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Genetic Contribution to the P3 in Young and Middle-Aged Adults

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Previous studies in young and adolescent twins suggested substantial genetic contributions to the amplitude and latency of the P3 evoked by targets in an oddball paradigm. Here we examined whether these findings can be generalized to adult samples. A total of 651 twins and siblings from 292 families participated in a visual oddball task. In half of the subjects the age centered around 26 (young adult cohort), in the other half the age centered around 49 (middle-aged adult cohort). P3 peak amplitude and latency were scored for 3 midline leads Pz, Cz, and Fz. No cohort differences in heritability were found. P3 amplitude (~50%) and latency (~45%) were moderately heritable for the 3 leads. A single genetic factor influenced latency at all electrodes, suggesting a single P3 timing mechanism. Specific genetic factors influenced amplitude at each lead, suggesting local modulation of the P3 once triggered. Genetic analysis of the full event-related potential waveform showed that P3 heritability barely changes from about 100 ms before to 100 ms after the peak. Age differences are restricted to differences in means and variances, but the proportion of genetic variance as part of the total variance of midline P3 amplitude and latency does not change from young to middle-aged adulthood.

The P3(00) event-related potential (ERP) is widely used to examine normal variation in cognitive function in healthy individuals as well as disturbed cognition in various clinical groups. By interspersing a low probability target stimulus (the oddball) into a sequence of a frequent nontarget stimulus, Sutton et al. (1965) and Desmedt et al. (1965) were first to elicit the P3. This 'classical' P3 component (or P3b), which peaks 300 to 600 ms after the target stimulus in such oddball paradigms, has a parietal distribution on the scalp and has been linked to the cognitive processes of context updating, context closure, and event categorization (Dien et al., 2004; Donchin & Coles, 1988; Kok, 2001; Verleger, 1988). For the P3 to occur it is necessary that the stimulus is relevant to the task at hand, and that the subject is conscious of this task relevancy: on missed target trials, such as in experiments on the attentional blink, the P3 is absent (Vogel & Luck, 2002; Vogel et al., 1998).

Like other ERP components, the P3 is characterized by large individual differences. These may be meaningful as markers of differences in mental health (Polich & Herbst, 2000). In normal aging, P3 latency has been found to increase and P3 amplitude to decrease as cognitive processing slows down, although the power of the P3 to differentiate between normal aging and dementia due to neural degenerative disorders such as Alzheimer's disease is inconclusive (e.g., Cohen et al., 1995; Pfefferbaum et al., 1990; Polich, 1998). Reduced P3 amplitude is also found in a variety of psychiatric and behavioral disorders, most notably schizophrenia (Levit et al., 1973; Verleger & Cohen, 1978) and alcoholism (e.g., Porjesz et al., 1980; Begleiter et al., 1984). The reduction in P3 amplitude is thought to reflect a genetic predisposition for these disorders rather than a mere functional consequence, because it is also found in unaffected relatives (Begleiter et al., 1984; Blackwood, 2000; Blackwood et al., 2001; Elmasian et al., 1982; Polich et al., 1994; Porjesz & Begleiter, 1990; Turetsky et al., 2000). A genetic influence on P3 amplitude and latency is supported by twin and family studies which indicates moderate to high heritability for both (for reviews see van Beijsterveldt & Boomsma, 1994; van Beijsterveldt & van Baal, 2002). However, the twin studies that have investigated P3 heritability investigated children or adolescent samples (Carlson et al., 2002; Katsanis et al., 1997; O'Connor et al., 1994; van Baal et al., 1998; van Beijsterveldt et al., 2001). To our knowledge, only one adult twin study with sufficient power to discriminate genetic from common environmental factors has looked at the P3 (Anokhin et al., 2004). Using a go/no-go task rather than an oddball task, P3 heritability was comparable (41% and 58% for go and no-go P3 respectively) to that in adolescent

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twins. However, the sample included only young adults with a maximum age of 28. In addition, the use of a go/no-go task may have invoked a P3 which contains more of the frontocentral P3a than the parietal P3b component in comparison to the oddball task (Dien et al., 2004).

Here we examined whether the heritability estimates for the P3 found in the oddball task at young ages can be generalized to adults. Because the P3 may reflect the admixture of several different processes (Kok, 2001) along the anterior–posterior axis of the brain (Bledowski, Prvulovic, Goebel, et al., 2004; Bledowski, Prvulovic, Hoechstetter, et al., 2004) we examined whether the genetic variance underlying frontal, central, and parietal midline P3 reflected a common or separate underlying set of genes as an indication of shared underlying neurobiology. In keeping with previous studies, heritability of the amplitude of the P3 was first established at its peak latency. Second, as the components of the late positive complex may each have slightly different time frames, we allowed the genetic underpinnings to vary within the time course of the P3 by applying our genetic analysis to the full ERP.

Method

Subjects

Subjects were recruited from the Netherlands Twin Registry (Boomsma, Vink, et al., 2002) as part of a large project on the genetics of cognition and adult brain functioning (Posthuma et al., 2001). Adult twins and their nontwin siblings were invited to participate. A total of 760 family members from 309 twin families participated in the study, and EEG data were available from 732 subjects from 305 families. Participating families consisted of one to seven siblings (including twins). For this study, we restricted the age range to young and middle-aged adulthood: only subjects in the range of 20 to 65 years were included. This resulted in a sample of 715 subjects from 303 families. The sample consisted of two age cohorts: a younger cohort (46.0% male, mean 26.5 years, *SD* 3.7) and a middle-aged cohort (41.3% male, mean 48.8 years, *SD* 6.2). Data from these cohorts will be analyzed separately. Cohort inclusion was determined on a per family basis and by the age of the twins on the day of measurement with the cut-off at 35 years. This resulted in two siblings younger than 35 being included in the middle-aged cohort on the basis of twins being over 35, and 11 siblings older than 35 being included in the young adult cohort on the basis of the twins being under 35.

Procedure

The study received prior approval by the institutional review body and ethical committee of the Vrije Universiteit medical centre. Informed consent was obtained from each subject. They were asked to participate in a 4.5-hour testing protocol. During one part of the experimental protocol, psychometric intelligence, inspection time, and reaction times were assessed. During the other, the subjects performed, among others, a visual oddball task. The order of the two parts of the protocol was randomized across family members. Consequently, half of EEG registration sessions were during morning hours, and half were in the afternoon.

During EEG recording subjects were seated in a comfortable reclining chair in a dimly lit, sound attenuated and electromagnetically shielded room. They were instructed to relax, and to minimize blinking, eye and body movement.

Stimuli

The oddball stimuli were white-on-black line drawings of cats and dogs by Snodgrass and Vanderwart (1980), balanced in the amount of physical stimulation. The dog stimuli were shown frequently (100/125) and were the standards. The cat stimuli were shown only infrequently (25/125) and were the targets. A stimulus set with an identical order of stimuli and intertrial intervals was presented to all subjects. Dog and cat stimuli were generated in an unpredictable order and trial duration varied randomly from 1500 to 2000 ms. Stimulus duration was 100 ms. Before the task, one example of each stimulus was presented. Subjects were instructed to silently count the number of targets (cats) shown on the computer screen positioned 80 cm in front of them. This distance was verified by use of a rod. The number of counted targets reported was recorded for each subject.

