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Genetic Correlation Between the P300 Event-Related Brain Potential and the EEG Power Spectrum

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Previous studies have demonstrated moderate heritability of the P300 component of event-related brain potentials (ERPs) and high heritability of background electroencephalogram (EEG) power spectrum. However, it is unclear whether EEG and ERPs are influenced by common or independent genetic factors. This study examined phenotypic and genetic correlations between EEG spectral power and P300 amplitude using data from 206 Dutch twin pairs, age 16 years. Multivariate genetic models (Cholesky decomposition) were fitted to the observed twin covariances using Mx software. In males, genetic correlations between P300 and EEG power measures were high (0.54–0.74); 30% of the total P300 variance could be explained by genetic factors influencing EEG delta power and 26% by P300-specific genetic factors (total heritability 56%). In females, 45% of P300 variance could be attributed to familial influences that were shared with the EEG. However, it was not possible to distinguish between the genetic versus shared environmental factors, consistent with previous analysis of P300 in this sample (van Beijsterveldt *et al.,* 1998). The results suggest that a substantial proportion of genetic influences on P300 amplitude can be explained by strong heritability of slow EEG rhythms contributing to P300.

KEY WORDS: EEG; ERP; P300; brain; electrophysiology; heritability.

INTRODUCTION

The P300 component of event-related brain potentials (ERPs) is typically elicited in simple discrimination "oddball" tasks when the subject is required to distinguish between frequent and rare stimuli presented in a random series, to respond to the rare ("target") stimulus, and to ignore the frequent stimulus (reviewed in Polich and Herbst, 2000). For ERP evaluation, fragments of the electroencephalogram (EEG) time-locked to the stimulus event are averaged across many (>20) trials in order to increase signal-to-noise ratio and to extract brain activity related to stimulus processing. Averaged waveforms obtained for the target stimulus typically contain a positive going potential with latency greater than 300 ms, which is referred to as P300 or P3. The P300 component is most commonly considered to be a manifestation of the central nervous system (CNS) activity that reflects attention to incoming stimulus information when memory representation of environment is updated (reviewed in Polich and Kok, 1995; Polich and Herbst, 2000). Because its amplitude and latency vary systematically as a function of task parameters, the P300 has been widely used in psychophysiological studies of information processing.

P300 amplitude appears to be diminished in a variety of neuropsychiatric disorders, most notably schizophrenia, alcoholism, and conduct disorder. Because the

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same deficit has also been found in nonaffected relatives of individuals with alcoholism and schizophrenia, reduced P300 components are often implicated in genetically transmitted neurobiological liability to these disorders and considered to be a neurophysiological marker of genetic risk (e.g., Begleiter and Porjesz, 1995; Carlson *et al.,* 1999; Hill *et al.,* 2000; Blackwood, 2000; Squires-Wheeler *et al.,* 1993; Polich and Herbst, 2000). P300 amplitude shows broad individual variability and good temporal stability, with a test-retest correlation of 0.6 (Segalowitz and Barnes, 1993). Twin and family studies have demonstrated significant genetic influences on P300, with heritability estimates ranging from 30% to 70%, depending on stimulus modality and task complexity (O'Connor *et al.,* 1994; Eischen and Polich, 1994; Katsanis *et al.,* 1997; van Beijsterveldt *et al.,* 1998; Almasy *et al.,* 1999).

Spontaneous (baseline) EEG is a complex continuous waveform consisting of superimposed oscillations at different frequencies, most of which are within the 1 to 30 Hz range. The amount of activity in different EEG frequency bands can be quantified using spectral analysis techniques. A number of twin and family studies have demonstrated high (60%–90%) heritability of the EEG spectral power measures and other characteristics (e.g., Vogel, 1970; Lykken *et al.,* 1974; Anokhin *et al.,* 1985; Eischen *et al.,* 1995; van Beijsterveldt *et al.,* 1996; also reviewed in van Beijsterveldt and Boomsma, 1994). In summary, previous studies, including analyses of the data used in this study (van Beijsterveldt *et al.,* 1996, 1998), have provided strong evidence for genetic influences on the spontaneous EEG and ERPs. However, little is known about the commonality of genetic factors influencing spontaneous EEG and ERPs.

