*Behavior Genetics, Vol. 31, No. 6, November 2001 (© 2001)*

# Genetic Influence on the Variance in P3 Amplitude and Latency

**Margaret J. Wright,[1,4] Narelle K. Hansell,[1,2] Gina M. Geffen,[2] Laurie B. Geffen,[2] Glen A. Smith,[3] and Nicholas G. Martin[1]**

The P3(00) event-related potential (ERP) component is widely used as a measure of cognitive functioning and provides a sensitive electrophysiological index of the attentional and working memory demands of a task. This study investigated what proportion of the variance in the amplitude and latency of the P3, elicited in a delayed response working memory task, could be attributed to genetic factors. In 335 adolescent twin pairs and 48 siblings, the amplitude and latency of the P3 were examined at frontal, central, and parietal sites. Additive genetic factors accounted for 48% to 61% of the variance in P3 amplitude. Approximately one-third of the genetic variation at frontal sites was mediated by a common genetic factor that also influenced the genetic variation at parietal and central sites. Familial resemblance in P3 latency was due to genetic influence that accounted for 44% to 50% of the variance. Genetic covariance in P3 latency across sites was substantial, with a large part of the variance found at parietal, central, and frontal sites attributed to a common genetic factor. The findings provide further evidence that the P3 is a promising phenotype of neural activity of the brain and has the potential to be used in linkage and association analysis in the search for quantitative trait loci (QTLs) influencing cognition.

**KEY WORDS:** P3 (P300); twin study; event-related potentials; cognition; quantitative genetic analyses.

## INTRODUCTION

The P3(00) event-related potential (ERP) is widely used to examine cognitive function in both normal individuals and various clinical groups (Rugg and Coles, 1995). It is typically elicited in an oddball task where a low probability target stimulus (oddball) is easily discriminated from a frequent non-target stimulus, and is thought to reflect stimulus identification and allocation of attentional resources and engagement of working memory processes, but it may also be related to more general aspects of cognitive processing (Picton, 1992). P3 amplitude is generally larger when attention is focused on the target stimulus and smaller when attention is directed to some other mental activity (e.g., Donchin, 1981; Duncan-Johnson and Donchin, 1977). P3 latency indexes stimulus evaluation time, with more difficult tasks or discriminations being accompanied by an increase in latency, and is relatively independent of response processes (Magliero *et al.*, 1984; McCarthy and Donchin, 1981).

Like other ERP components, the P3 is characterized by large individual differences with several lines of evidence attributing the variation to differences in cognitive ability. The association between P3 and cognitive ability is dependent on the type of task, with processing requirements influencing the precise relationship, and greater P3 amplitudes and shorter P3 latencies

[1] Genetic Epidemiology Laboratory, Queensland Institute of Medical Research.
[2] Cognitive Psychophysiology Laboratory, University of Queensland, Australia.
[3] School of Psychology, University of Queensland, Australia.
[4] To whom correspondence should be addressed. Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia. Fax: +617 3362 0225. e-mail: margieW@qimr.edu.au



0001-8244/01/1100-0555$19.50/0 

are not invariably linked to higher ability. For example, larger P3 values elicited in a choice reaction time task and an N-back task have been associated with higher reading spans (Nittono *et al.,* 1999) and IQ (Gevins and Smith, 2000), respectively, but smaller P3s elicited to the probe in a Sternberg memory-scanning task and during several cognitive tasks have also been found to be correlated (albeit weakly) with higher IQ (Houlihan *et al.,* 1998; McGarry-Roberts *et al.,* 1992), whereas no consistent relation between P3 amplitude and cognitive ability has been found using the oddball task (Howard and Polich, 1985; O'Donnell *et al.,* 1992; Polich and Martin, 1992; Polich *et al.,* 1990). In contrast, by using an oddball task, several studies have found a shorter P3 latency is associated with higher cognitive ability (Egan *et al.,* 1992; Howard and Polich, 1985; O'Donnell *et al.,* 1992; McGarry-Roberts *et al.,* 1992; Polich and Martin, 1992; Polich *et al.,* 1983; 1990) but using more complex tasks latency has been both positively and negatively correlated with IQ (Houlihan *et al.,* 1998). Although there is some evidence that ERPs may be modulated by state such that those of higher ability employ a different strategy to do the task (Schafer, 1985), there is generally more support for the interpretation that P3 amplitude/latency differences reflect biologically based differences in cognitive ability. Several ERP correlates of early stages of stimulus processing are modulated by performance demands and individual differences related to task performance are evident even where stimuli impose no special processing demands (e.g., Pelosi and Blumhardt, 1992).

Clinical studies provide evidence that the amplitude and latency of the P3 is a correlate of biologically based differences (e.g., Begleiter and Porjesz, 1995; Ford *et al.,* 1994, Porjesz and Begleiter 1996; Porjesz *et al.,* 1980; Roth *et al.,* 1980; Turetsky *et al.,* 1998). These studies have shown reduced P3 amplitude in a variety of psychiatric and behavioral disorders, most notably schizophrenia and alcoholism. The reduction in P3 is thought to reflect liability, rather than functional changes, because it is also found in unaffected relatives (e.g., Begleiter *et al.,* 1984; Blackwood *et al.,* 1991; Polich *et al.,* 1994; Turetsky *et al.,* 2000), thus suggesting P3 amplitude may be useful as a phenotypic marker of disease. Moreover, in a linkage screen of P3 amplitude, evidence of linkage to chromosomes 4 and 5 has been found (Almasy *et al.,* 2001; Begleiter *et al.,* 1998; Williams *et al.,* 1999). In clinical studies, differences in P3 latency have more commonly been associated with neural degenerative disorders such as Alzheimer's disease (P3 latency increases) (e.g., O'Donnell *et al.,* 1990). In normal aging, P3 latency has been found to increase and also P3 amplitude to decrease as cognitive processing slows down, although the power of P3 to differentiate between normal aging and dementia is inconclusive (e.g., Pfefferbaum *et al.,* 1990; Polich, 1998).