EEG registration

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 (TMS, Enschede, the Netherlands) for 612 subjects and Neuroscan SynAmps 5083 amplifier (Compumedics, El Paso, TX) for 103 subjects. Signals were continuously represented online on a Nec multisync 17" computer screen using Poly 5.0 software or Neuroscan Acquire 4.2 (Compumedics, El Paso, TX). Standard 10-20 positions were F7, F3, F1, Fz, F2, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 and O2 (American EEG Society, 1991; Jasper, 1958). For Neuroscan subjects Fp1, Fp2, and Oz were also included. The vertical electro-oculogram (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 of the left eye and 1 cm right of 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, digitized at 250 Hz and stored for offline processing. Amplifier filter settings for TMS were a single order FIR band-pass filter with cut-off

frequencies of 0.05 Hz and 30.0 Hz. Neuroscan filter settings were a low-pass filter at 50.0 Hz and no high pass filtering. Strong DC shifts were manually reset before the start of the experiment.

Data Processing

The three midline leads Pz, Cz, and Fz were selected for further analysis. The signals were recalculated with averaged earlobes as reference and analyzed using Neuroscan Edit (Compumedics, El Paso, TX). Next, if the signals were absent or the signals were deemed extremely noisy upon visual inspection, the subject was excluded from further analysis. This resulted in the removal of 26 subjects. Signals from all leads were then reviewed for artifactual episodes (swallowing, muscle artifacts, eye movements (not blinks), and technical problems such as clipping). These episodes were removed and excluded from the analyses. Next, blink artifact reduction was performed following the procedure introduced by Semlitsch et al. (1986). Epochs were created from 100 ms prestimulus up to 700 ms poststimulus with baseline offset correction including only epochs that did not overlap with artifactual episodes. Ten subjects with less than 15 valid epochs in the target condition were excluded from further analysis for both target and nontarget conditions. One subject was excluded because she had counted nontargets instead of targets. The P3 peak amplitude and latency were extracted from each subject's average waveform for leads Fz, Cz and Pz. The time window for peak picking was determined by inspecting the histograms for latency scores. Both the lower and upper bounds of the window were adjusted to create a maximally normal distribution of latency scores across the three leads. The window was thus set from 290 to 590 ms poststimulus. Lower values of the lower bound resulted in a clear second peak in the histogram of latency scores on the left side of the mean that most likely reflected the erroneous picking of a P2 peak in some of the subjects. Adjusting the upper bound did not critically alter peak-picking scores as shown by the latency histograms. Visual checking confirmed that the peak was correctly chosen. Subjects with no clear peak due to either multiple peaks or very low ERP amplitude on each lead were set to missing for that particular lead. Two peaks close in latency were not considered incorrect, and the larger of the two peaks was chosen.

Genetic Analyses

Resemblance (covariance) in ERP traits between twins and siblings derive from genetic relatedness or shared environmental influences (Falconer & Mackay, 1996). If the correlation between dizygotic (DZ) twins or siblings, who share on average 50% of their genetic make-up, is half the correlation between monozygotic (MZ) twins, who are genetically identical, this is seen as evidence for additive genetic influences (A). If the correlation between DZ twins or siblings is less than half the correlation between MZ twins this is seen as evidence for dominant (nonadditive) genetic influences (D). If the correlations between MZ and DZ twins/siblings are comparable and nonzero this is evidence for shared environmental influences (C). If the correlation between MZ twins is not unity this is evidence for environmental effects unique to each individual (E). By comparing MZ and DZ/sibling correlations, using structural equation modeling as implemented in, for example, Mx (Neale, 2004), we can obtain maximum likelihood estimates of the relative contributions of each of these factors to the total trait variance. Heritability is defined as the proportional contribution of genetic effects (A + D) to the total variance (A + C + D + E). In a twin-sibling design, however, the effects of both C and D cannot be estimated simultaneously. The relative size of the DZ/sibling correlation guides which is selected. If

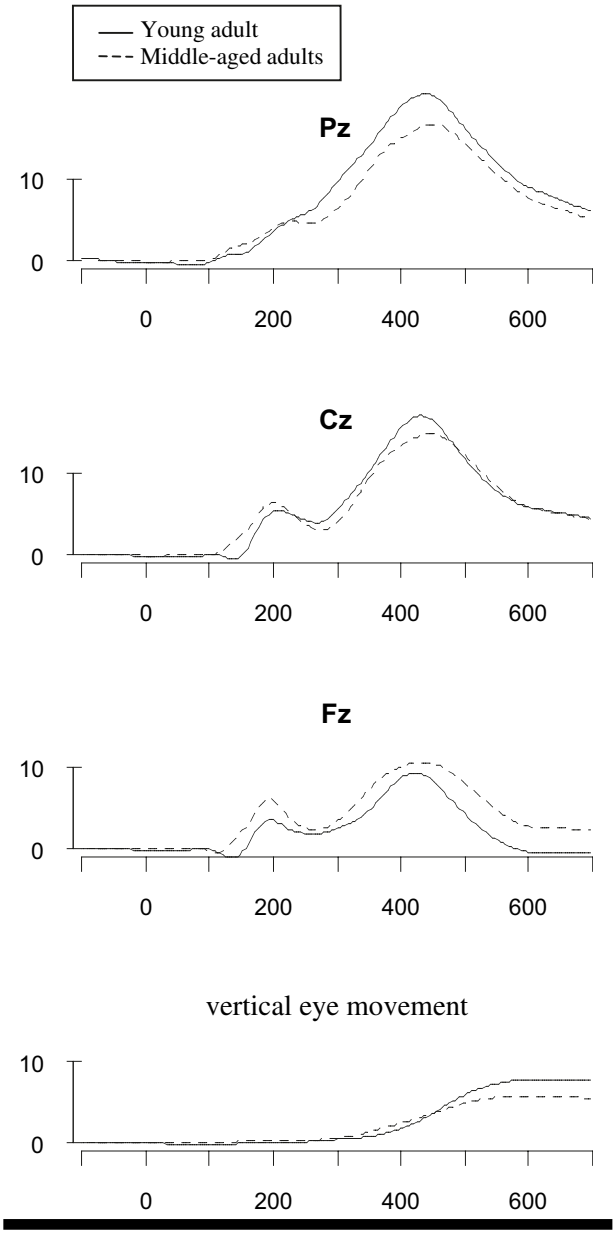

Figure 1
Fz, Cz, and Pz grand average waves for each cohort.