A number of studies have shown that ERP amplitude is positively correlated with EEG spectral power both within and across subjects. Subjects with high-amplitude EEG variants showed greater amplitude of sensory evoked potentials (Vogel *et al.,* 1986). Between-subject correlations computed among P300 amplitude and EEG spectral band powers ranged from 0.3 to 0.6, were highest for low frequency EEG bands (delta and theta), and were consistent across different stimulus modalities and age groups (Intrilligator and Polich, 1994; Polich, 1997; Basar *et al.,* 1984). Theta and alpha power of the pre-stimulus and post-stimulus EEG showed significant correlations with the amplitude of averaged ERPs (Basar *et al.,* 1984; Jasiukaitis and Hakerem, 1988).

Possible mechanisms of the relationship between spontaneous EEG rhythms and the ERPs have been investigated in several studies. Livanov (1938) suggested that evoked potentials may result from superimposition and time-locking of spontaneous EEG rhythms. In a series of experimental studies, evoked potentials recorded from rabbit brain could be modeled as a sum of sine waves that were phase-locked to the stimulus onset. Frequencies and amplitudes of these sine waves corresponded to the dominant rhythms of spontaneous EEG recorded from the same brain area. The resulting simulated waveform showed a striking resemblance with evoked potentials elicited by light flashes in the same brain areas (Livanov, 1938). Other studies conducted both in animal and human subjects have provided further evidence supporting this view (Basar *et al.,* 1984; Basar-Eroglu *et al.,* 1992). A recent study using several experimental ERP paradigms has demonstrated that human P300 potential waveform is determined by the superimposition of EEG oscillatory responses at different frequency ranges (Karakas *et al.,* 2000a, 2000b). Specifically, delta and theta oscillations, taken together, explained most of the variance in the P300 component. Correlations between the actual ERP component amplitudes and those of the reconstructed components were close to 1. In another study, Klimesch *et al.* (2000) examined the relationship between the band power of single-trial evoked response and the P300 in a verbal memory task. Target words that elicited larger P300 components also produced an increase in induced delta and theta band power, suggesting functional relationship between P300 and low-frequency EEG oscillations. According to Klimesch *et al.* (2000), these induced oscillations may reflect hippocampal theta rhythm and associated inhibitory processes necessary for a highly selective memory processing. The relationship between P300 and EEG appears to be the strongest in the low frequency part of the EEG spectrum (delta and theta bands), although some studies have also found increased alpha band activity following the stimuli that elicited P300 (Yordanova and Kolev, 1998; Spencer and Polich, 1999).

Based on the evidence for statistical and functional relationship between P300 and low-frequency EEG components, it was hypothesized that individual variability of P300 and spontaneous EEG rhythms is influenced by common genetic factors. Specifically, one can expect that individuals with genetically determined high EEG amplitude may produce larger P300 response when challenged with a P300-eliciting task and, conversely, individuals with low voltage "desynchronized" EEG would produce smaller P300 components. If this hypothesis is true, then heritability of P300 can be at

least partially explained by genetic influences on baseline EEG.

Accordingly, the objective of the present study was to evaluate the extent to which P300 amplitude is influenced by the same genes that determine low-frequency EEG rhythms and, conversely, to determine whether there are also P300-specific genetic factors (i.e., genetic influences on P300 that are independent from genetic influences on the resting EEG). To address this aim, a conjoined multivariate genetic analysis of P300 amplitude and EEG spectral power measures was conducted using structural equation modeling techniques. This is the first report of genetic correlations between spontaneous and event-related brain activity (EEG and ERPs, respectively).

METHODS

Subjects

The subjects were 213 pairs of 16-year-old Dutch twins, including 39 monozygotic male (MZM), 36 dizygotic male (DZM), 52 monozygotic female (MZF), 38 dizygotic female (DZF), and 48 opposite sex dizygotic (OS) pairs, who were tested in the Psychophysiology Laboratory at the Free University of Amsterdam, The Netherlands. The subjects were drawn from a community-based sample of subjects participating in a large epidemiological study of health-related behaviors. Zygosity was determined by genotyping for 114 same-sex twins and by a questionnaire completed by the mother of the twins. Agreement between zygosity diagnoses based on questionnaire and genotyping was 95%.