Genetic studies indicate that P3 amplitude is moderately heritable, with heritability estimates ranging from 39% to 79% (Almasy *et al.,* 1999; Katsanis *et al.,* 1997; O'Connor *et al.,* 1994; van Beijsterveldt *et al.,* 1998). There is also some evidence that P3 latency is influenced by genetic factors but it is unclear as to what extent (Almasy *et al.,* 1999; Eischen and Polich, 1994; Katsanis *et al.,* 1997; Surwillo, 1980; Polich and Burns, 1987; Rogers and Deary, 1991). However, many previous studies are limited by their small sample size and only a few have used genetic modeling techniques (Katsanis *et al.,* 1997; van Beijsterveldt *et al.,* 1998). Of the more recent twin studies, O'Connor *et al.* (1994), using 59 MZ and 39 DZ twin pairs, reported a moderate heritability for P3 amplitude (60%) but no genetic influence for P3 latency. Similarly, Katsanis *et al.,* (1997), in a sample of 30MZ and 34 DZ twin pairs, found a significant genetic influence for P3 amplitude for both an easy and difficult task condition ($h^2$ = 79%). For P3 latency, a genetic influence for the difficult condition but not the easy condition was found, thus suggesting that P3 latency may be heritable only when the task is cognitively demanding.

The present study examined the influence of genetic factors on individual differences in the amplitude and latency of the P3 elicited in a delayed-response, working memory task. In this task, the location of a target stimulus that is briefly presented has to be remembered for a short time, and then a motor response is required to indicate the target's location. The cognitive demands of this task are likely to be higher than those of the oddball task, which requires minimal effort to achieve perfect performance. It was anticipated that greater processing demands in this study may be associated with a larger genetic influence and enable the familial resemblance of the P3 to be clearly identified. All participants were part of an ongoing study of cognition in adolescent Australian twins in which several behavioral and electrophysiological correlates of cognitive ability are collected (Wright *et al.,* 2001). P3 data were available for 335 twin pairs, the largest sample to date, and given the power estimates of van Beijsterveldt *et al.* (1998), it was expected that a reasonably

accurate estimate of the genetic influence on P3 would be obtained. ERP recordings were from 15 sites, so the extent to which covariation among different brain regions for the P3 might be due to genetic factors was examined. Amplitude and latency of the P3 at different scalp recording sites may be influenced by a common genetic factor because there is evidence of coupling between activity in different, well-separated parts of the brain. These analyses constitute one in a series of studies to identify markers of some of the key processes that contribute to individual differences in cognitive ability and its genetic variance.

## METHOD

### Participants

Participants (386 females, 322 males) with a mean age of 16.8 years (range 15.6–17.4 years) included twin pairs and their non-twin siblings from 354 families. A total of 264 families consisted of a twin pair, 42 of a twin pair and one sibling, 6 of a single twin and one non-twin sibling, and 42 of a single twin. Of the 306 twin pairs, there were 140 MZ (81 female, 59 male) and 166 DZ (46 female, 42 male, 78 opposite sex). Participants are part of a 1996 ongoing study which is using a range of measures to investigate both the genetic influences on cognition and the genetic covariation among the cognitive indices (Wright *et al.*, 2001). They were located through the Brisbane Adolescent Twin database that was set-up in 1992 for a study of melanocytic naevi development (Aitken *et al.*, 1994).

Zygosity of twin pairs of the same-sex was determined by analysis of 9 independent highly polymorphic DNA markers using a commercial kit (AmpF1STR Profiler Plus Amplification Kit, ABI). These results were cross-checked with blood group results (ABO, Rh, MNS) from the Australian Red Cross Blood Service and/or phenotypic data (eye, skin and hair colour, hair texture, height, and weight), giving an overall probability of zygosity of greater than 99.9%. All participants had normal or corrected vision (better than 6/12 Snellen equivalent) and had no history of head injury or neurological or psychiatric conditions. Participants were instructed to avoid consuming caffeine-containing foods or drinks for 2 hr before their visit and no participants were currently taking prescribed medication with central nervous system effects.

Each participant attended a 3- to 4-hr morning testing session, with co-twins attending together but tested separately. The session consisted of two parts: (1) measurement of psychometric IQ and information processing, and (2) measurement of ERP and performance indices of working memory using the delayed response (DR) task, and resting EEG, with one co-twin starting with the DR task and the other the IQ session. Non-twin siblings were tested separately, with order of testing counter-balanced across participants. Written, informed consent was obtained from participants and their parents, and all data were stored and analyzed by numbers rather than names and treated confidentially.

### Delayed Response Task

The task required participants to focus on a black fixation spot (0.5° visual angle), in the center of a computer screen, and use their peripheral vision to note the location of a "target" soccer ball (1.5° visual angle) that was flashed briefly (150 ms) on the screen, 250 ms after fixation onset, and on an annulus (9.25° radius) from the fixation point. After a delay of several seconds (1 or 4 s), signaled by the disappearance of the fixation, participants showed they remembered the soccer ball's location by lifting their hand, resting on a 5 × 5 cm response pad placed centrally in front of them, and touching the position on the touch-sensitive screen with a pencil shaped pointer. Visual fixation was required to be maintained while the fixation spot was present, and responses were required to be prompt (150–1500 ms post-fixation offset) and within a 2° radius of the target center. Participants received a monetary reward dependent on performance ($20–$35)—2 cents to 10 cents per correct trial (graded on pointing accuracy) with incorrect trials incurring a penalty of 5 cents. After each trial, feedback was shown on the screen showing the amount of money won.

Randomly interspersed with the memory trials were an equal number of sensory trials in which the peripheral target remained present throughout the delay and response interval (i.e., identical to memory trials, except that the target position did not have to be remembered). In 50% of both memory and sensory trials, a distractor identical to the target was briefly (150 ms) presented peripherally, 300 to 700 ms after target onset. Distractors occurred on the same 9.25° annulus but not within a 15° radius of the preceding target.

Following training and practice on the task, participants completed a total of 432 (6 blocks of 72 trials) or 240 trials. Accuracy of response was measured by the percentage of correct trials and position accuracy—distance (in mm) between the target center and screen

touch point. Speed measures included response initiation (RI)—latency from fixation offset to break of hand contact with the response pad, and movement time—latency from RI to screen touch time. Overall performance was measured as the amount of money won.

Testing took place in an electrically shielded, sound-attenuated cubicle with the light level set to low. The computer monitor was positioned approximately 45 cm in front of the participant, just below eye level. The screen background was dark grey and the intensity was adjusted so that stimuli could be clearly distinguished with minimal after-image effects. A black hood with a 205-mm diameter hole in the middle was fitted so that targets at all locations were an equal distance from the edge of the screen.

### ERP Recording

The ECI-Electrocap was used to record from 15 sites (Fp1, Fp2, F7, F3, Fz, F4, F8, C3, Cz, C4, P3, Pz, P4, O1, O2) referenced to linked ears. EOG was recorded from the supra-orbital ridge and the outer canthus of the left eye and all electrode impedances were maintained below 5 kohms. EEG signals were band-pass filtered (0.01 to 100 Hz) and amplified with Grass amplifiers, and sampled at 500 Hz from 100 ms prior to fixation onset to 200 ms post-fixation offset. ERPs were derived from correct trials without excessive artifact or eye movements (over 50 uV RMS), and eyeblinks were removed using an eyeblink correction procedure as used by Geffen *et al.* (1997).

