00)	22.06	3.63
O1	13.00	(4.73)	12.18	(4.66)	19.97	2.31
O2	15.81	(5.80)	15.97	(5.52)	20.28	2.25

The first two columns represent estimated means (M) and S.D. of the amplitude of P300 targets and nontargets separately for males and females on electrode positions: C3, Cz, C4, P3, Pz, P4, O1 and O2. The third column represent the results of the model fitting test for the differences in means and S.D. between MZ and DZ twin pairs. Differences in means and S.D. between the MZ and DZ twin pairs were significant when the χ^2 (with 16 df) exceeds the value of 26.29. The model fitting statistics of the test of differences in means and S.D. between males and females are given in the last column. Differences are significant when the χ^2 difference deteriorate more than 5.99 compared to the previous model of equal means and variances between MZ and DZ twins.

[a] Critical value of χ^2 by comparison MZ = DZ with 16 df = 26.29.

[b] Critical value of χ^2 by comparison males = females with 2 df = 5.99.

*Difference is significant at alpha = 0.05.

In the genetic analyses, the central, parietal and occipital leads were used. A substantial number of our subjects displayed no recognizable P300 waveforms in the frontal and temporal leads. To maintain adequate power in the genetic modeling, a relatively large number of complete twin pairs is essential. Therefore, it was decided to discard the data from the frontal and temporal leads in the genetic modeling, rather than leaving out these subjects.

3.1. Means and variances

Table 1 contains the means and S.D. of the central, parietal and occipital leads for the target and the nontargets. Results are given for males and females in the second and third column, respectively. In addition, Table 1 contains the model

fitting results for the test of differences in means and variances between the zygosities and between males and females. The fit of the first model, in which the means and S.D. were constrained to be equal between zygosities, was compared with a model without any constraints. The differences in χ^2 (df = 16) for each lead are shown in the fourth column. No significant differences were found between the means and variances of the MZ and DZ twin pairs. The fifth column of the table contains χ^2 (df = 2) for the hypothesis that the means and S.D. were equal for males and females. None of the leads for the P300 target and nontarget comparisons, except Cz of the nontargets, showed a significant sex differences for means and variances.

3.2. Twin correlations

In Fig. 2 examples of individual waveforms for the targets of the first and second twin of MZ and DZ twin pairs are shown. On the two upper rows, the individual P300 target of two MZ twin pairs are depicted and on the two lower rows the P300 target of two DZ twin pairs. These figures clearly show that the P300 amplitude varied greatly across individuals. Furthermore, the amplitude of the P300 targets of the MZ twins shows a clear resemblance. The resemblance of the P300 amplitude is smaller in the DZ twins.

In the upper part of Table 2 twin correlations are presented for the P300 amplitude for targets and nontargets. The MZM correlations were higher than the DZM correlations for most leads, both in the target and nontarget trials. The higher MZM correlations suggest genetic influences on the P300 amplitude in response to both targets and nontargets. For females, similar evidence of genetic influences was found on the P300 amplitude in parietal and central leads in response to nontargets. In response to the targets and nontargets occipital leads, however, the MZ and DZ correlations showed a different pattern. The DZ correlations were lower, although not significant (except C4), than the MZ correlations. This pattern is difficult to interpret. The nontarget occipital leads showed identical MZ and DZ correlations. This suggests that the P300 in females may be influenced by shared environmental influences (Neale and Cardon, 1992). The difference in genetic versus environmental determination of the P300 in males and females would predict correlations in the opposite sex twins that are close to zero. Indeed, for targets and occipital nontargets, low DOS correlations were found, corroborating the sex related difference in P300 amplitude determinants. Pooled correlations, over males and females, are given to make comparisons with other investigations possible. For targets and nontargets at central, parietal and occipital electrode locations MZ correlations were larger than DZ correlations.