ERP and EEG Recording and Evaluation

The recording of the ERPs and spontaneous EEG was performed consecutively during a single laboratory session, with ERP experiment preceding the resting EEG recording. Brain electric activity was recorded using Electro-cap with electrode placement according to the International 10–20 System. Linked earlobes were used as references according to the method described in Pivik *et al.* (1993) to prevent imbalances in electrode impedance. Electrode impedance was kept below 5 kOhm, the time constant was 5 s, the low-pass filter was set at 35 Hz cut-off, and the sampling rate was 250 Hz. To monitor horizontal eye movements tin electrodes were placed at the outer canthus of each eye. Vertical eye movements were recorded using intra- and supra-orbital electrodes, positioned in line with the pupil of the left eye. The vertical electro-oculogram (EOG) was subsequently used for the elimination of eye movement-related artifacts from the EEG.

ERPs were recorded during a visual oddball task. Twenty-five target stimuli and 100 non-target stimuli were presented in a pseudo-random order, with stimulus duration of 100 ms and variable inter-stimulus intervals (1.5–2 s, mean 1.75 s). The stimuli were white line drawings of cats and dogs presented against a black background. The stimulus build-up time was less than 20 ms. During the interstimulus intervals, the subjects were asked to fixate on a square shown in the center of the monitor. The subjects were instructed to silently count the infrequent (target) stimuli and to report the result after the task.

Eyeblink artifacts were removed off-line using the "matched filter" procedure for EOG-EEG transfer correction in the frequency domain (Brillinger, 1975). In this procedure, a Fast Fourier Transformation (FFT) is applied to all EEG and EOG time series to convert the signals from the time domain into the frequency domain. The resulting gain and phase functions are used to determine the attenuation and delay between the two signals. The EEG periodograms were corrected by subtracting the weighted EOG periodogram from the EEG periodogram for each epoch. Latency jitter was reduced by means of a Woody filter. The P300 peak was automatically detected in the latency window of 300 to 600 ms, and its amplitude was scored relative to 100 ms pre-stimulus baseline (for further details see previous publications involving these data: van Beijsterveldt *et al.,* 1996, 1998).

After the ERP experiment, 3 min of the resting EEG were recorded with eyes closed. At least thirty 2-second artifact-free EEG epochs were subjected to FFT and broadband spectral power was assessed in the main frequency bands: delta (1.5–3.5 Hz), theta. (4–7.5 Hz) alpha (8–12.5 Hz), and beta (13–25 Hz). Spectral power measures were log-transformed (base 10) to increase the normality of the distribution. For the analyses reported here, EEG and ERP data from central, parietal, and occipital scalp sites in both hemispheres (C3, C4, P3, P4, 01, 02) were used. These sites were selected because both EEG and ERP data from these scalp locations were available, and because visual P300 recorded in oddball tasks is most pronounced and can be evaluated reliably in central and posterior brain areas. Preliminary analyses of this dataset have shown that these six electrodes provide a good global measure of P300 amplitude and adding further electrodes does not lead to substantial gain of information. For exam-

ple, global measure computed using larger set of electrodes (after adding midline electrodes Cz and Pz) correlated at 0.99 with the global measure obtained from the six electrodes.

EEG data were available for all 213 pairs, whereas the ERP data were available from 206 pairs due to exclusion of ERP recordings with technical artifacts. Therefore, analyses involving P300 are based on a slightly smaller number of pairs (37, 35, 50, 37, and 47 for MZM, DZM, MZF, DZF, and OS zygosity groups, respectively).

Data Analysis

Data reduction was performed by computing individual scores on the first unrotated principal component extracted from inter-correlations of the P3 amplitudes measured at the six scalp locations. Then, a similar data reduction procedure was performed separately for each three sets of EEG band powers (delta, theta, and alpha power, each measured at six scalp locations). For example, in the case of delta power, the correlations among six scalp locations were computed (all of which were >0.75) and the first principal component was extracted, which explained 88.3% of the total variance of the original six variables. For each individual subject, factor scores for the first principal components were computed as a linear combination of the standardized values (z-scores) of the six original variables that were weighted with coefficients corresponding to their factor loadings normalized by the eigenvalue. The resulting component scores represented global measures of EEG power in the three frequency bands and P300 amplitude and were used for multivariate genetic analysis. The total number of variables included in subsequent genetic analysis was thus reduced from 24 to 4.