Following artifact rejection trials were averaged using a pre-target baseline of 350 ms, collapsed over trial type for measurement of P3, the focus of this study. Memory and sensory trials are indistinguishable for the first 150 ms (post-target onset), a difference that became apparent only once the target has been extinguished in memory trials or, in the case of sensory trials where the target is continuously present, when it is estimated that the target has been on longer than 150 ms. Preliminary analyses showed the P3 to memory and sensory trials to be the same amplitude and latency, suggesting the cognitive demands and stimulus salience in both trials is the same at this point, in which visuo-spatial information is encoded and attention is maintained centrally in anticipation of responding.

Data that involved too few trials due to artifact rejection or where there were hardware or software problems with data collection (48 single twins, 3 siblings) were not included. The original sample comprised 364 twin pairs and 51 siblings, of which ERP data were not collected for 10 twin pairs.

### Measurement of P3 Amplitude and P3 Latency

ERP waveforms were digitally filtered with a low-pass triangular filter (5 Hz) prior to peak picking. A computer program was then used to locate the largest positive peak within the latency window 150 to 500 ms post-target. This window was chosen following inspection of the grandmean waveforms that showed a positive component to be elicited around 300 ms and showed no other positive peaks were elicited in this window. The program divided the search window into sub-windows of 10 ms. The slope of each sub-window was then determined by fitting a line of best fit (least squares approximation) to the data points in the sub-window. A peak was said to exist within two adjacent sub-windows if the slopes were of different sign. The P3 was confirmed by direct visual inspection at 15 sites by a research assistant who was blinded to participant zygosity. Where there were multiple peaks or the amplitude of the P3 was small, information from the other sites was used to guide selection of the peak. Where a peak could not be selected with a high degree of certainty, peak latency was coded as missing. P3 amplitude was measured as peak amplitude relative to the 350 ms pre-stimulus baseline. P3 latency was defined as the time point of maximum positive peak amplitude.

### Statistical Analyses

Maximum likelihood (ML) analysis of the individual observations in which hypotheses about the means, variances, and covariances are tested, was used to investigate effects of birth order, zygosity (6 groups), and sex using the structural equation modelling package, Mx (Neale, 1997). In addition, means and variances were tested for equality across twins and siblings. Models were fitted to the data, progressing from the most saturated to the more restrictive, with the fit of each model tested by the likelihood ratio chi-squared test against the preceding, more complex model within which it is nested (Neale and Cardon, 1992). Twin correlations and 95% confidence intervals were also computed by ML and correlations were tested for homogeneity. It was assumed that sib-pairs correlate the same as DZ twin pairs.

To examine the sources and pattern of covariation across site for P3 amplitude and P3 latency, and specifically whether there are common genetic influences, a

Cholesky decomposition was used. A complete decomposition for the three sources of variance—additive genes (A), shared environment (C), and individual environment (E)—was specified initially. This full model was then simplified by successive dropping of nonsignificant parameters, i.e., by determining whether dropping a parameter resulted in a significant increase in the goodness-of-fit chi-square. The same principles of parsimony were applied in arriving at the preferred model as described above (Neale and Cardon, 1992).

## RESULTS

### Preliminary Analyses

P3 amplitude was highly inter-correlated across site (Table I). The correlations between respective lateral sites, and midline and lateral sites within a region were higher (0.84 to 0.95) than the correlations between different regions (e.g., frontal and parietal sites). Among the regions, the correlations were higher for proximate sites (0.68 to 0.80) and successively less so with more distant sites (0.35 to 0.37). However, for the anterior temporal sites, which were the farthermost laterally placed electrodes from the midline, the correlation between left and right lateral sites (0.63) was lower than for other lateral sites. Inter-correlations for P3 latency were even higher than those found for P3 amplitude, with correlations between corresponding lateral, and midline and lateral sites all above 0.90, except for anterior temporal sites (0.81). Correlations among regions showed a similar pattern to that of P3 amplitude, with proximate sites being more highly correlated than between more distant sites.

Given the high correlation among lateral and midline sites, a mean P3 amplitude and P3 latency for frontal, central, and parietal regions was computed by averaging across the respective midline and lateral sites. These data were used in all further analyses. Because the correlations among pre-frontal and frontal sites were all $>0.88$, as were correlations between occipital and parietal sites, it was assumed that little additional information was lost by not including pre-frontal and occipital sites. Also, data from anterior temporal sites were not included in the analyses because the P3 was smaller and more difficult to identify at these sites.

Table II shows the mean and standard deviations (*SD*) for P3 amplitude and P3 latency for frontal, central, and parietal regions averaged across left, right, and midline sites in each case. Maximum-likelihood analysis showed there were no significant mean differences or differences in variance between co-twins, zygosity groups, or sex for any of the amplitude or latency measures, and found that means and variances for twins and siblings were homogeneous. Covariances of MZ females and MZ males also could be equated for each of the amplitude and latency measures, and similarly covari-

**Table I.** Correlations Between the Various Electrode Sites for P3 Amplitude (below diagonal) and P3 Latency (above diagonal)