Table 1

Number of Families Split by Composition, Cohort, and Zygosity

Family composition[a]	Families with an MZ twin	Families with a DZ twin	Total
	Young cohort		
Both twins only	35	36	71
Both twins + 1 sibling	12	21	33
Both twins + 2 or more siblings	4	4	8
One twin only[b]	4	7	11
One twin + 1 sibling	5	10	15
One twin + 2 or more siblings	1	1	2
1 sibling[b]	2	4	6
2 or more siblings	1	0	1
Total	64	83	147
Family composition[a]	Families with an MZ twin	Families with a DZ twin	Total
	Middle-aged cohort		
Both twins only	31	39	70
Both twins + 1 sibling	19	13	32
Both twins + 2 or more siblings	3	2	5
One twin only[b]	11	9	20
One twin + 1 sibling	3	4	7
One twin + 2 or more siblings	1	4	5
1 sibling[b]	2	3	5
2 or more siblings	1	0	1
Total	71	74	145

Note: [a]Family composition was based on the participating offspring only. For example, a family with 'both twins only' could consist of more than two children, but these did not participate in the EEG experiment.
[b]Families with only one twin or only one sibling cannot contribute to the estimation of sibling covariance, but are retained to improve the estimation of means and variances.

the DZ/sibling correlation is less than half the MZ correlation, then D is modeled. If it is more than half the MZ correlation, C is modeled. For more information on genetic modeling we refer to Boomsma, Busjahn, et al. (2002) and Posthuma et al. (2003).

For the peak latency and amplitude at peak latency we used a multivariate approach that looked at the P3 at multiple leads across the scalp simultaneously. This multivariate genetic analysis can be used to detect the degree of overlap in the genetic and environmental factors influencing each of the traits (Posthuma et al., 2003). For this study, we specified three genetic and three unique environmental factors that could account for P3 amplitude at the Pz, Cz, and Fz leads following a Cholesky decomposition of the genetic variance. We then restricted the model by reducing the number of genetic factors. This multivariate analysis was then repeated for P3 latency.

Finally, for each lead separately, we tested heritability of the amplitudes along the full P3 waveform by repeatedly performing a univariate genetic analysis on the amplitude at each time point. Because the amplitude at a fixed time-point is confounded with the latency of the P3 wave, we aligned the P3 waveform to individual peak latency and selected only the amplitudes in a time window from 150 ms before to 150 ms after peak latency.

Due to the large sample size and multiple tests all statistical testing was performed against a significance level of $\alpha = .01$.

Results

After EEG data cleaning and visual inspection 673 subjects from 296 families had sufficient error free data on at least one lead for genetic analyses. On average, 2.3 participants per family participated. The vast majority of 591 subjects reported the correct number of counted targets (25), 60 subjects (32 young adult, 28 middle-aged) had miscounted on a single trial, and 22 subjects miscounted on two or more trials. The latter subjects were removed from further EEG analyses. For the final sample of 651 subjects, Table 1 shows the frequency of families grouped by zygosity of the twin probands, the number of participating twins, and the number of participating siblings.

Effects of Cohort and Sex on the Means

Table 2 shows Fz, Cz, and Pz amplitude and latency for each of the sex by age cohort groups. The last two columns show the mean differences between the sex groups collapsed over age cohort and cohort differences collapsed over the sexes. Structural equation modeling software package Mx was used to test significance of these differences, which allowed familial

Table 2
P3 Amplitude and Latency Descriptives and Effects of Sex and Cohort

	Cohort													
	Young						Middle-aged						Group differences[a]	
	Female			Male			Female			Male				
	N	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	Sex[b]	Cohort[c]
Amplitude														
Fz	170	12.79	5.92	138	10.62	5.79	177	13.61	4.97	124	12.23	4.40	1.83***	–1.23*
Cz	173	20.83	7.19	149	16.99	6.58	182	17.71	5.78	126	16.54	5.23	2.45***	1.82***
Pz	178	24.56	6.68	146	19.90	6.64	181	19.74	5.57	130	17.50	4.72	3.37***	3.66***
Latency														
Fz	170	418.3	40.3	138	425.7	40.7	177	432.5	50.6	124	424.3	51.6	0.48	–7.52*
Cz	173	429.2	37.9	149	435.7	38.6	182	444.9	50.6	126	436.2	45.3	1.26	–9.14**
Pz	178	432.1	42.0	146	439.3	41.8	181	443.7	53.2	130	438.5	49.0	–0.97	–6.16

Note: Amplitude in μV and latency in ms.
[a]Sex group effects are collapsed across cohort, and cohort group effects are collapsed across sex groups. Significance was determined with structural equation modeling package Mx.
[b]Females compared to males.
[c]Young adult compared to middle-aged.
*$p < .05$; **$p < .01$; ***$p < .001$

dependencies in the data to be taken into account. The older cohort showed higher P3 amplitude on Fz ($\chi^2 = 15.38$, $df = 1$, $p < 10^{-4}$), but lower amplitude on Cz ($\chi^2 = 23.58$, $df = 1$, $p < 10^{-5}$) and Pz ($\chi^2 = 43.93$, $df = 1$, $p < 10^{-10}$). Females showed higher amplitude than males on all three leads (Fz: $\chi^2 = 4.34$, $df = 1$, $p < .05$; Cz: $\chi^2 = 11.72$, $df = 1$, $p < .001$; Pz: $\chi^2 = 45.12$, $df = 1$, $p < 10^{-10}$). A slowing of cognitive processing with age was revealed by a significant effect of age cohort on the latency scores on two of the three leads (Fz: $\chi^2 = 4.67$, $df = 1$, $p < .05$; Cz: $\chi^2 = 6.79$, $df = 1$, $p < .01$). To account for these effects, sex and cohort were retained as covariates in subsequent genetic modeling.

Lead position interactions with cohort and sex were also modeled in Mx. There was no significant three-way interaction of lead by cohort by sex for P3 amplitude. The lead by cohort interaction was significant ($\chi^2 = 98.6$, $df = 2$, $p < 10^{-21}$). As in the aforementioned, young adults showed higher amplitude than middle-aged adults at Cz and Pz, whereas at Fz the young adults showed lower amplitude. Also, the lead by sex interaction was significant ($\chi^2 = 12.50$, $df = 2$, $p = .002$). Females showed increased amplitude compared to males, and this difference decreases from the posterior to the anterior lead.

For P3 latency no significant interaction effects with lead position were found.

Effects of Cohort and Sex on Variances and Correlations

In addition to the effect on the means, the cohorts showed differences in variances on all three leads for both amplitude and latency. For amplitude the middle-aged cohort showed lower variance than the young adult cohort, whereas for latency they showed larger variance. Further genetic modeling took these difference in variances into account by using a so-called scalar model (Neale & Cardon, 1992). The cohorts did not differ in MZ and DZ/sibling correlations suggesting that the relative contribution of A, C or D, and E did not differ across cohorts. No sex differences were found in either variances or sibling correlations.

Comparability of MZ Twins, DZ Twins, and Singletons

To test whether twins are representative of the singleton population we examined if there were significant group differences for latency and amplitude on each of the three leads. Correlations between DZ twins, between siblings and between twins and siblings (that is, all fraternal sibling relationships) did not differ significantly. There were also no significant differences in variances and means between DZ twins/siblings in any of these variables. Also, we found no differences between the means and variances of MZ and DZ twins/siblings.