Genetic and environmental sources of covariance among these measures were examined using multivariate structural equation modeling techniques. Basic issues of twin methodology and application of the model fitting approach to twin data are discussed in Plomin *et al.* (2001); a more detailed and technical description of genetic model fitting can be found in Neale and Cardon (1992). It can be assumed that covariation between two given variables can arise from the following sources: additive genetic influences (A), shared environment (environmental influences shared by members of a twin pair), and non-shared or individual-specific environment (E). These sources of covariation between two or more variables can be investigated using joint analysis of different types of correlations available from twin data: (1) within-twin, cross-trait correlation (phenotypic correlation between two traits computed across subjects); (2) cross-twin, within-trait correlation (within-pair twin resemblance on a single variable), and (3) cross-twin, cross-trait correlation (e.g., EEG theta power measured in one member of the twin pair and P300 amplitude measured in the other twin).

Variance and covariance matrices among four measures of brain activity were computed separately for each of the five zygosity groups, and structural equation models were fitted to these data using the Mx software (Neale, 1999). Model fitting included multivariate Cholesky models, as well as common-factor models (Neale and Cardon, 1992). The analyses started with the full model that included additive genetic, shared environmental, and nonshared (individual) environmental paths to each of the four variables included in the model. Then, different submodels were tested by dropping individual paths from the full model. The goodness-of-fit of reduced models compared with the full model was assessed using the χ^2 difference between the full and reduced models, taking into account the change in the number of degrees of freedom as parameters were dropped. If dropping a specific genetic or environmental path produced a significant worsening of fit, this path was considered significant and retained in the model. When dropping a path resulted in a significant improvement of fit (indicated by a significant reduction in χ^2), the path was dropped. Models that did not differ significantly by χ^2 difference criterion were compared using Akaike's information criterion (AIC, computed as $\chi^2 - 2df$), which provides a combined measure of goodness-of-fit and parsimony of a given model at the same time (Akaike, 1987). A model with the-lowest AIC (e.g., largest negative) was considered the best fitting. Next, based on the best-fitting model, the proportion of variance in P300 amplitude that is shared with EEG power was estimated. Due to the relatively large number of models tested, only the best fitting model is presented in detail.

RESULTS

Phenotypic Correlations and Data Reduction

The results of the data reduction are presented in Table I. Principal component analysis was performed separately for the four sets of variables, each representing measurements taken at the six recording sites.

Table I. Data Reduction: Principal Component Analysis of EEG and ERP Measures From Different Scalp Locations[a]

Set of variables for which a factor score was computed	% Variance accounted for by the first principal component[b]	Range of intercorrelations[c]
P300 amplitude	75	.52–.88
Delta power (1.5–3.5 Hz)	88	.75–.96
Theta power (4–7.5 Hz)	92	.82–.98
Alpha power (8–12.5 Hz)	90	.78–.96

[a] For each set of variables measurements taken at six scalp locations: C3, C4, P3, P4, O1, and O2 (left and right central, left and right parietal, and left and right occipital, respectively) were used to generate factor scores. Data reduction was performed within each of these sets independently, and individual factor scores were computed for each set, e.g., P300 amplitude factor, delta power factor, etc.
[b] Percent of the total variance within each set of variables accounted for by the corresponding first principal component.
[c] The range of correlations among variables within each set. A total of 15 correlations (all possible pairings of the six scalp locations) were computed for each set. All correlations are significant at $p < 0.001$ level.

Within each set, intercorrelations among scalp sites were all positive and highly significant. The first unrotated principle components accounted from 75% to 92% of the total variance within each set of measurements. Individual scores on the first components were computed and used in further analyses as global measures of EEG frequency bands power and P300 amplitude.