| | | | | | | | | | | | | | | | *P3 latency* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Fz | Cz | Pz | F7 | F8 | Fp1 | Fp2 | F3 | F4 | C3 | C4 | P3 | P4 | O1 | O2 |
| Fz | | 0.81 | 0.67 | 0.83 | 0.84 | 0.84 | 0.84 | 0.95 | 0.95 | 0.81 | 0.79 | 0.66 | 0.65 | 0.56 | 0.57 |
| Cz | 0.73 | | 0.83 | 0.64 | 0.64 | 0.63 | 0.63 | 0.79 | 0.80 | 0.94 | 0.92 | 0.82 | 0.80 | 0.69 | 0.70 |
| Pz | 0.47 | 0.84 | | 0.53 | 0.50 | 0.48 | 0.47 | 0.67 | 0.66 | 0.85 | 0.85 | 0.93 | 0.93 | 0.83 | 0.84 |
| F7 | 0.66 | 0.59 | 0.46 | | 0.81 | 0.90 | 0.99 | 0.91 | 0.85 | 0.70 | 0.66 | 0.55 | 0.52 | 0.44 | 0.44 |
| F8 | 0.57 | 0.56 | 0.46 | 0.63 | | 0.84 | 0.87 | 0.84 | 0.88 | 0.65 | 0.69 | 0.51 | 0.52 | 0.43 | 0.45 |
| Fp1 | 0.74 | 0.49 | 0.36 | 0.81 | 0.68 | | 0.99 | 0.87 | 0.85 | 0.66 | 0.65 | 0.50 | 0.49 | 0.41 | 0.43 |
| Fp2 | 0.73 | 0.49 | 0.36 | 0.77 | 0.75 | 0.95 | | 0.86 | 0.86 | 0.65 | 0.65 | 0.48 | 0.48 | 0.41 | 0.43 |
| F3 | 0.91 | 0.76 | 0.55 | 0.83 | 0.65 | 0.82 | 0.79 | | 0.96 | 0.82 | 0.78 | 0.67 | 0.65 | 0.56 | 0.56 |
| F4 | 0.91 | 0.77 | 0.56 | 0.72 | 0.77 | 0.76 | 0.78 | 0.91 | | 0.81 | 0.81 | 0.67 | 0.67 | 0.56 | 0.58 |
| C3 | 0.69 | 0.91 | 0.82 | 0.67 | 0.54 | 0.54 | 0.52 | 0.80 | 0.75 | | 0.91 | 0.86 | 0.82 | 0.71 | 0.70 |
| C4 | 0.62 | 0.89 | 0.82 | 0.54 | 0.63 | 0.44 | 0.47 | 0.67 | 0.76 | 0.84 | | 0.83 | 0.85 | 0.70 | 0.73 |
| P3 | 0.44 | 0.79 | 0.94 | 0.47 | 0.42 | 0.34 | 0.34 | 0.54 | 0.52 | 0.84 | 0.77 | | 0.93 | 0.87 | 0.84 |
| P4 | 0.42 | 0.78 | 0.92 | 0.40 | 0.44 | 0.32 | 0.33 | 0.48 | 0.52 | 0.73 | 0.82 | 0.87 | | 0.86 | 0.87 |
| 01 | 0.26 | 0.58 | 0.80 | 0.36 | 0.34 | 0.27 | 0.26 | 0.38 | 0.36 | 0.60 | 0.58 | 0.83 | 0.79 | | 0.94 |
| 02 | 0.22 | 0.54 | 0.79 | 0.35 | 0.38 | 0.27 | 0.27 | 0.35 | 0.35 | 0.56 | 0.59 | 0.78 | 0.83 | 0.89 | |
| | *P3 amplitude* | | | | | | | | | | | | | | |

**Table II.** Means (*SD*) for P3 Amplitude and P3 Latency

| | Females ($N$ = 379–386) | Males ($N$ = 313–322) |
|---|---|---|
| P3 amplitude (uv) | | |
| Frontal | 3.9 (3.2) | 4.2 (3.3) |
| Central | 4.2 (3.5) | 5.2 (3.9) |
| Parietal | 4.7 (3.9) | 6.4 (4.5) |
| P3 latency (ms) | | |
| Frontal | 291 (50) | 294 (52) |
| Central | 289 (58) | 294 (57) |
| Parietal | 297 (68) | 310 (63) |

ances of same sex DZ and opposite sex DZ twin pairs were homogeneous, indicating no sex limitation of genetic or environmental influences.

Fig. 1 shows the ERP waveforms for co-twins of a representative MZ and DZ twin pair. The amplitude of the P3 is more similar for the MZ than the DZ pair and this resemblance between co-twins is seen at frontal central and parietal sites. The similarity in P3 latency for the MZ pair and difference in P3 latency for co-twins of the DZ pair is also clearly evident. In both MZ and DZ twin pairs, there was variation in the topography of the P3. For some participants, P3 was largest at parietal sites and in others it was of similar amplitude at frontal, central, and parietal sites. The latency of P3 is on average 300 ms (post-target), somewhat fast for a visual P3. Given that the target is preceded by a salient fixation stimulus, presented 250 ms pre-target that marks the beginning of the trial, this latency is not wholly unexpected.

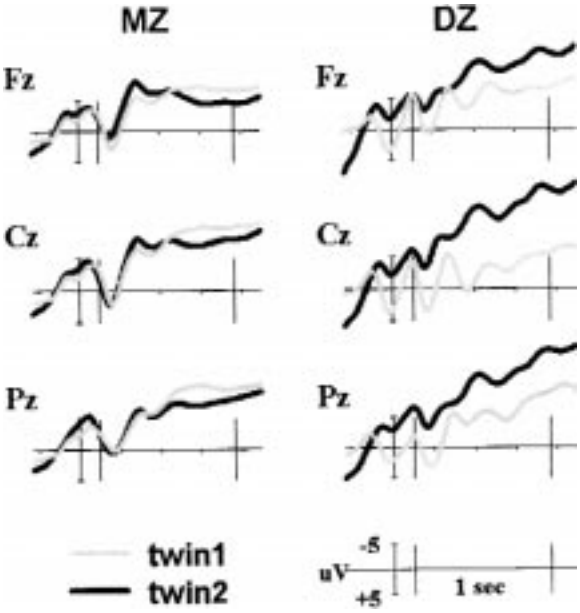


**Fig. 1.** These waveforms show the P3(00) recorded at FZ, CZ, and PZ for a representative MZ and DZ twin pair. The vertical bars represent target onset (0 ms), target offset in memory trials (150 ms), and fixation offset (1100 ms) for trials with a 1-sec delay.

## Genetic Analyses

Twin correlations are shown in Table III. The MZ correlations for P3 amplitude ranged from 0.50 to 0.64 and were approximately twice those for DZs, which ranged from 0.24 to 0.33, indicating additive genetic control of familial aggregation for P3 amplitude. The genetic influence appeared to be quite similar across frontal, central, and parietal regions, with the highest MZ correlation evident at parietal. Moreover, the MZ and DZ correlations for males and females separately showed a similar pattern to those pooled across males and females. Correlations for opposite sex pairs (DOS) could be equated to the same sex DZ correlations, suggesting that P3 amplitudes were not influenced by the sex of the participant.

For P3 latency, MZ correlations ranged from 0.44 to 0.54 and were higher than their DZ counterparts (0.20 to 0.29), suggesting a genetic influence on P3 latency, and one that was similar across sites. A similar pattern was evident for females, with MZF correlations being approximately twice those for DZF at frontal and parietal sites. At central sites, a smaller difference in the zygosity correlations was indicated because the DZF correlation is higher than for frontal and parietal sites. In males, the difference between MZM and DZM correlations is smaller than that indicated for females. However, for each of these measures both the MZ male and female correlations, and the DZ same and opposite sex correlations, were homogeneous. In the following analyses, MZ and DZ groups are pooled over sex.