Twin Correlations and Heritability of P3 Amplitude and Latency

Table 4 shows the correlations between MZ twins and DZ twins/siblings. The correlations suggest additive (A) plus dominant (D) genetic influences on both amplitude and latency as the DZ correlations are less

Table 3

Model Fitting of P3 Amplitude and Latency

		Fz					Cz					Pz				
Model	Tested against model number	−2LL	*df*	χ^2	Δ*df*	p	−2LL	*df*	χ^2	Δ*df*	*p*	−2LL	*df*	χ^2	Δ*df*	*p*
Amplitude																
Cohort effects																
0 saturated		3691.81	596				4028.67	616				3992.48	621			
1 eq variances Y = MA	0	3702.63	597	10.83	1	.001	4040.59	617	11.92	1	.001	4008.71	622	16.24	1	.000
2 eq correlations Y = MA	0	3692.94	598	1.13	2	.567	4032.44	618	3.78	2	.151	3998.87	623	6.40	2	.041
Decomposition[a]																
3 ADE + COH scalar	2	3692.94	598	1.13	2	.567	4032.44	618	3.78	2	.151	3998.87	623	6.40	2	.041
4 D = 0	3	3693.20	599	0.26	1	.611	4032.55	619	0.11	1	.742	3999.42	624	0.54	1	.462
5 D = 0, A = 0	4	3739.02	600	45.82	1	.000	4072.78	620	40.24	1	.000	4038.71	625	39.29	1	.000
Latency																
Cohort effects																
0 saturated		6294.68	596				6445.59	616				6583.53	621			
1 eq variances Y = MA	0	6307.57	597	12.89	1	.000	6457.05	617	11.46	1	.001	6591.80	622	8.27	1	.004
2 eq correlations Y = MA	0	6295.48	598	0.80	2	.670	6446.59	618	1.00	2	.606	6589.25	623	5.72	2	.05
Decomposition[a]																
3 ADE + COH scalar	2	6295.46	598	0.79	2	.675	6447.73	618	2.14	2	.343	6589.24	623	5.72	2	.057
4 D = 0	3	6296.50	599	1.04	1	.308	6454.07	619	6.34	1	.012	6590.15	624	0.91	1	.340
5 D = 0, A = 0	4	6324.61	600	28.11	2	.000	6479.85	620	25.78	2	.000	6625.71	625	35.56	2	.000

Note: Y = young adult; MA = middle-aged; COH = cohort.

Significance was tested with an alpha level of .01. The saturated model fitted a two correlations, one variance, and a means model (one mean, one age and one sex regression) for each of the cohorts, for a total of 10 parameters.

[a]Decomposition was performed on the model allowing variances to differ across cohorts (a scalar model). All models fitted a full means model for each cohort.

Table 4

MZ and DZ/Sibling Correlations with Heritability Estimates of P3 Amplitude and Latency

	Fz			Cz			Pz		
	r_{MZ}	r_{SIB}	h^2	r_{MZ}	r_{SIB}	h^2	r_{MZ}	r_{SIB}	h^2
Amplitude	.55***	.24***	.56***	.50***	.23**	.51***	.51***	.21***	.50***
Latency	.45***	.15*	.42***	.52***	.06	.43***	.48***	.17**	.45***

Note: Sibling correlations (r_{SIB}) are based on all DZ twins, twin-sib and sib-sib pairings. Heritabilities (h^2) are derived from the trivariate models fitting on data from three leads.
*$p < .05$; **$p < .01$; ***$p < .001$.

than half the MZ correlations (Falconer & Mackay, 1996). Formal testing shows that the dominant genetic effects were not significant for any of the leads as shown in Table 3. The most parsimonious model, therefore, estimates additive genetic and unique environmental effects on the variance of each variable.

Figure 2 shows the relative contributions of the three genetic and three environmental factors in the multivariate models. Note that the factor loadings in the figure, when squared, represent proportions of variance explained by the genetic and environmental factors. For P3 amplitude, there are significant contributions from all three genetic factors on all three leads along the anterior-posterior axis (all χ^2s > 13.0, ps < .001). For P3 latency a single genetic factor was sufficient for all of the genetic variance in all three leads. Loadings from the first genetic factor contributed significantly to the variance (χ^2s > 35.9, ps < .001). Loadings from the second and third genetic factors did not contribute significantly (ps > .05). The final column in Table 4 shows the heritabilities derived from these models.

Heritability of the P3 Time Series

Figure 3 shows the development of heritability under the AE model over the time course of the aligned P3 component on leads Fz, Cz and Pz. Alignment of the ERP to targets results in a markedly pointier waveform indicating that alignment was successful in reducing the attenuation of the grand average P3 due to individual differences in peak latency. However, P3 heritability does not vary much around peak amplitude for all three leads. For Cz and Fz highest heritability is seen about 50 ms before and after peak amplitude, but the difference was not significant as revealed by the confidence interval around the heritability. Significant drops in heritability were

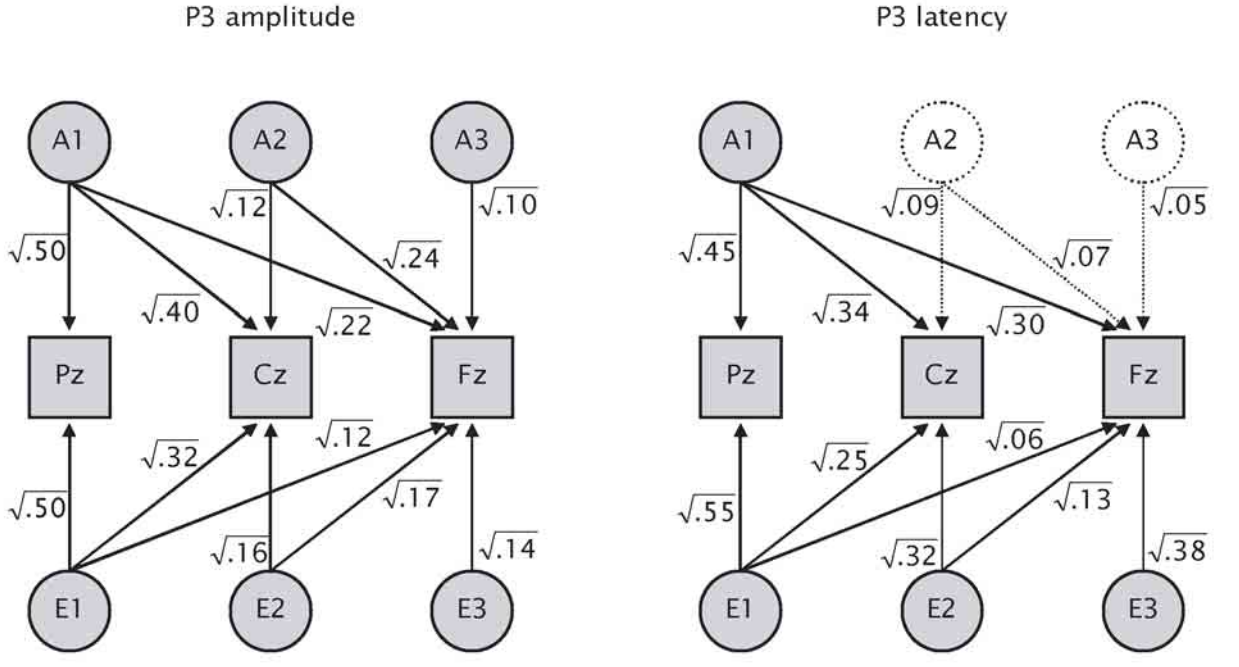

Figure 2

Structural equation models for P3 amplitude and latency each with 3 genetic factors ('A' circles) and 3 environmental factors ('E' circles), explaining variance of 3 observed variables (squares). The values under the root sign are standardized squared factor loadings representing proportions of variance explained by the factors. For example, environmental factor 2 explains 16% of the variance of Cz amplitude. All the arrows into one variable sum up to unity; for example, the explained variance of Pz latency.