3.3. Genetic modeling

Table 3 shows the χ^2 goodness-of-fit indices for the various models tested. Three models were fitted to test sex differences in the individual variation of the P300 amplitude. The first model included different estimates for males and females and

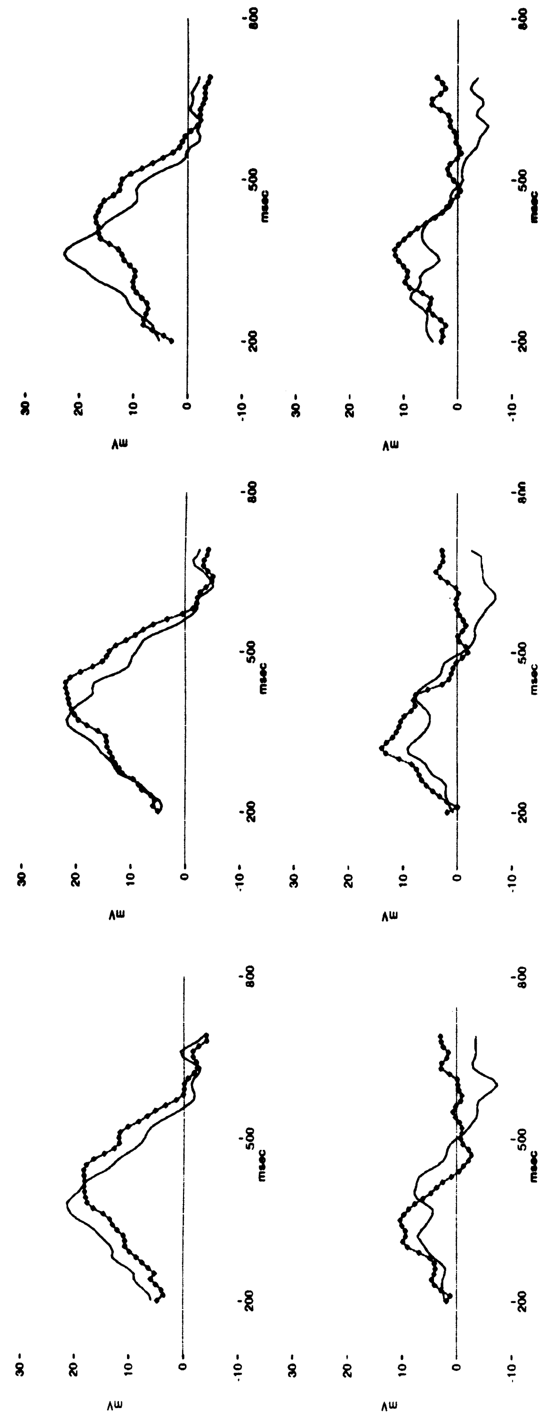

Fig. 2. Example of the P300 targets measured on P3, Pz and P4. In all the figures is the P300 target depicted of the youngest (line) and oldest (line with dots) of two MZ twin pairs (two upper rows) and two DZ twin pairs (two lowest rows).