To dissect the relative contributions of genes and environment to the covariation between P3 amplitude at the three sites, a Cholesky decomposition for three sources of variance—additive genes, shared environment, and individual environment (ACE model)—was specified giving a fit of $-2LL_{2094} = 9702.1$. Dropping the genetic factors from the model (CE model) significantly worsened the fit ($\Delta\chi^2_6 = 34.8$ (critical value of $\chi^2_6 = 12.59(1)$), whereas dropping the shared environment factors from the ACE model resulted in a $\Delta\chi^2_6 = 1.0$ (ns), indicating a good fit to the model. Thus,

**Table III.** ML Twin Correlations (95% confidence intervals) of P3 Amplitude and Latency for Frontal, Central, and Parietal Sites

| | P3 amplitude | | | P3 latency | | |
|---|---|---|---|---|---|---|
| | Frontal | Central | Parietal | Frontal | Central | Parietal |
| MZ | 0.51 | 0.57 | 0.65 | 0.44 | 0.47 | 0.54 |
| (*N* = 132–140 prs) | (0.38–0.61) | (0.46–0.66) | (0.55–0.73) | (0.30–0.55) | (0.33–0.58) | (0.41–0.65) |
| DZ | 0.24 | 0.27 | 0.33 | 0.21 | 0.29 | 0.20 |
| (*N* = 155–166 prs) | 0.09–0.38 | (0.12–0.40) | (0.19–0.45) | (0.06–0.35) | (0.15–0.43) | (0.06–0.33) |
| MZM | 0.58 | 0.65 | 0.70 | 0.45 | 0.43 | 0.57 |
| (*N* = 54–59 prs) | (0.37–0.68) | (0.50–0.75) | (0.56–0.78) | (0.22–065) | (0.19–0.60) | (0.36–0.71) |
| MZF | 0.47 | 0.50 | 0.61 | 0.60 | 0.50 | 0.53 |
| (*N* = 78–81 prs) | (0.26–0.61) | (0.31–0.64) | (0.45–0.72) | (0.45–0.71) | (0.33–0.63) | (0.34–0.66) |
| DZM | 0.16 | 0.33 | 0.38 | 0.32 | 0.35 | 0.42 |
| (*N* = 39–42 prs) | (−0.14–0.41) | (0.02–0.55) | (0.10–0.58) | (−0.06–0.54) | (−0.02–0.59) | (0.12–0.62) |
| DZF | 0.26 | 0.24 | 0.30 | 0.29 | 0.47 | 0.22 |
| (*N* = 41–46 prs) | (−0.02–0.47) | (−0.08–0.49) | (−0.08–0.54) | (0.04–0.52) | (0.21–0.64) | (−0.05–0.44) |
| DZOS | 0.29 | 0.25 | 0.32 | 0.23 | 0.15 | 0.22 |
| (*N* = 75–78 prs) | (0.06–0.47) | (0.05–0.42) | (0.14–0.46) | (0.06–0.41) | (−0.03–0.33) | (0.08–0.41) |

these data suggest that additive genes are an important source of variation in P3 amplitude and covariation in P3 amplitude between sites, and that it is not necessary to further invoke shared environment as a source of familial correlation.

The principal features of the AE model can be seen in Fig. 2. A common genetic factor (A1) was indicated,

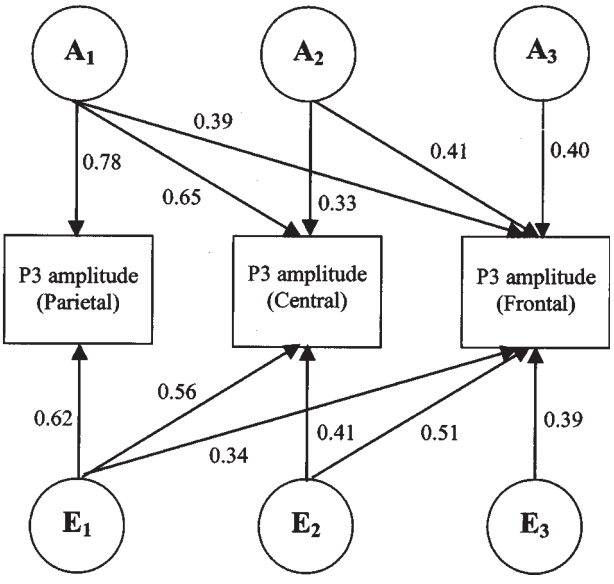


**Fig. 2.** Path diagram showing latent genetic and environmental influences on P3 amplitude.

accounting for 61% ($0.78^2$) of the variance in P3 amplitude at parietal sites, 42% ($0.65^2$) of the variance in P3 amplitude at central sites, and 15% of the variance at frontal sites, such that genetic influences which increased P3 amplitude at parietal sites also increased P3 amplitude at central and frontal sites. A second independent genetic factor (A2) accounted for 11% ($0.33^2$) and 17% ($0.41^2$) of the variance at central and frontal sites, respectively. A third (A3) genetic factor accounted for 16% ($0.40^2$) of the genetic variance at frontal sites. Thus, for P3 amplitude the genetic factor influencing amplitude at parietal sites also influences amplitude at central and frontal sites. Because individual environmental variance also subsumed any errors of measurement, it was expected that the vertical paths from E1, E2, and E3 to the corresponding first, second, and third variables, respectively, would be large. There was also significant cross loading of the E factors on P3 amplitude.

The same model fitting was applied to P3 latency. Dropping the genetic factor (CE model) from the ACE model ($\chi^2_{2066} = 21019.8$) worsened the fit of the model but not significantly ($\Delta\chi^2_6 = 10.6$ [ns]). However, dropping the shared environment from the ACE model caused only a small increase in chi-square ($\Delta\chi^2_6 = 0.5$ [ns]). Although either an AE or CE model was acceptable, the AE model provided the better fit to the data, suggesting that additive genes are a more important source of variation in P3 latency and covariation in P3 latency among frontal, central, and parietal sites. Further