The P300 amplitude factor correlated significantly with spectral power factors across different EEG frequency bands, most notably in delta and theta. Phenotypic correlations between EEG factors and the P300 factor were within the 0.3 to 0.6 range (Table II).

Twin Correlations and Cross-Correlations

Twin correlations and cross-correlations between P300 and EEG power are presented in Table III. MZ correlations for EEG power measures were very high (most of them >0.90), whereas DZ correlations were half as large, suggesting very high heritability of factor scores. This result is consistent with previous analysis of this dataset that showed high heritability of EEG measures at individual scalp locations (van Beijsterveldt *et al.,* 1996). Twin correlations for the P300 factor score were generally lower. Moreover, higher DZ than MZ correlation was observed in females, consistent with the previous analysis of P300 at individual scalp locations which revealed greater DZ than MZ correlations for some of the P300 measures (van Beijsterveldt *et al.,* 1998).

Cross-correlations between P300 factor and each of the EEG power factors ranged from 0.32 to 0.55 in MZ twins (all significant) and from 0 to 0.37 in DZ twins, suggesting a strong contribution of genetic

Table II. Phenotypic Correlations Among P300 Amplitude and EEG Power in Different Frequency Bands[a]

	P300 amplitude	EEG delta	EEG theta	EEG alpha
	Females			
P300 amplitude	—	.56	.51	.36
EEG delta	.60	—	.85	.66
EEG theta	.49	.85	—	.77
EEG alpha	.40	.63	.79	—
	Males			

[a] All correlations are significant at $p < 0.001$ level. Correlations were computed across subjects separately for males (lower triangle) and females (upper triangle).

Table III. Twin Correlations and Cross-Correlations for P300 Amplitude and EEG Frequency Bands Power Measures[a]

	Zygosity				
	MZM 37 pairs	DZM 35 pairs	MZF 50 pairs	DZF 37 pairs	DZOS 47 pairs
Intrapair correlations[b]					
P300	.56**	.25	.38**	.60**	−.12
EEG delta	.91**	.37*	.81**	.60**	.37*
EEG theta	.94**	.50**	.90**	.54**	.36*
EEG alpha	.96**	.46**	.94**	.43**	.44**
Cross-correlations[c]					
P300 and EEG delta	.50**	.27	.55**	.37*	.02
P300 and EEG theta	.41*	.21	.55**	.36*	.03
P300 and EEG alpha	.38*	.19	.32*	.35*	−.04

[a] Significance: *$p < 0.05$; **$p < 0.01$. Analyses involving EEG variables only are based on slightly larger number of pairs (39, 36, 52, 38, and 48 for MZM, DZM, MZF, DZF, and DZOS, respectively).

[b] Cross-twin, within-trait correlations, e.g., correlation between P300 amplitude values in the members of a twin pair (computed across pairs). This correlation shows the degree of within-pair twin resemblance with respect to a given trait.

[c] Cross-twin, cross-trait correlations, e.g., correlation between P300 in twin 1 and EEG delta in twin 2 and the correlation between EEG delta in twin 1 and P300 in twin 2. For each pair of traits, the average of two reciprocal cross-correlations is presented.

factors to the observed phenotypic covariances between EEG and P300. Moreover, the magnitude of MZ pair cross-correlations was very close to that of the corresponding phenotypic correlations within individuals (0.37 to 0.54, Table II), suggesting that the observed phenotypic covariances are largely determined by shared familial factors.

Multivariate Genetic Analysis

The best fitting Cholesky model (Fig. 1) showed better fit than the best fitting common factor model, so only the former is reported here in detail (Cholesky: $\chi^2 = 149.0$; $df = 144$, $p = 0.37$, AIC $= -139.1$, Common-Factor: $\chi^2 = 175.9$; $df = 141$, $p = 0.02$, AIC $= -106.1$). The best fitting Cholesky model included A and E paths in males and A, C, and E paths in females, where A is additive genetic, C is shared environmental, and E is nonshared (individual-specific) environmental path. In this reduced model, all shared environmental paths could be dropped in males. However, in females, shared environment could not be dropped without a significant deterioration of fit. In males, neither of the genetic paths to P300 could be dropped without significant loss of fit. In particular, dropping the genetic path from EEG delta power to P300 led to an increase in the χ^2 from 149.0 to 192.4, with the difference ($\Delta\chi^2_1 = 43.3$) being significant ($p < 0.01$). This analysis, which represented a direct test of the main hypothesis of this study, has demonstrated that genetic influences common with the EEG play significant role in the determination of P300 amplitude. Dropping the P300-specific genetic path also led to significant worsening of fit, so this path was retained in the model. In contrast, in females, dropping genetic paths to P300 resulted in only insignificant reduction of fit. Even when the path from EEG delta power to P300 was retained in the best fitting model, it accounted only for 3% of the phenotypic variance of P300 amplitude in females.