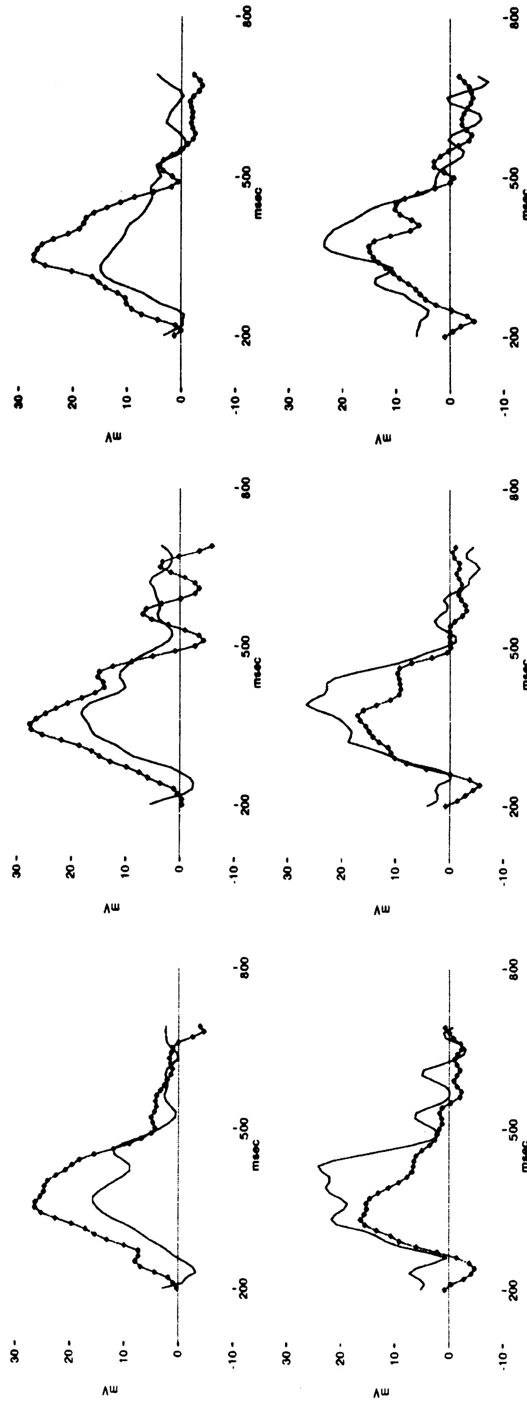

Fig. 2. (*Continued*)

Table 2
Twin correlations of P300 amplitude and latency for eight leads (C3, CZ, C4, P3, Pz, P4, O1 and O2), separately for targets and nontargets

P300 Amplitude

	Target								Nontarget							
	C3	Cz	C4	P3	Pz	P4	O1	O2	C3	Cz	C4	P3	Pz	P4	O1	O2
MZM (37)	0.34	0.10	0.42	0.45	0.47	0.52	0.54	0.51	0.24	0.57	0.56	0.56	0.54	0.47	0.55	0.67
DZM (35)	0.33	0.32	0.16	0.03	0.10	0.21	0.21	0.26	0.35	0.17	0.45	0.19	0.30	0.32	0.15	0.28
MZF (48)	0.22	0.25	0.25	0.33	0.52	0.50	0.50	0.58	0.40	0.42	0.53	0.37	0.53	0.42	0.47	0.54
DZF (37)	0.44	0.55	0.64	0.54	0.56	0.56	0.55	0.56	0.08	0.33	0.33	0.24	0.26	0.42	0.55	0.58
DOS (47)	0.11	0.15	0.11	−0.23	0.03	−0.07	−0.08	0.04	0.31	0.15	0.32	0.08	0.17	0.11	0.20	0.09
Twin correlations pooled over males and females:																
MZ (85)	0.27	0.19	0.29	0.38	0.49	0.48	0.52	0.54	0.34	0.48	0.54	0.45	0.54	0.43	0.51	0.61
DZ (119)	0.27	0.33	0.31	0.12	0.24	0.23	0.21	0.27	0.26	0.22	0.36	0.16	0.22	0.24	0.29	0.29

In the first row the twin correlations were given for each zygosity group (MZM, DZM, MZF, DZF, OS). In the second row the twin correlations were pooled over males and females.

included the correlations between genetic factors of males and females in the DOS as freely estimated parameters (i.e. not fixed to equal 0.5). A lower correlation is expected when different sets of genes influence the P300 amplitude in males and females. To test this hypothesis, this model is compared with the second model, in which the genetic correlation in the DOS group was fixed at a value of 0.5. For both targets and nontargets, the χ^2 did not increase significantly, indicating that the same genes seem to act on the amplitude of the P300 for males and females. In the third model the estimates, *a*, *c* and *e* were constrained to be equal in males and females and the genetic correlation in the DOS group was fixed at 0.5. When the χ^2 of this model is compared to the χ^2 of the second model, the differences χ^2 were found to just exceed the critical value, associated with an alpha of 0.05. Thus, for targets and nontargets, the best fitting model specified sex differences in parameters estimates.