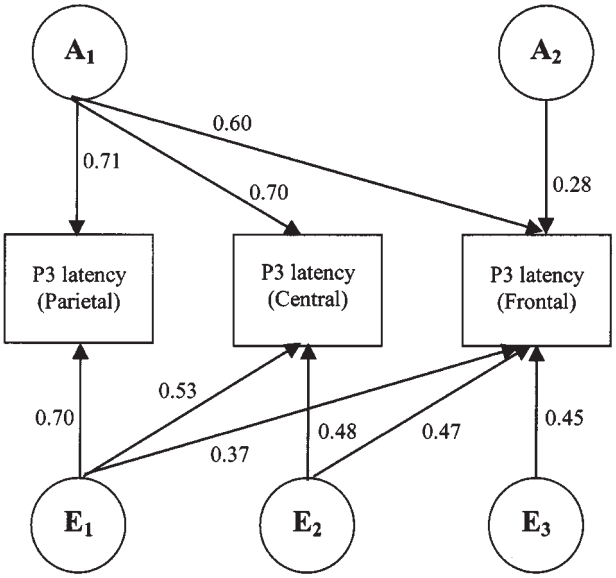


**Fig. 3.** Path diagram showing latent genetic and environmental influences on P3 latency.

simplification of the additive genetic factor structure by successive dropping of nonsignificant parameters resulted in the model shown in Fig. 3. A common genetic factor accounted for 50% ($0.71^2$) of the variance in P3 latency at parietal sites, 49% ($0.70^2$) at central sites, and 36% ($0.60^2$) at frontal sites. A second genetic factor accounted for the remainder of the variance at frontal sites (8% [$0.28^2$]). The vertical paths from the unique environmental factors E1, E2, and E3 to the corresponding first, second, and third variables, respectively, were large and there was also significant cross loading of the E factors on P3 latency.

The genetic and environmental correlations and heritability estimates for amplitude and latency are shown in Table IV. A slightly higher heritability estimate was indicated for P3 amplitude at parietal sites than at frontal sites. In contrast, P3 latency heritability estimates were of similar magnitude at all three sites.

## DISCUSSION

This study investigated the extent to which genetic and environmental factors influenced the variance in the amplitude and latency of the P3(00) elicited in a delayed response working memory task in a large sample of adolescent twin pairs. A significant proportion of the variance in P3 amplitude was attributed to genetic factors and a substantial familial resemblance for P3 latency was indicated, with a strong suggestion that P3 latency was also influenced by genetic factors. The multivariate genetic models showed that a common genetic factor(s) contributed to individual differences measured at different brain regions.

The magnitude of the genetic influence on P3 amplitude ranged from 48% to 61%. This is similar to values estimated by van Beijsterveldt *et al.* (1998), who reported heritabilities averaged across site of 42% for targets and 62% for non-targets. A higher heritability (79%) was estimated by Katsanis *et al.* (1997), which may be attributed to differences between the studies, e.g., stimuli used and age of participants, but may also have been inflated due to low DZ correlations and small sample size. van Beijsterveldt *et al.* (1998) and a follow-up study (van Beijsterveldt *et al.* [this issue]) found a substantial familial resemblance for P3 amplitude but were unable to clearly differentiate between an AE and CE model. They calculated that 597 twin pairs would be required to reject a CE model (power = 0.80) given a heritability of 40% for P3 amplitude. The present study included data from 306 twin pairs as well as additional sib-pairs, compared with 213 twin pairs in

**Table IV.** Genetic Correlations (below diagonal) and Nonshared Environmental Correlations (above diagonal) for P3 Amplitude and P3 Latency at Frontal, Central, and Parietal sites (the variation explained by genetic factors ($h^2$) is given in the last row)

| | P3 amplitude | | | P3 latency | | |
|---|---|---|---|---|---|---|
| | Frontal | Central | Parietal | Frontal | Central | Parietal |
| Frontal | | 0.79 | 0.46 | | 0.76 | 0.54 |
| Central | 0.77 | | 0.81 | 0.98 | | 0.78 |
| Parietal | 0.56 | 0.89 | | 0.83 | 0.90 | |
| $h^2$ | 0.48 | 0.53 | 0.61 | 0.44 | 0.49 | 0.50 |
| (95% CIs) | (0.35–0.58) | (0.41–0.62) | (0.51–0.70A) | (0.34–0.56) | (0.37–0.59) | (0.39–0.62) |

the study of van Beijsterveldt *et al.,* and this significantly larger sample size has provided an increase in power to differentiate between genetic and shared environmental causes of familial aggregation.

It has been suggested that task difficulty may influence the magnitude of the genetic influence on the variance in P3 amplitude, because a difficult task requires more cognitive effort than an easy task, and therefore may be more likely to tap processes that are under genetic control (Polich and Burns, 1987; van Beijsterveldt *et al.,* 1998). However, Katsanis *et al.* (1997) found heritability estimates of P3 amplitude for the easy and difficult condition to be highly similar and van Beijsterveldt *et al.* (1998) found P3 amplitude to targets (oddballs) was less heritable than for non-target (common) stimuli. In the present study, the task would have required more processing resources than an oddball task, and the small P3 amplitude may reflect this increase in cognitive effort, but our heritability estimate for P3 amplitude was no larger than that found by van Beijsterveldt *et al.* (1998). If the heritability of P3 amplitude is not influenced by task difficulty, and further work is needed to examine this, it suggests that one of the genetically mediated processes indexed by the P3 may be a low level cognitive process, such as conscious controlled attention, which is essential for performance of all cognitive tasks of varying difficulty. Few studies have examined the covariance between the amplitude of the P3 elicited in different tasks or the covariance between different cognitive components. However, recently an average genetic correlation of 0.77 between P3 amplitude and the amplitude of N4(00) was reported, suggesting a substantial overlap in the genes influencing the two components (Almasy *et al.,* 2001) and providing some support for a common genetic influence on processing requirements.

The genetic correlations among parietal, central, and frontal sites were high and indicated substantial but not complete overlap in the genes influencing P3 amplitude at these sites. As much as a third of the genetic variance in P3 amplitude at frontal sites was attributable to a common genetic factor influencing the variance in P3 amplitude at parietal and central sites. A further third of the genetic variance at frontal sites was due to the genetic influence at central sites, and the remaining third of the variance was due to a specific genetic factor. This suggests that there may be at least two different genetic influences on P3 amplitude, one influencing all sites and the other frontal sites. The genetic influence on frontal sites may stem from the task requirement to engage working memory and maintain attention focused at the fixation that is a major attribute of frontal lobe function. If the specific (frontal) and common genetic factors are influencing functionally distinct cognitive processes, it suggests there may be more than one neural generator of P3 as indicated by lesion studies (e.g., Polich and Squire 1993; Verleger *et al.,* 1994).