Genetic correlations estimated between P300 and EEG power measures ranged from 0.51 to 0.73 in males and could not be reliably estimated in females due to the lack of significant genetic paths to P300. The results also suggested that most of the observed phenotypic covariance between EEG power measures and P300 (>80%) was due to common genetic factors in males and common shared environmental influences in females. Exploratory analyses performed using EEG and P300 measures at individual scalp locations (not

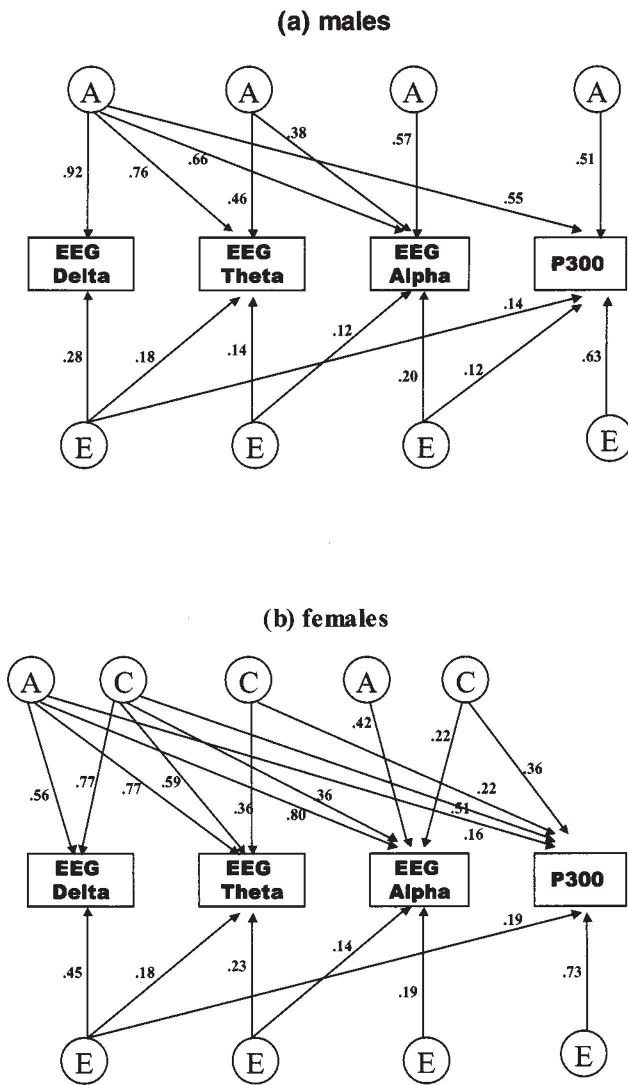

Fig. 1. Best fitting quadrivariate Cholesky decomposition model for EEG power spectrum components and P300 amplitude: (a) males; (b) females. Unstandardized parameter estimates are shown with each path. A: additive genetic factors; C: shared environmental factors; E: non-shared (individual) environmental factors. Goodness-of-fit statistics are presented in Table II.

shown here) produced similar results for the left and right hemisphere.

Fig. 2 summarizes the sources of individual variability in P300 amplitude estimated based on the best fitting quadrivariate Cholesky decomposition model. It should be noted that in females the genetic variance component is shown for comparison only, since it could be dropped without significant change in the goodness of fit.