In the next submodels the significance of the A and C factors was tested. As shown in Table 3, dropping either A or C in both males and females, did not result in a significant deterioration of goodness-of-fit of the model. However when A and

Table 3
Goodness-of-fit tests for different models applied to P300 amplitude for eight leads (C3, Cz, C4, P3, Pz, P4, O2 and O2)

Models	Targets			Nontargets	
	df	χ^2	$\Delta\chi^2$	χ^2	$\Delta\chi^2$
Test of sex differences:					
1. Males ace, females a′c′e′, rg free[a]	456	743.7	—	725.8	—
2. Males ace, females a′c′e′	464	744.4	0.7	727.9	2.1
3. Same a,c,e males and females	572	887.2	142.8*	868.5	140.6*
Dropping A or C separately in males or females: (tested against 2, Δdf = 36[b])					
4. Males ae, females a′c′e′	500	765.5	21.1	746.4	18.5
5. Males ace, females a′e′	500	773.5	29.1	753.4	25.5
6. Males ce, females a′c′e′	500	764.2	19.8	747.7	19.8
7. Males ace, females c′e′	500	749.9	5.5	740.7	12.8
Dropping A or C in both males and females: (tested against 2, Δdf = 72[c])					
8. Males ce, females c′e′	536	765.7	21.3	767.7	39.8
9. Males ae, females a′e′	536	780.5	36.1	762.8	34.9
Dropping A and C: (tested against 9/10, Δdf = 72[d])					
10. Males e, females e′	608	909.6	129.1*	926.7	159.1*

For each model χ^2, probability and differences in χ^2 ($\Delta\chi^2$) are given. a,c,e are the loadings estimated for males, a′,c′,e′ are loadings estimated for females.
[a] Rg free means that the genetic correlation between males and females in the DOS group is estimated instead of fixed at 0.5.
[b] Critical value of χ^2 with 36 df = 50.99.
[c] Critical value of χ^2 with 72 df = 92.80.
[d] Critical value of χ^2 with 8 df = 15.51.
*Significant decrease in fit.

C are both dropped from the model, there is a significant deterioration of the fit, for both targets and nontargets. Thus for targets and nontargets there is clearly familial relatedness, but it is not possible to attribute this to either A or C factors. Because no distinction could be made between A and C factors, both the results of an AE model (Table 4) and the results of an AE model (Table 5) are presented. In the lower row of the table the percentage variance explained by genetic (heritability) and by environmental factors is given. For targets, 25–42% of the variance averaged over all leads, is explained by familial relatedness. For nontargets, the amount of variance explained by familial relatedness, is somewhat higher. For both sexes and both kind of stimuli, the amount of variance explained by genetic factors is usually larger than the amount of variance explained by environmental factors. Still, in both males and females, a substantial portion of the variance in target and nontarget P300 amplitude is due to nonshared environmental influences.

The phenotypic correlation may be attributable to the genetic and/or environmental factor in the model. In the upper part of Tables 4 and 5, the genetic and environmental correlations are given. For targets there is one homogeneous block of high genetic correlations (≈ 0.9, see Table 3) among the central and parietal leads. A second block with high genetic correlations is formed by the occipital leads. In contrast with the structure of genetic correlations, the nonshared correlations are lower and lack a clear pattern. A similar pattern of genetic correlations is found for the nontargets, two blocks of highly homogeneous genetic correlations, one for the central and parietal leads and one for the occipital leads. The structure of genetic correlations do not show large differences between males and females. The nonshared environmental correlations, however, were larger in the female sample. Except for central leads, for which males have larger heritabilities, no other differences in heritability were found.