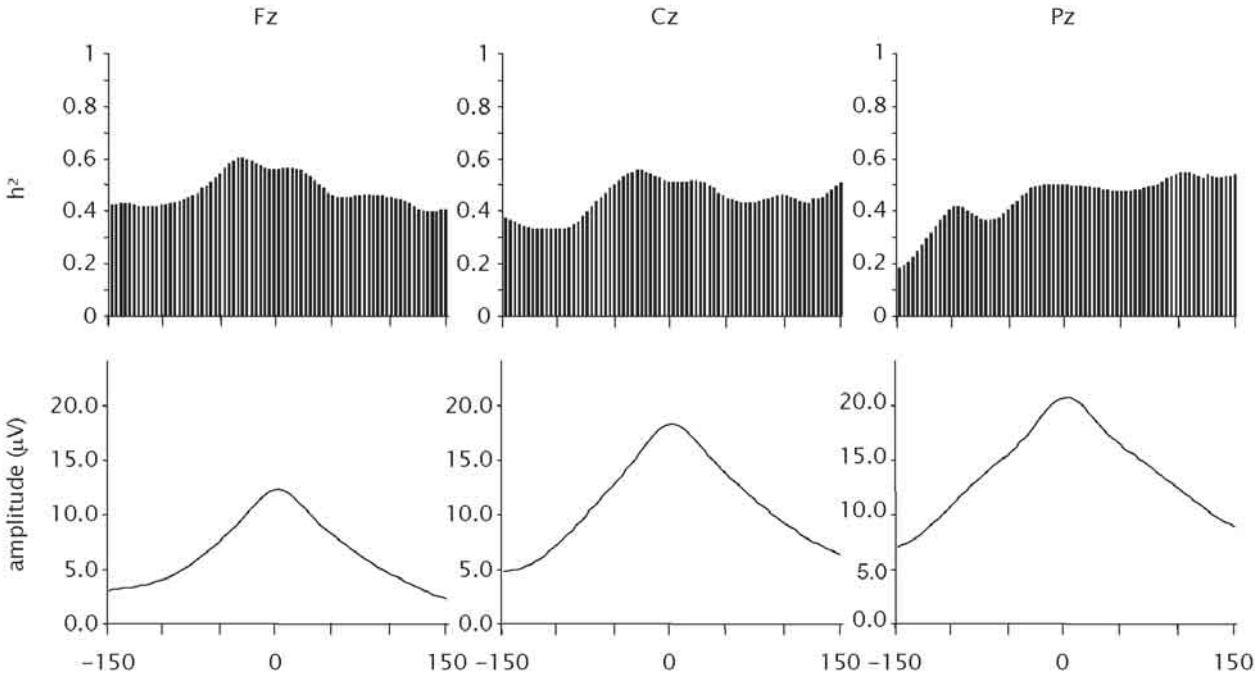

Figure 3

Grand average P3 after alignment on individual peak latency with the corresponding heritability.

found only at larger distances from the peak (> 100 ms).

We tested whether pre- and postpeak amplitude were influenced by the same genes as amplitude at the peak itself. To this end, we applied a bivariate model that estimated the genetic correlations (the proportion of overlapping genetic variance) between peak amplitude and amplitude at –100, –80, –60, –40, –20, +20, +40, +60, +80, and +100 ms around the peak. Table 5 summarizes the results. Within a range of -60 to 60 ms relative to the peak the genetic correlations remained over .90. Within 80 ms of the peak the genetic correations remained over .80, and within 100 ms they remained at or over .69. Inspection of the 99% confidence intervals revealed that all genetic correlations were significantly different from zero.

Discussion

A significant proportion of interindividual variation in adult P3 amplitude was found to be under genetic control. P3 amplitude (~50%) and latency (~45%) were moderately heritable for the three leads. A single genetic factor influenced latency at all electrodes. Specific genetic factors influenced amplitude at each lead. Genetic analysis of the full ERP waveform showed that P3 heritability barely changes from about 100 ms before to 100 ms after the peak.

No differences in heritability were found between young and middle-aged subjects. However, the age cohorts differed significantly in variances, suggesting that both genetic variance and environmental variance decreased with age for P3 amplitude, and both increased for latency. A lead by cohort interaction effect was observed consistent with the effect reported by Walhovd and Fjell (2002; but see also Polich, 1997). Across age cohorts, a relative increase of frontal P3 amplitude was found in the middle-aged cohort in comparison to the young cohort whereas a decrease was found in the parietal P3. From these data it seems that the P3 shows a shift towards the frontal/central areas with increasing age which is congruent with previously reported findings (for example, Brown et al., 1983: 0.15 μV per year decrease; Picton et al., 1984: 0.18 μV per year decrease).

Heritability for Pz amplitude at peak latency (50%) was slightly lower than the heritability estimate to targets (60%) reported in a meta-analysis by van Beijsterveldt and van Baal (2002). This slightly lower heritability may reflect the age of the subjects: it is slightly lower than large twin studies to the P3 in adolescents (van Beijsterveldt et al., 2001: 59%; Katsanis et al., 1997: 79%; Wright et al., 2001: 61%), but more comparable to twin studies in young adults (Anokhin et al., 2004: 41% at ages 18 to 28 years; O'Connor et al., 1994: 49%, ages 22 to 44), and a large family study in subjects 16 to 70 years of age (Almasy et al., 1999: 51%). Heritability of Pz latency, 45%, was also comparable to those in the extant literature. The meta-analysis by van Beijsterveldt and van Baal reported an estimated 51% heritability across studies.

It should be noted that our study differed in the exact oddball design from previous studies. P3

characteristics (amplitude, latency) are known to be sensitive to various variables such as the percentage of targets, task difficulty, speed versus accuracy instructions, and intensity and complexity of the stimulus (Pfefferbaum & Ford, 1988; Polich & Bondurant, 1997; Sugg & Polich, 1995; Woestenburg et al., 1983). The oddball task used in this study was somewhat different from most oddball tasks, in terms of the visual stimuli themselves (Snodgrass figures, which are perhaps more difficult). Furthermore, in our study subjects were instructed to silently count the number of targets, whereas others used button press to signal targets. Silent-counting, rather than button-press responses, may lead to higher P3 amplitude and longer latencies (Salisbury et al., 2001). Taken the sensitivity of the P3 to the antecendent task conditions, the heritability estimates across our and previous studies are surprisingly consistent.