DISCUSSION

The results suggest a substantial overlap between genetic influences on P300 amplitude and resting EEG in males, thus supporting the main hypothesis of this study that interindividual variability in P300 amplitude is largely determined by genetically transmitted individual differences in EEG spectral power. Genetic factors specific to P300 accounted for only 26% of the total P300 variance in males. The present analysis suggests that familial influences on P300 in females are common with the EEG spectral power, because all P300-specific familial influences, including both genetic and shared environmental paths, could be dropped without significant loss of fit. However, analyses could not reliably distinguish between genetic and shared environmental sources of P300 and EEG covariances in female twins. This result is consistent with previous analysis of the same dataset (van Beijsterveldt *et al.,* 1998), which demonstrated significant familial transmission of P300 amplitude in females but was unable to distinguish between genetic and environmental transmission. Thus, genetic influences on P300 amplitude in females, if any, also appear to be mediated by baseline EEG power.

It remains unclear, however, why shared environmental factors appear to be more important for the determination of ERP amplitude and low-frequency EEG activity in females. Inspection of twin correlations (Table III) suggests that both reduced MZ correlations and elevated DZ correlations in females compared to males may contribute to this effect. The present findings raise a possibility that shared familial environment may play a greater role in certain aspects of neurocognitive development in adolescent girls compared with boys. This possibility will be tested in the ongoing follow-up study of the same twin sample. If sex differences in genetic and environmental architecture persist in the older age, assessment of familial environments and within-pair interactions in male and female twins (e.g., diet, exercise, and other aspects of lifestyle) could help to elucidate familial factors that might influence twin resemblance with respect to characteristics of neurocognitive functioning.

The results of the present study are in very good agreement with increasing evidence that ERPs are generated by stimulus-induced synchronization of spontaneous EEG rhythms, especially in the low-frequency range—delta and theta (e.g., Klimesch *et al.,* 2000; Karakas *et al.,* 2000). The present study suggests that this relationship also holds for individual differences:

Table IV. Genetic Correlations Among P300 Amplitude and EEG Frequency Bands Power Measures[a]

	P300 amplitude	EEG delta	EEG theta	EEG alpha
P300 amplitude	—	—	—	—
EEG delta	.74	—	.99	.72
EEG theta	.63	.87	—	.89
EEG alpha	.54	.71	.81	—

[a] Lower triangle of the correlation matrix: males; upper triangle: females. Genetic correlations involving P300 are not shown for females, because genetic paths to P300 accounted only for a very small portion of P300 variance (up to 5%) and could be dropped without significant reduction in fit.

Those individuals who show abundant slow-wave activity in their background resting EEG tend to exhibit larger P300 components. Because the amount of activity in the lower frequency range is highly heritable (e.g., van Beijsterveldt *et al.,* 1996, and the present analysis), some of the observed genetic variation in P300 amplitude may simply be a byproduct of heritable individual differences in EEG spectral power. It should be noted that the resting (background) EEG represents a "baseline" mode of brain activity that exists