For the shared environmental factors the same structure was found as for the structure of genetic of factors (Table 4). There is a pattern of high correlations for central and parietal leads and a second block of higher correlations for the occipital leads. The correlation structure of nonshared environmental factors lacks a clear pattern and showed lower correlations among leads.

4. Discussion

The aim of this study was to estimate the genetic and environmental contributions to the variances and covariances of P300 parameters. Because P300 greatly varies with age (Courchesne, 1983; Wijker et al., 1989) and different genetic and environmental sources may be active at different ages (Molenaar et al., 1991), we ensured that the subjects in the present study were about the same age (mean age = 16.18, S.D. = 0.55). To investigate sex differences in genetic influences, the twin sample included an approximately equal number of males and females. In addition, multivariate genetic models tested whether the same genes and/or environmental influences contributed to individual differences measured at different brain locations.

Table 4
Genetic correlations (below diagonal) and nonshared environmental correlations (above diagonal) for males and females, as a result of an AE model

	Males								Females							
	C3	Cz	C4	P3	Pz	P4	O1	O2	C3	Cz	C4	P3	Pz	P4	O1	O2
Targets																
C3	—	0.69	0.61	0.59	0.49	0.50	0.23	0.31	—	0.76	0.72	0.77	0.75	0.66	0.63	0.53
Cz	0.98	—	0.73	0.53	0.61	0.56	0.27	0.37	0.99	—	0.75	0.68	0.75	0.62	0.51	0.43
C4	0.92	0.96	—	0.48	0.46	0.51	0.24	0.31	0.97	0.99	—	0.61	0.66	0.72	0.50	0.48
P3	0.89	0.88	0.93	—	0.86	0.77	0.67	0.55	0.89	0.90	0.91	—	0.85	0.77	0.78	0.68
Pz	0.86	0.92	0.97	0.90	—	0.85	0.65	0.60	0.88	0.91	0.91	0.99	—	0.83	0.70	0.67
P4	0.70	0.74	0.88	0.91	0.91	—	0.69	0.61	0.86	0.87	0.87	0.98	0.96	—	0.70	0.75
O1	0.68	0.67	0.70	0.78	0.73	0.74	—	0.70	0.53	0.53	0.52	0.80	0.79	0.84	—	0.81
O2	0.60	0.59	0.65	0.79	0.72	0.80	0.96	—	0.61	0.61	0.60	0.80	0.79	0.86	0.93	—
h^2	53	29	58	39	45	47	57	55	27	34	34	39	54	50	49	56
Nontargets																
C3	—	0.53	0.45	0.59	0.46	0.42	0.29	0.44	—	0.70	0.68	0.62	0.60	0.41	0.45	0.30
Cz	0.85	—	0.55	0.35	0.29	0.28	0.15	0.41	0.99	—	0.66	0.44	0.55	0.37	0.41	0.30
C4	0.97	0.83	—	0.36	0.42	0.38	0.20	0.28	0.97	0.99	—	0.42	0.48	0.49	0.43	0.36
P3	0.80	0.89	0.85	—	0.76	0.69	0.39	0.42	0.87	0.88	0.89	—	0.76	0.59	0.64	0.44
Pz	0.78	0.93	0.82	0.94	—	0.82	0.34	0.42	0.86	0.87	0.86	0.96	—	0.73	0.53	0.42
P4	0.64	0.79	0.76	0.93	0.91	—	0.39	0.48	0.84	0.85	0.84	0.97	0.96	—	0.56	0.57
O1	0.49	0.57	0.57	0.86	0.73	0.79	—	0.65	0.28	0.30	0.33	0.66	0.61	0.72	—	0.81
O2	0.45	0.51	0.60	0.83	0.75	0.88	0.93	—	0.42	0.42	0.41	0.71	0.68	0.81	0.94	—
h^2	49	59	71	62	59	61	62	72	41	43	61	47	59	58	49	59

In the upper part correlations for targets are given and in the lower part correlations for nontargets. Below each matrix of correlations the variation explained by genetic factors is given (h^2).