No significant effects of common environment were found on the P3 variables. This concurs with most previous studies using a genetically informative twin design, but not many studies may have had sufficient power to detect such an influence. Ideally, two features must be present: the design must have information on identical and nonidentical sibling relations and it must have a large enough sample size (Posthuma & Boomsma, 2000). Two studies, both in adolescents (van Beijsterveldt et al., 2001; Wright et al., 2002), possessed these features. Van Beijsterveldt et al., in a sample of 426 subjects, found a trend for common environmental effects in females but the effect was absent in males. Wright et al. (2002) found no evidence for common environmental influences in an even larger sample of 1023 subjects. Our current results are in agreement with this finding.

The multivariate models revealed that the genetic variance of P3 amplitude was best explained by a model with three genetic factors that revealed specific contributions to the genetic variance of each lead (straight arrows in Figure 2), but also contributions to the genetic covariance between the leads (oblique arrows in Figure 2). These findings are comparable to those found in adolescents by Wright et al. (2001). Heritabilities for Pz, Cz, and Fz in their study were comparable to our estimates in adults, and they also found three genetic factors for P3 amplitude. Regarding P3 latency, heritabilities found by Wright et al. (2001) were again comparable, but instead of a single genetic factor, a second genetic factor was found. It must be noted, however, that the second genetic factor in their model explained only 8% of the variance of Fz latency.

If the P3 wave consists of different components operating at different time points, reflecting different aspects of cognitive functioning (Kok, 2001), it could be hypothesized that the genetic underpinnings vary across the time course of the P3. The current results, however, do not seem to support such a view. Pre- and postpeak heritability is largely equivalent for the three midline leads. Heritability of amplitude scores do not differ significantly in a range of about 60 ms before or after the P3 peak. Genetic overlap is close to perfect (> 90%), indicating that within this 120 ms range amplitude is influenced by the same set of genes. The genetic make-up of P3 amplitude differs significantly from that at the peak only at latencies of 100 ms before or after the peak, and within this large range 70% of the genes influencing individual variation in amplitude are still shared with variation in peak amplitude. Two possible explanations for this result are (1) peak amplitude as well as pre- and postpeak amplitude reflect for the most part similar cognitive processes that are influenced by the same set of genes, (2) peak amplitude and pre- and postpeak amplitude reflect different cognitive processes, but are influenced by a spurious genetic factor like skull thickness.

Insofar as the P3 parameters are temporally stable, their heritability classifies them as potentially useful endophenotypes (de Geus, 2002) to detect genetic influences on a number of psychiatric disorders that are associated with a deviant P3 (Begleiter et al., 1984; Cohen et al., 1995; Elmasian et al., 1982; Iacono et al., 2003; Pfefferbaum et al., 1991; Polich & Herbst, 2000; Porjesz & Begleiter, 1990; van der Stelt et al., 1998). First attempts at identification of genes which influence variation in P3 characteristics have pointed to areas on chromosomes 2, 6, and 7 as the most promising regions (Begleiter et al., 1998; Jones et al., 2004; Porjesz et al., 1998, 2002). When P3 amplitude was considered simultaneously with the liability to alcoholism, an increase in the linkage signal was found on chromosome 4 around a locus known for coding alcohol dehydrogenase (Williams et al., 1999).

Finding genetic polymorphisms that influence the P3 may be helpful just for understanding downstream

Table 5

Genetic Correlations of Peak Amplitude with Pre- and Postpeak Amplitude

	Genetic correlation		
Timing relative to peak (in ms)	Fz	Cz	Pz
–100	.72	.69	.77
–80	.82	.83	.86
–60	.92	.92	.92
–40	.96	.97	.95
–20	.99	1.00	.99
0	1	1	1
20	1.00	1.00	.00
40	.98	.99	.98
60	.91	.96	.96
80	.81	.91	.93
100	.73	.82	.87

Note. The genetic correlations are derived from bivariate models fitting additive genetic and unique environmental variance.

psychiatric disorders (Dick et al., 2006; Williams et al., 1999). However, it may also help elucidate the neurobiology of the P3 generator systems. Several competing P3 generating systems have been proposed in the literature (for reviews: Picton, 1992; Nieuwenhuis et al., 2005; Hansenne, 2000; Soltani & Knight, 2000). The recent review by Nieuwenhuis et al. (2005) stresses the role of the norepinephrine (NE) projections from the locus coeruleus (LC) to the cortex in P3 generation. It is hypothesized that the LC is recruited by input from cortical afferent projections that monitor the motivational aspects (or salience) of a stimulus. The activated LC then modulates cortical activation and information processing via coeruleo-cortical NE projections in a pathway from anterior to posterior areas (Aston-Jones & Cohen, 2005). Thus, the LC-NE system acts as a central modulator of cortical generators of the P3, which are localzed mainly in the temporal-parietal junction (TPJ) and the lateral prefrontal cortex. Nieuwenhuis et al. (2005) based this hypothesis on the grounds of multiple sources of evidence, including lesion studies, covariation between LC phasic responses and P3 amplitude, and psychopharmacological evidence.

The current results are consistent with the role of the LC as a central timing mechanism of P3 midline activity. If the LC plays a key role in P3 generation (Aston-Jones & Cohen, 2005; Nieuwenhuis et al., 2005) P3 latency should be related to LC activity. Heimer (1983) describes how NE projections from the LC first reach the prefrontal areas before passing on to the more posterior regions. These are nonmyelinated fibers and therefore relatively slow. This may explain why the frontal P3 occurred slightly earlier than the posterior P3. In addition, the finding that P3 latency reflected a single genetic source may be more consistent with a central timing mechanism as in the proposed LC-NE system than, for example, with multiple independent cortical generators. Regarding the findings of P3 amplitude we speculate that the genetic variance common to the three midline leads reflected modulation by the LC system whereas the specific factors reflected the contribution of local P3 generators at for example the TPJ or lateral frontal cortex. Overall, we conclude that separating genetic from environmental variance has provided some insights into the biological processes underlying the P3.

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References

Almasy, L., Porjesz, B., Blangero, J., Chorlian, D. B., O'Connor, S. J., Kuperman, S., Rohrbaugh, J., Bauer, L. O., Reich, T., Polich, J., & Begleiter, H. (1999). Heritability of event-related brain potentials in families with a history of alcoholism. *American Journal of Medical Genetics, 88,* 383–390.

American Electroencephalographic Society (1991). Guidelines for standard electrode position nomenclature. *Journal of Clinical Neurophysiology, 3,* 38–42.

Anokhin, A. P., Heath, A. C., & Myers, E. (2004). Genetics, prefrontal cortex, and cognitive control: A twin study of event-related brain potentials in a response inhibition task. *Neuroscience Letters*, *368*, 314–318.

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, *28*, 403–450.

Begleiter, H., Porjesz, B., Bihari, B., & Kissin, B. (1984). Event-related brain potentials in boys at risk for alcoholism. *Science*, *225,* 1493–1496.

Begleiter, H., Porjesz, B., Reich, T., Edenberg, H. J., Goate, A., Blangero, J., Almasy, L., Foroud, T., Van Eerdewegh, P., Polich, J., Rohrbaugh, J., Kuperman, S., Bauer, L. O., O'Connor, S. J., Chorlian, D. B., Li, T. K., Conneally, P. M., Hesselbrock, V., Rice, J. P., Schuckit, M. A., Cloninger, R., Nurnberger, J., Jr., Crowe, R., & Bloom, F. E. (1998). Quantitative trait loci analysis of human event-related brain potentials: P3 voltage. *Electroencephalography and Clinical Neurophysiology*, *108*, 244–250.