P3 latency was found to exhibit significant familial aggregation at frontal, central, and parietal sites. Because there was a strong suggestion that the familial resemblance was due to genetic factors, an AE model was adopted and 44% to 50% of the variance of P3 latency was attributed to a genetic influence. This finding is in agreement with the pattern seen in several previous studies that found evidence for genetic influences on target P3 latency (Almasy *et al.,* 1999; Eischen and Polich, 1994; Katsanis *et al.,* 1997; Polich and Burns, 1987; Rogers and Deary, 1991; Surwillo, 1980). However, there have been two twin studies (O'Connor *et al.,* 1994; van Beijsterveldt *et al.,* 1998) that have found no effects of either genetic or shared environmental factors. The latter suggested that the low cognitive demands of their simple oddball task may have precluded uncovering a genetic influence. Indeed, Katsanis *et al.* (1997) found a substantial difference in the heritability of P3 latency for the easy and difficult conditions. P3 latency reflects the speed with which attentional resources are allocated for the processing of new stimuli and this may be heritable only when the task is cognitively demanding.

A substantial part of the phenotypic variance of both the amplitude and latency of the P3 was attributable to nonshared (unique) environmental influences. Because individual environmental variance also subsumes any errors of measurement, it is to be expected that the vertical paths will be large. However, there are also significant cross-loadings of the nonshared environmental factors on the measures, and the environmental correlations among sites for both amplitude and latency were high, indicating substantial overlap in nonshared environmental influences at the recording sites. This common nonshared environmental variance most likely reflects the fact that the recordings from all the sites are done simultaneously and any factor, such as a loud noise outside the testing cubicle, will influence all recordings.

In summary, the present study using a large number of twin pairs has shown that individual variation in the amplitude of the P3 at parietal, central, and frontal sites and elicited in delayed response working memory task was mediated by genetic factors. A strong sug-

gestion for a genetic influence on P3 latency was also found. Because the genetic influence on P3 amplitude was of similar magnitude to that found in previous studies using a less demanding oddball task, it is suggested that the heritability of P3 amplitude is not influenced by the greater processing requirements of the task. A prospective analysis, including the amplitude of the P3 and the ERP slow wave (SW) that is elicited to the maintenance of the target location in working memory (Hansell *et al.*, this issue), will provide a better understanding of the genetic factor structure of cognitive ability that is indexed by P3 amplitude. These analyses will be extended further to incorporate other measures of cognitive ability that we have collected concurrently (i.e., performance measures), as well as separately (i.e., psychometric and information processing measures) to examine to what extent low and higher level cognitive processes or neural mechanisms are influenced by the same set of genes.

## ACKNOWLEDGMENTS

We greatly appreciate the support from the twins and their family, and for their willingness to participate in this study. We thank research assistants Kathleen Moore, Marlene Grace, and Ann Eldridge for data collection and recruitment of twin pairs. This work was carried out with the support of the Australian Research Council (Grant Numbers: A79600334, A79906588, A79801419) and the Human Frontier Science Program (Grant Number: RG0154/1998-B).

## REFERENCES

Aitken, J. F., Green, A. C., Eldridge, A., Green, L., Pfitzner, J., and Martin, N. G. (1994). Comparability of naevus counts between and within examiners, and comparison with computer image analysis. *Br. J. Cancer* **69**:487–491.

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

Almasy, L., Porjesz, B., Blangero, J., Goate, A., Edenberg, H. J., Chorlian, D. B., Kuperman, S., O'Connor, S. J., Rohrbaugh, J., Bauer, L. O., Foroud, T., Rice, J. P., Reich, T., and Begleiter, H. (2001). Genetics of event-related brain potentials in response to a semantic priming paradigm in families with a history of alcoholism. *Am. J. Hum. Genet.* **68**:128–135.

Begleiter, H., and Porjesz, B. (1995). Neurophysiological phenotypic factors in the development of alcoholism. In Begleiter, H., and Kissin, B. (eds.), *Alcohol and alcoholism,* Vol. 1, New York, Oxford University Press, pp. 269–293.

Begleiter, H., Porjesz, B., Bihari, B., and Kissin, B. (1984). Event-related brain potentials in boys at risk for alcoholism. *Science* **225**:1493–1495.

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., Schukit, M. A., Cloninger, R., Nurnberger Jr, J., Crowe, R., and Bloom, F. E. (1998). Quantitative trait loci analysis of human event-related brain potentials: P3 voltage. *Electroenc. Clin. Neurophysiol.* **108**:244–250.

Blackwood, D. H. R., St. Clair, D. M., Muir, W. J., and Duffy, J. C. (1991). Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Arch. Gen. Psychiatry* **48**:899–909.

Donchin E. (1980). Presidential address, 1980. Surprise! . . . Surprise? *Psychophysiology* **18**:493–513.

Duncan-Johnson, C. C., and Donchin, E. (1977). On quantifying surprise: The variation of event-related potentials with subjective probability. *Psychophysiology* **14**:456–467.

Egan, V. G., Chiswick, A., Brettle, R. P., and Goodwin, G. M. (1992). The Edinburgh cohort of HIV-positive drug users: The relationship between auditory P3 latency, cognitive function and self-rated mood. *Psychol. Med.* **23**:613–622.

Egan, V. G., Chiswick, A., Santosh, C., Naidu, K., Rimmington, J. E., and Best, J. J. K. (1994). Size isn't everything: A study of brain volume, intelligence and auditory evoked potentials. *Pers. Indiv. Differ.* **17**:357–367.

Eischen, S., and Polich, J. (1994). P300 from families. *Electroenc. Clin. Neurophysiol.* **92**:369–372.

Ford, J. M., White, P., Lim, K. O., and Pfefferbaum, A. (1994). Schizophrenics have fewer and smaller P300s: A single-trial analysis. *Biol. Psychiat.* **35**:96–103.

Geffen, G. M., Wright, M. J., Green, H. J., Gillespie, N. A., Smyth, D. C., Evans, D. M., and Geffen, L. B. (1997). Effects of memory load and distraction on performance and event-related slow potentials in a visuospatial working memory task. *J. Cogn. Neurosci.* **9**:743–757.

Gevins, A., and Smith, M. E. (2000). Neurophysiological measures of working memory and individual differences in cognitive ability and cognitive style. *Cereb. Cortex* **10**:829–839.

Hansell, N. K., Wright, M. J., Geffen, G. M., Geffen, L. B., Smith, G. A., and Martin, N. G. (2001). Genetic influence on ERP slow wave measures of working memory. *Behav. Genet.* **31**: 603–613.

Houlihan, M., Stelmack, R., and Campbell, K. (1998). Intelligence and the effects of perceptual processing demands, task difficulty and processing speed on P300, reaction time and movement time. *Intelligence* **26**:9–25.

Howard, L., and Polich, J. (1985). P300 latency and memory span development. *Dev. Psychol.* **21**:283–289.