Table 5
Shared environmental correlations (below diagonal) and nonshared environmental correlations (above diagonal) for males and females, as a result of a CE model.

	Males								Females							
	C3	Cz	C4	P3	Pz	P4	O1	O2	C3	Cz	C4	P3	Pz	P4	O1	O2
Targets																
C3	—	0.73	0.75	0.69	0.61	0.60	0.44	0.48	—	0.76	0.71	0.78	0.78	0.66	0.63	0.54
Cz	0.99	—	0.78	0.60	0.67	0.61	0.39	0.45	0.99	—	0.75	0.69	0.74	0.61	0.48	0.43
C4	0.85	0.85	—	0.66	0.65	0.65	0.50	0.52	0.98	0.98	—	0.63	0.66	0.71	0.52	0.49
P3	0.82	0.82	0.72	—	0.88	0.83	0.73	0.65	0.87	0.91	0.88	—	0.86	0.79	0.78	0.70
Pz	0.87	0.89	0.93	0.81	—	0.89	0.72	0.69	0.88	0.93	0.88	0.98	—	0.84	0.69	0.68
P4	0.56	0.61	0.82	0.80	0.82	—	0.74	0.69	0.85	0.90	0.85	0.98	0.96	—	0.72	0.77
O1	0.48	0.49	0.44	0.66	0.54	0.62	—	0.81	0.48	0.57	0.47	0.79	0.80	0.81	—	0.82
O2	0.37	0.38	0.37	0.65	0.52	0.72	0.91	—	0.56	0.62	0.56	0.79	0.78	0.84	0.93	—
c^2	30	17	25	18	21	23	35	35	26	33	38	34	48	46	46	52
Nontargets																
C3	—	0.64	0.62	0.67	0.57	0.52	0.36	0.46	—	0.77	0.77	0.69	0.69	0.54	0.45	0.35
Cz	0.81	—	0.68	0.53	0.49	0.43	0.26	0.40	0.99	—	0.76	0.56	0.66	0.51	0.41	0.35
C4	0.92	0.76	—	0.59	0.62	0.54	0.33	0.40	0.96	0.98	—	0.56	0.64	0.61	0.41	0.40
P3	0.77	0.95	0.82	—	0.84	0.80	0.61	0.64	0.82	0.83	0.85	—	0.82	0.67	0.62	0.48
Pz	0.73	0.95	0.72	0.94	—	0.87	0.52	0.58	0.81	0.81	0.80	0.93	—	0.80	0.53	0.47
P4	0.57	0.81	0.73	0.89	0.87	—	0.58	0.67	0.80	0.80	0.79	0.98	0.95	—	0.57	0.61
O1	0.50	0.64	0.60	0.82	0.68	0.72	—	0.80	0.23	0.25	0.30	0.72	0.62	0.74	—	0.82
O2	0.39	0.55	0.62	0.77	0.69	0.84	0.87	—	0.38	0.38	0.36	0.75	0.69	0.81	0.94	—
c^2	33	34	45	31	37	37	33	42	22	24	41	32	42	47	45	53

In the upper part correlations for targets are given, in the lower part correlations for nontargets are given. Below each matrix of correlations the variation explained by shared environmental experiences is given (c^2).

Table 6
Number of subjects required to reject, at the 0.05 level and 80% power, a CE model when the true model is AE and the ratio MZ to DZ pairs is 1:1

Heritability	Number of twins
$h^2 = 80\%$	52
$h^2 = 60\%$	180
$h^2 = 40\%$	597

h^2 refers to true heritability.