Blackwood, D. (2000). P300, a state and a trait marker in schizophrenia. *The Lancet*, *355*, 771–772.

Blackwood, D. H., Fordyce, A., Walker, M. T., St Clair, D. M., Porteous, D. J., & Muir, W. J. (2001). Schizophrenia and affective disorders—cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: Clinical and P300 findings in a family. *American Journal of Human Genetics*, *69*, 428–433.

Bledowski, C., Prvulovic, D., Goebel, R., Zanella, F. E., & Linden, D. E. (2004). Attentional systems in target and distractor processing: A combined ERP and fMRI study. *Neuroimage*, *22*, 530-540.

Bledowski, C., Prvulovic, D., Hoechstetter, K., Scherg, M., Wibral, M., Goebel, R., & Linden, D. E. (2004). Localizing P300 generators in visual target and distractor processing: A combined event-related potential and functional magnetic resonance imaging study. *Journal of Neuroscience, 24*, 9353–9360.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Review Genetics*, *3*, 872–882.

Boomsma, D. I., Vink, J. M., van Beijsterveldt, T. C., de Geus, E. J., Beem, A. L., Mulder, E. J., Derks, E. M., Riese, H., Willemsen, G. A., Bartels, M., van den Berg, M., Kupper, N. H., Polderman, T. J., Posthuma, D., Rietveld, M. J., Stubbe, J. H., Knol, L. I., Stroet, T., & van Baal, G. C. (2002). Netherlands Twin Register: A focus on longitudinal research. *Twin Research*, *5*, 401–406.

Brown, W. S., Marsh, J. T., & LaRue, A. (1983). Exponential electrophysiological aging: P3 latency. *Electroencephalography and Clinical Neurophysiology, 55*, 277–285.

Carlson, S. R., Iacono, W. G., & McGue, M. (2002). P300 amplitude in adolescent twins discordant and concordant for alcohol use disorders. *Biological Psychology, 61*, 203–227.

Cohen, R. A., O'Donnell, B. F., Meadows, M. E., Moonis, M., Stone, W. F., & Drachman, D. A. (1995). ERP indices and neuropsychological performance as predictors of functional outcome in dementia. *Journal of Geriatric Psychiatry and Neurology, 8*, 217–225.

De Geus, E. J. (2002). Introducing genetic psychophysiology. *Biological Psychology*, *61*, 1–10.

Desmedt, J. E., Debecker, J., & Manil, J. (1965). [Demonstration of a cerebral electric sign associated with the detection by the subject of a tactile sensorial stimulus. The analysis of cerebral evoked potentials derived from the scalp with the aid of numerical ordinates]. *Bulletin de l'Académie Royale de Médecine de Belgique, 5,* 887–936.

Dick, D. M., Jones, K., Saccone, N., Hinrichs, A., Wang, J. C., Goate, A., Bierut, L., Almasy, L., Schuckit, M., Hesselbrock, V., Tischfield, J., Foroud, T., Edenberg, H., Porjesz, B., & Begleiter, H. (2006). Endophenotypes successfully lead to gene identification: Results from the collaborative study on the genetics of alcoholism. *Behavior Genetics*, *36*, 112–126.

Dien, J., Spencer, K. M., & Donchin, E. (2004). Parsing the late positive complex: Mental chronometry and the ERP components that inhabit the neighborhood of the P300. *Psychophysiology*, *41*, 665–678.

Donchin, E., & Coles, M. (1988). Is the P300 component a manifestation of context updating? *The Behavioural and Brain Sciences, 11,* 357–427.

Elmasian, R., Neville, H., Woods, D., Schuckit, M., & Bloom, F. (1982). Event-related brain potentials are different in individuals at high and low risk for developing alcoholism. *Proceedings of the National Academy of Sciences, 79*, 7900-7903.

Falconer, D. S., & MacKay, T. F. (1996). *Quantitative genetics*. Harlow: Prentice Hall.

Hansenne, M. (2000). [The p300 cognitive event-related potential. I. Theoretical and psychobiologic perspectives]. *Neurophysiologie Clinique*, *30*, 191–210.

Heimer, L. (1983). *The human brain and spinal cord*. New York: Springer Verlag.

Iacono, W. G., Malone, S. M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *International Journal of Psychophysiology*, *48*, 147–178.

Jasper, H. H. (1958). Report of the committee on methods of clinical exam in EEG. *Electroencephalography and Clinical Neurophysiology, 10,* 370-375.

Jones, K. A., Porjesz, B., Almasy, L., Bierut, L., Goate, A., Wang, J. C., Dick, D. M., Hinrichs, A., Kwon, J., Rice, J. P., Rohrbaugh, J., Stock, H., Wu, W., Bauer, L. O., Chorlian, D. B., Crowe, R. R., Edenberg, H. J., Foroud, T., Hesselbrock, V., Kuperman, S., Nurnberger Jr, J., O'Connor, S. J., Schuckit, M. A., Stimus, A. T., Tischfield, J. A., Reich, T., & Begleiter, H. (2004). Linkage and linkage disequilibrium of evoked EEG oscillations with CHRM2 receptor gene polymorphisms: Implications for human brain dynamics and cognition. *International Journal of Psychophysiology*, *53*, 75–90.

Katsanis, J., Iacono, W. G., McGue, M. K., & Carlson, S. R. (1997). P300 event-related potential heritability in monozygotic and dizygotic twins. *Psychophysiology*, *34*, 47–58.

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology, 38*, 557–577.

Levit, R. A., Sutton, S., & Zubin, J. (1973). Evoked potential correlates of information processing in psychiatric patients. *Psychology Medicine*, *3*, 487–494.

Neale, M. C. (2004). *Mx: Statistical modeling* (Version 1.57) [Computer Software]. Richmond, VA.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht, the Netherlands: Kluwer Academic Publisher.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychology Bulletin*, *131*, 510-532.

O'Connor, S., Morzorati, S., Christian, J. C., & Li, T. K. (1994). Heritable features of the auditory oddball event-related potential: Peaks, latencies, morphology and topography. *Electroencephalography and Clinical Neurophysiology*, *92*, 115–125.

Pfefferbaum, A., & Ford, J. M. (1988). ERPs to stimuli requiring response production and inhibition: Effects of age, probability and visual noise. *Electroencephalography and Clinical Neurophysiology, 71*, 55–63.

Pfefferbaum, A., Ford, J. M., & Kraemer, H. C. (1990). Clinical utility of long latency 'cognitive' event-related potentials (P3): the cons. *Electroencephalography and Clinical Neurophysiology, 76*, 6–12; discussion 11.

Pfefferbaum, A., Ford, J. M., White, P. M., & Mathalon, D. (1991). Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcohol, Clinical and Experimental Research*, *15*, 839–850.

Picton, T. W. (1992). The P300 wave of the human event-related potential. *Journal of Clinical Neurophysiology*, *9*, 456–479.