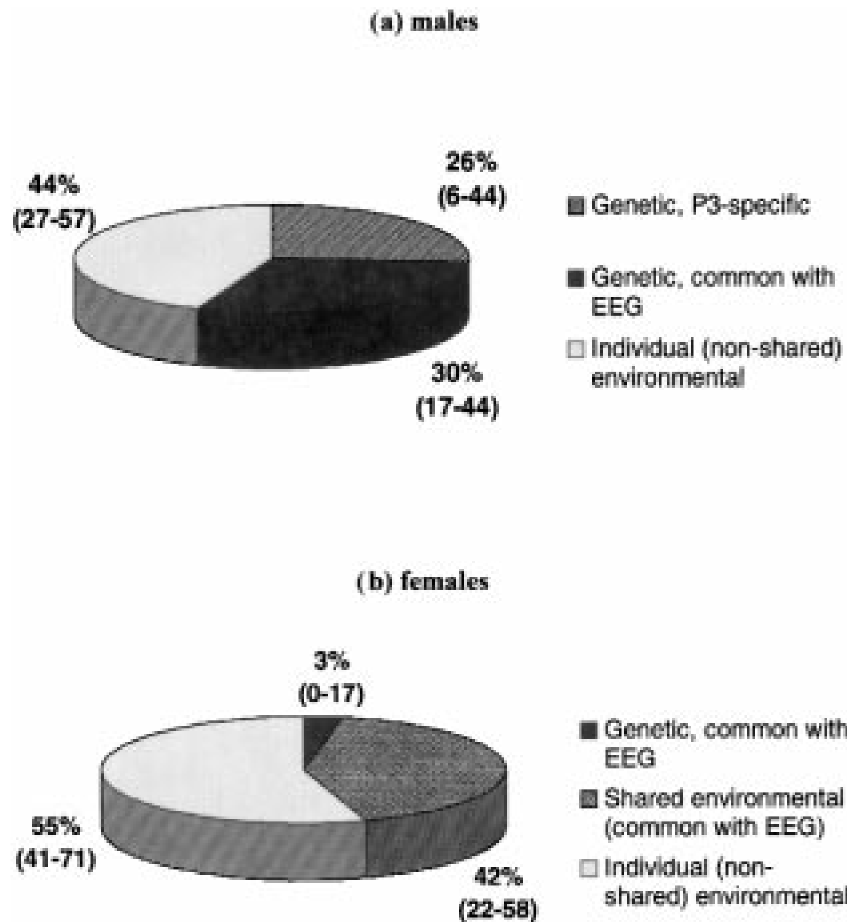

Fig. 2. Sources of individual variability in P300 amplitude estimated based on the quadrivariate Cholesky decomposition model. The diagrams show variance component estimates (95% confidence intervals are indicated in brackets). Note that genetic variance component in females, but not in males, could be dropped without significant change in the goodness of fit.

prior to any task and can therefore be considered as primary phenomenon in relation to the ERPs that represent transient phasic changes of the ongoing EEG systematically related to specific events in a specific task context. Consequently, a causal relationship between EEG and ERP can only be unidirectional, i.e., characteristics of background EEG can determine ERP characteristics, but not vice versa.

The present study suggests that individual differences in visual P300 and, perhaps, other types of the ERPs should be interpreted with caution, especially in the context of genetic high-risk studies such as family studies of schizophrenia and alcoholism. It is often assumed that low P300 amplitude observed in some individuals may indicate an underlying neurocognitive deficit. This assumption is largely based on evidence from psychophysiological studies showing systematic variation of P300 amplitude as a function of cognitive processing demands that can be manipulated experimentally by changing task parameters. It is important, however, that these well-established relationships between P300 and cognition have been obtained using *within-subject* comparisons and their functional interpretation cannot be simply generalized to *between-subject* trait-like differences in P300 amplitude. The present results suggest that substantial proportion of inter-individual variability in P300 amplitude is confounded by genetically determined variation in background EEG spectral power and, therefore, reflects some baseline characteristics of brain neurophysiology rather than differences in cognitive processing. There is also a possibility that some of the genetic influences on EEG and ERP amplitude may be mediated by biological and behavioral factors that are not directly related to neurocognitive functioning, but still might affect P300 and EEG characteristics. Such factors may include skull thickness, overall cortical size, physical exercise, etc. (e.g., Polich and Kok, 1995; Polich and Lardon, 1997). Still, it is important to note that in males evidence also exists for modest but significant P300-specific genetic influences that are independent of baseline EEG.

The results of the present study have important practical implications for studies focusing on trait-like variability in ERP amplitude. If the primary focus of the study is on individual differences in task related cognitive processing, then ERP-specific variance unconfounded by baseline EEG differences needs to be isolated. Therefore, it can be recommended that baseline EEG characteristics be included as covariates in analyses concerned with inter-individual differences in ERP amplitude. For example, in familial risk studies of psychopathology, including alcoholism, individual P300 amplitude values can be corrected for between-subject differences in baseline EEG spectrum. Residualized P300 values may prove more informative for the assessment of individual differences in cognitive processing that might be relevant to the cause of the disorder. The results of the present study suggest that after such an adjustment there is a significant, although modest, residual genetic variance in P300 amplitude, albeit only in males.

In conclusion, the present study provides evidence that genetic influences on the P300 ERP are largely confounded by high heritability of baseline EEG. A conjoined analysis of EEG and ERPs is recommended in studies focusing on genetic variation in the ERPs.

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