4.1. The heritability of the P300?

The MZ and DZ correlations found for the targets P300 suggest genetic influence for males and influence of shared environmental factors for females. For non-targets, both for females and males, the correlation (Table 1), are more in line with the presence of genetic influences. Generally the MZ correlations exceed the DZ correlations. However the results of model fitting indicate that we cannot distinguish between genetic and shared environmental influences. Although we cannot identify its causes, the presence of family resemblance is beyond doubt: dropping both the genetic and environmental factors results in a significant deterioration of the goodness-of-fit. The failure to distinguish between the CE and AE model is due to insufficient statistical power. We investigated the issue of power by creating covariance matrices according to an AE model and, subsequently fitting a CE model to these matrices. To ease presentation, gender effects were not considered. We calculated the number of MZ and DZ twins that there required to reject the false CE model with an alpha of 0.05 and a power of 0.80. In Table 6 the number of subjects are given. Given a heritability of 0.40, it is clear that we require many more subjects that are available in the present study. To make a distinction between genetic and shared environmental factors for the P300 a larger sample will be needed.

Because it was not possible to distinguish between an AE and a CE model, we presented results for both. In the case of the AE model, the variance explained by genetic factors is, averaged over leads, 42% for targets and 62% for nontargets. Differences between males and females in this respect were small. In the case of the CE model, the amount of variance explained by familial factors was smaller. For both targets and nontargets, the amount of variance explained by shared environmental factors is 25% for males and 40% for females.

The amount of variance explained by familial resemblance ranged from 25 to 43% for the targets and was somewhat larger for nontargets. Among the electrode positions no large differences were found. These heritabilities were somewhat lower than those reported in earlier studies of Katsanis et al. (1997) and O'Connor et al. (1994). In the last study involving an auditory oddball task, caudal heritabilities ≈ 0.60 was reported for targets. Differences between O'Connor et al. (1994) and the present study could be due to the use of the auditory instead of the visual modality.

Another possible explanation is the difference in age of the subjects in the two studies. Genetic and environmental contributions to phenotypic individual differences may vary greatly over the lifespan. In individuals in the age range of our subjects, brain maturation is still incomplete and it is possible that genetic differences are yet not fully expressed.

Katsanis et al. (1997) used subjects of the same age as the present subjects. In addition, the modality of the oddball task was the same as here. Nonetheless, Katsanis et al. (1997) reported considerably higher heritabilities. However, in contrast to our simple task, their task required a much greater cognitive effort. It is possible that the heritability of the P300 is higher as cognitive demands increase.

In contrast with the results of the study of Katsanis et al. (1997), O'Connor et al. (1994) found evidence that beside additive genetic effects, dominance effects plays a role. Dominance is due to interaction of alleles at a locus. In the twin method the presence of dominance is suggested by MZ correlations that are substantially larger than two times the DZ correlations. In the O'Connor et al. (1994) study the DZ correlations were very low. By pooling our MZ and DZ correlations over males and females, we can compare our results with those of O'Connor et al. (1994). We found no indication for the presence of genetic dominance: the DZ correlations were about half the MZ correlations. The modality of the stimuli in the O'Connor et al. (1994) study differed from the modality in the present study and the Katsanis et al. (1997) study. This could explain the differences in the mode of the genetic effect. Johnson (1989) posited different generators of the P300 activity for auditive and visual modalities. Possibly different genes contribute to phenotypic individual with respect these generators.

As much as half of the phenotypic variance in both targets and nontargets P300 amplitude was attributable to nonshared environmental influences. Such influences include measurement error. The average test-retest reliability of 0.62–0.81 has been reported for a period ranging from a few weeks (Fabiani et al., 1987) to 2 years (Segalowitz and Barnes, 1993). This suggest that the variance attributable to measurement error ranges from ≈ 0.20 to 0.40. It is likely that the unshared environmental variance consists for a substantial part of error variance. In calculating standardized components of variance, the presence of measurement error introduces bias. For instance, heritability is calculated as follows $Va/[Va + Vc + Ve]$. The presence of error variance in the term Ve clearly results in an underestimation of the heritability.