Picton, T. W., Stuss, D. T., Champagne, S. C., & Nelson, R. F. (1984). The effects of age on human event-related potentials. *Psychophysiology, 21*, 312–325.

Polich, J. (1997). EEG and ERP assessment of normal aging. *Electroencephalography and Clinical Neurophysiology*, *104,* 244–256.

Polich, J. (1998). P300 clinical utility and control of variability. *Journal of Clinical Neurophysiology, 15,* 14–33.

Polich, J., & Bondurant, T. (1997). P300 sequence effects, probability, and interstimulus interval. *Physiology and Behavior, 61,* 843–849.

Polich, J., & Herbst, K. L. (2000). P300 as a clinical assay: rationale, evaluation, and findings. *International Journal of Psychophysiology, 38*, 3–19.

Polich, J., Pollock, V. E., & Bloom, F. E. (1994). Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychology Bulletin, 115*, 55–73.

Porjesz, B., & Begleiter, H. (1990). Event-related potentials in individuals at risk for alcoholism. *Alcohol, 7,* 465–469.

Porjesz, B., Begleiter, H., & Garozzo, R. (1980). Visual evoked potential correlates of information processing deficits in chronic alcoholics. *Advances in Experimental Medicine and Biology, 126,* 603–623.

Porjesz, B., Begleiter, H., Reich, T., Van Eerdewegh, P., Edenberg, H. J., Foroud, T., Goate, A., Litke, A., Chorlian, D. B., Stimus, A., Rice, J., Blangero, J., Almasy, L., Sorbell, J., Bauer, L. O., Kuperman, S., O'Connor, S. J., & Rohrbaugh, J. (1998). Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: preliminary results from the COGA Project. Collaborative Study on the Genetics of Alcoholism. *Alcohol, Clinical and Experimental Research, 22,* 1317–1323.

Porjesz, B., Begleiter, H., Wang, K., Almasy, L., Chorlian, D. B., Stimus, A. T., Kuperman, S., O'Connor, S. J., Rohrbaugh, J., Bauer, L. O., Edenberg, H. J., Goate, A., Rice, J. P., & Reich, T. (2002). Linkage and linkage disequilibrium mapping of ERP and EEG phenotypes. *Biological Psychology, 61,* 229–248.

Posthuma, D., Beem, A. L., de Geus, E. J., van Baal, G. C., von Hjelmborg, J. B., Iachine, I., & Boomsma, D. I. (2003). Theory and practice in quantitative genetics. *Twin Research, 6,* 361–376.

Posthuma, D., & Boomsma, D. I. (2000). A note on the statistical power in extended twin designs. *Behavior Genetics, 30,* 147–158.

Posthuma, D., Neale, M. C., Boomsma, D. I., & de Geus, E. J. (2001). Are smarter brains running faster? Heritability of alpha peak frequency, IQ, and their interrelation. *Behavior Genetics, 31,* 567–579.

Salisbury, D. F., Rutherford, B., Shenton, M. E., & McCarley, R. W. (2001). Button-pressing affects P300 amplitude and scalp topography. *Clinical Neurophysiology, 112,* 1676–1684.

Semlitsch, H. V., Anderer, P., Schuster, P., & Presslich, O. (1986). A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology, 23*, 695–703.

Snodgrass, J., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory, 2,* 174–215.

Soltani, M., & Knight, R. T. (2000). Neural origins of the P300. *Critical Reviews in Neurobiology, 14,* 199–224.

Sugg, M. J., & Polich, J. (1995). P300 from auditory stimuli: intensity and frequency effects. *Biological Psychology, 41,* 255–269.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150,* 1187–1188.

Turetsky, B. I., Cannon, T. D., & Gur, R. E. (2000). P300 subcomponent abnormalities in schizophrenia: III. Deficits In unaffected siblings of schizophrenic probands. *Biological Psychiatry, 47,* 380-390.

Van Baal, G. C. M., de Geus, E. J. C., & Boomsma, D. I. (1998). Longitudinal study of genetic influences on ERP-P3 during childhood. *Developmental Neuropsychology, 14,* 19–45.

Van Beijsterveldt, C. E., & Boomsma, D. I. (1994). Genetics of the human electroencephalogram (EEG) and event-related brain potentials (ERPs): a review. *Human Genetics, 94,* 319–330.

Van Beijsterveldt, C. E., & van Baal, G. C. (2002). Twin and family studies of the human electroencephalogram: a review and a meta-analysis. *Biological Psychology, 61,* 111–138.

Van Beijsterveldt, C. E., van Baal, G. C., Molenaar, P. C., Boomsma, D. I., & de Geus, E. J. (2001). Stability of genetic and environmental influences on P300 amplitude: a longitudinal study in adolescent twins. *Behavior Genetics, 31,* 533–543.

Van der Stelt, O., Geesken, R., Gunning, W. B., Snel, J., & Kok, A. (1998). P3 scalp Topographyaphy to target and novel visual stimuli in children of alcoholics. *Alcohol*, *15*, 119–136.

Verleger, R. (1988). Event-related potentials and cognition: A critique of the context updating hypothesis and an alternative interpretation of P3. *The Behavioral and Brain Sciences*, *11,* 343–427.

Verleger, R., & Cohen, R. (1978). Effects of certainty, modality shift and guess outcome on evoked potentials and reaction times in chronic schizophrenics. *Psychology Medicine*, 8, 81–93.

Vogel, E. K., & Luck, S. J. (2002). Delayed working memory consolidation during the attentional blink. *Psychonomic Bulletin and Review, 9*, 739–743.

Vogel, E. K., Luck, S. J., & Shapiro, K. L. (1998). Electrophysiological evidence for a postperceptual locus of suppression during the attentional blink. *Journal of Experimental Psychology Human Perception and Performance, 24*, 1656–1674.

Walhovd, K. B., & Fjell, A. M. (2002). One-year test-retest reliability of auditory ERPs in young and old

adults. *International Journal of Psychophysiology, 46*, 29–40.

Williams, J. T., Begleiter, H., Porjesz, B., Edenberg, H. J., Foroud, T., Reich, T., Goate, A., Van Eerdewegh, P., Almasy, L., & Blangero, J. (1999). Joint multipoint linkage analysis of multivariate qualitative and quantitative traits. II. Alcoholism and event-related potentials. *American Journal of Human Genetics, 65*, 1148–1160.

Woestenburg, J. C., Verbaten, M. N., & Slangen, J. L. (1983). Stimulus information and habituation of the visual event related potential and the skin conductance reaction under task-relevance conditions. *Biological Psychology, 16*, 225–240.

Wright, M. J., Hansell, N. K., Geffen, G. M., Geffen, L. B., Smith, G. A., & Martin, N. G. (2001). Genetic influence on the variance in P3 amplitude and latency. *Behavior Genetics, 31*, 555–565.

Wright, M. J., Luciano, M., Hansell, N. K., Geffen, G. M., Geffen, L. B., & Martin, N. G. (2002). Genetic sources of covariation among P3(00) and online performance variables in a delayed-response working memory task. *Biological Psychology, 61*, 183–202.