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

Magliero, A., Bashore, T. R., Coles, M. G., and Donchin E. (1984). On the dependence of P300 latency on stimulus evaluation processes. *Psychophysiology* **21**:171–186.

McCarthy, G., and Donchin, E. (1981). A metric for thought: A comparison of P300 latency and reaction time. *Science* **211**:77–80.

McGarry-Roberts, P. A., Stelmack, R. M., and Campbell, K. B. (1992). Intelligence, reaction time, and event-related potentials. *Intelligence* **16**:289–313.

Neale, M. C., and Cardon, L. R. (1992). *Methodology for genetic studies of twins and families,* The Netherlands, Kluwer Academic Publishers.

Neale, M. C. (1997). *Mx: Statistical Modeling,* Department of Psychiatry, Box 126 MCV, Richmond, VA 23298.

Nittono, H., Nageishi, Y., Nakajima, Y., and Ullsberger, P. (1999). Event-related potential correlates of individual differences in working memory capacity. *Psychophysiology* **36**:745–754.

O'Connor, S., Morzorati, S., Christian, J. C., and Li, T.-K. (1994). Heritable features of the auditory oddball event-related potential:

Peaks, latencies, morphology and topography. *Electroenceph. Clin. Neurophysiol.* **92**:115–125.
O'Donnell, B. F., Friedman, S., Squires, N. K., Maloon, A., Dracman, D. A., and Swearer, J. M. (1990). Active and passive P3 latency in dementia: Relationship to psychometric, electroencephalographic, and computed tomographic measures. *Neuropsy. Neuropsy. Behav.* **3**:164–179.
O'Donnell, B. F., Friedman, S., Swearer, J. M., and Drachman, D. A. (1992). Active and passive P3 latency and psychometric performance: Influence of age and individual differences. *Int. J. Psychophysiol.* **12**:187–195.
Pelosi, L., and Blumhardt, L. D. (1992). 'Memory-scanning' event-related potentials: Correlations with verbal and performance scores. *Acta Neurol.* **14**:304–312.
Pfefferbaum, A., Ford, J. M., and Kraemer, H. C. (1990). Clinical utility of long latency "cognitive" event-related potentials (P3): The cons. *Electroenc. Clin. Neurophysiol.* **76**:6–12.
Picton, T. W. (1992). The P300 wave of the human event-related potential. *J. Clin. Neurophysiol.* **9**:456–479.
Polich, J. (1998). P300 clinical utility and control of variability. *J. Clin. Neurophysiol.* **15**:14–33.
Polich, J., and Burns T. (1987). P300 from identical twins. *Neuropsychologia* **25**:299–304.
Polich, J., and Martin, S. (1992). P300, cognitive capability, and personality: A correlational study of university undergraduates. *Person. Indiv. Differ.* **13**:533–543.
Polich, J., and Squire. L. (1993). P300 from amnesic patients with bilateral hippocampal lesions. *Electroenc. Clin. Neurophysiol.* **86**:408–417.
Polich, J., Howard, L., and Starr, A. (1983). P300 latency correlates with digit span. *Psychophysiology* **20**:665–669.
Polich, J., Ladish, C., and Burns, T. (1990). Normal variation of P300 in children: Age, memory span, and head size. *Int. J. Psychophysiol.* **9**:237–248.
Polich, J., Pollock, V. E., and Bloom, F. E. (1994). Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychol. Bull.* **115**:55–73.
Porjesz, B., and Begleiter, H. (1996). Effects of alcohol on electrophysiological activity of the brain. In Begleiter, H., and Kissin, B. (eds.), *The pharmacology of alcohol and alcohol dependence.* New York, Oxford University Press, pp. 207–247.
Porjesz, B., Begleiter, H., and Samuelly, I. (1980). Cognitive deficits in chronic alcoholics and elderly subjects assessed by evoked brain potentials. *Acta Psychiatr. Scand.* **62**:15–29.
Rogers, T. D., and Deary, J. (1991). The P300 component of the auditory event-related potential in monozygotic and dizygotic twins. *Acta Psychiatr. Scand.* **83**:412–416.
Roth, W. T., Pfefferbaum, A., Horvath, T. B., Berger, P. A., and Kopell, B. S. (1980). P3 reduction in auditory evoked potentials of schizophrenics. *Electroenc. Clin. Neurophysiol.* **49**:497–505.
Rugg, M. D., and Coles, M. G. H. (1995). *Electrophysiology of the mind: Event related potentials and cognition.* Oxford, Oxford University Press.
Schafer, E. (1985). Neural adaptability: A biological determinant of g factor intelligence. *Behav. Brain. Sci.* **8**:240–241.
Surwillo, W. W. (1980). Cortical evoked potentials in monozygotic twins and unrelated subjects: Comparison of exogenous and endogenous components. *Behav. Genet.* **10**:201–209.
Turetsky, B., Colbath, E. A., and Gur, R. E. (1998). P300 subcomponent abnormalities in schizophrenia: II. Longitudinal stability and relationship to symptom change. *Biol. Psychiat.* **43**:31–39.
Turetsky, B. I., Cannon, T. D., and Gur, R. E. (2000). P300 subcomponent abnormalities in schizophrenia: III. Deficits in unaffected siblings of schizophrenic probands. *Biol. Psychiat.* **47**:380–390.
van Beijsterveldt, C. E. M., Molenaar, P. C. M., de Geus, E. J. C., and Boomsma, D. I. (1998). Individual differences in P300 amplitude: A genetic study in adolescent twins. *Biol. Psychol.* **47**:97–120.
Verleger, R., Heide, W., Butt, C., and Kompf, D. (1994). Reduction of P3b in patients with temporoparietal leasions. *Cog. Brain Res.* **2**:102–116.
Williams, J. T., Begleiter, H., Porjesz, B., Edenberg, H. J., Foroud, T., Reich, T., Goate, A., Van Eerdewegh, P., Almasy, L., and Blangero, J. (1999). Joint multipoint linkage analysis of multivariate qualitative and quantitative Traits: II. Alcoholism and event-related potentials. *Am. J. Hum. Gen.* **65**:1148–1160.
Wright, M., de Geus, E., Ando, J., Luciano, M., Posthuma, D., Ono, Y., Hansell, N., van Baal, C., Hiraishi, K., Hasegawa, T., Smith, G., Geffen, G. M., Geffen, L., Kanba, S., Miyake, A., Martin, N., and Boomsma, D. (2001). Genetics of cognition: Outline of collaborative twin study. *Twin Res.* **4**:48–56.