4.2. Sex differences

This is the first twin study of ERP in which possible sex differences in genetic architecture were investigated by means of model fitting. Segalowitz and Barnes (1993), who used subjects of the same age as in our sample, found a larger P300 amplitude for target in females than in males, while at 17 years the opposite was observed—larger amplitude in males than in females. Gender differences in maturational rate could account for these results. Gender differences in genetic influences could also be due to differences in processing strategies between males and

females (Friedman et al., 1985). It has been argued that differences between sexes in hemispheric specialization for visuo-spatial task (McGlone, 1980), or structural anatomic differences (Steinmetz et al., 1995; Witelson and Kigar, 1992) could underlay these differences.

Clearly, if shared environmental factors really influence the P300 amplitude, the question of the nature of these influences has to be addressed. What could both MZ and DZ twins have in common that would account for their likeness in P300 amplitude? Half of the twin pairs were tested in the morning and the other half were tested in the afternoon. Within each twin pair no more than 1 h elapsed between the EEG measurement. Synchronization of circadian rhythms (Geisler and Polich, 1992), therefore, may be a possible explanation of a shared environmental effect. Since P300 amplitude is known to be sensitive to state anxiety effects created by an experimental setting (Grillon and Ameli, 1994), a tentative explanation would point to twin resemblance in arousal induced by the experimental setup and the visit to the laboratory. Secondly, the shared environment created by the experimental setting could play a role, especially in the more active part of the experiment. The oddball task is not a particularly challenging task for adolescents. Obviously, these explanations are speculative. A longitudinal follow-up is currently underway which hopefully will produce less ambiguous results.

4.3. Multivariate analysis

The phenotypic correlations of the P300 among the various electrode positions were quite high. Covariation can arise if the same genetic and/or the same environmental factors influence the P300 amplitude at different cortical regions. The multivariate genetic analyses yields an insight into the sources of covariation between amplitudes at different scalp locations. Estimated environmental and genetic correlations provide an indication of the extent to which the same genes or environmental factors contribute to the observed phenotypic correlations. Regardless of the model fitted (AE or CE), the pattern of latent genetic/shared environmental correlations was systematic and homogeneous for the central and parietal leads and was somewhat different for the more caudal leads. This could point towards the influence of the same genes/shared environment for P300 measured at the central and parietal leads with an additional genetic/shared environmental factor influencing the P300 amplitude in the occipital positions. If this second factor is significant, then it could be used as a possible indicator of more than one neural generator of the P300. In contrast, the matrix of nonshared environmental correlations did not show a systematic pattern and probably could be interpreted as measurement error.

4.4. Latency

An association between the TaqI A D2 dopamine receptor allele and phenotypic P300 latency was reported by Noble et al. (1994). A higher allele frequency, related to longer P300 latencies, were found in 10–14 year old boys of alcoholic fathers

than in control group. Three previous studies also reported high heritabilities for P300 latency (Surwillo, 1980; Polich and Burns, 1987; Rogers and Deary, 1991). In our study no effects of either genetic or shared environmental factors were suggested for P300 latency. Our data are in good agreement with O'Connor et al. (1994) who also found no genetic effects on P300 latency in an auditory task. Also Katsanis et al. (1997) did not find any genetic influence on the P300 latency in a condition, comparable in difficulty with our task. Since in our laboratory the same study is done in much younger twins (Van Baal et al., in press), the task was simple enough that the younger twins could also perform it. The low cognitive demands of this simple oddball task could explain the absence of genetic influences for the P300 latency.

To summarize, we have observed a clear familial resemblance in the P300 amplitude. Both for targets and nontargets half of the variance in the P300 amplitude is attributable for factors shared by family members. However, it remains unclear whether this resemblance is attributable to shared environmental or genetic influences. In contrast, the heritability of the rest-EEG of the same group of twins was very high (Van Beijsterveldt et al., 1996).

The P300 has been proposed as genetic marker for alcoholism. In view of our failure to distinguish between shared environmental and genetic contributions to individual differences in P300 amplitude, care should be taken in using the P300 as a genetic marker.

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