American Journal of Medical Genetics (Neuropsychiatric Genetics) 88:383–390 (1999)

Heritability of Event-Related Brain Potentials in Families With a History of Alcoholism

L. Almasy,[1]* B. Porjesz,[2] J. Blangero,[1] D.B. Chorlian,[2] S.J. O'Connor,[3] S. Kuperman,[4] J. Rohrbaugh,[5] L.O. Bauer,[6] T. Reich,[5] J. Polich,[7] and H. Begleiter[2]

[1]Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, Texas
[2]Department of Psychiatry, SUNY Health Science Center, Brooklyn, New York
[3]Indiana University School of Medicine, Indianapolis, Indiana
[4]Department of Psychiatric Research, University of Iowa, Iowa City, Iowa
[5]Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri
[6]Department of Psychiatry, University of Connecticut Health Center, Farmington, Connecticut
[7]Department of Neuropharmacology, The Scripps Research Institute, La Jolla, California

Event-related brain potentials (ERPs) are altered in patients with a variety of psychiatric disorders and may represent quantitative correlates of disease liability that are more amenable to genetic analysis than disease status itself. Estimates of heritability are presented for amplitude and latency of the N1 and P3 components of the ERP measured at 19 scalp locations in response to visual and auditory stimuli for 604 individuals in 100 pedigrees ascertained as part of the Collaborative Study on the Genetics of Alcoholism. Significant heritabilities were found for visual P3 amplitude in response to all stimuli and for visual P3 latency in response to target and novel, but not non-target, stimuli. Heritability of visual N1 latencies was uniformly low, whereas heritability of visual N1 amplitude was significant for all electrodes in response to the non-target stimuli but only for posterior electrodes in the other two stimulus conditions. Heritabilities for auditory target P3 were similar to those of the visual stimuli, with auditory target P3 amplitudes and latencies both demonstrating significant heritability. For auditory P2 in response to non-target stimuli, peak amplitude was heritable, but latency was not. Auditory N1 amplitude and latency were significantly heritable for both target and non-target conditions and did not demonstrate the anterior/posterior patterning obtained for visual N1 amplitude. This study represents the first systematic assessment of heritability of these potential neurophysiological markers in families with a history of alcoholism and suggests that many of these ERP phenotypes have heritabilities strong enough to justify genomic screening for loci jointly influencing ERP abnormalities and liability to alcoholism. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88:383–390, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: variance decomposition; event-related brain potentials; statistical genetics; P300; N100

INTRODUCTION

Event-related brain potentials (ERPs) have been shown to be altered in patients with a variety of psychiatric disorders, and in members of their families, compared with the general population. In particular, alcoholic subjects have a reduction of P3 amplitude that remains after long periods of abstinence from alcohol [Porjesz and Begleiter, 1985] and is also present in their young alcohol-naive sons [Begleiter et al., 1984]. Although some studies have not observed a reduction in P3 amplitude in family members of alcoholics, meta-analysis suggests that these inconsistencies may be due to differences in stimulus modality and task difficulty of the paradigms used to elicit the P3 [Polich et al., 1994]. Alcoholics also show abnormalities in N1 amplitude, with equivalent N1 amplitudes in response to stimuli in the task-relevant modality as well as stimuli in the task-irrelevant modality. In contrast, nonalcoholic subjects show an increased N1 amplitude in response to stimuli in the relevant modality [Porjesz and Begleiter, 1979]. Characteristic ERP response patterns also have been demonstrated in schizophrenic pa-

Contract grant sponsor: U.S. Public Health Service; Contract grant number: AA08401; Contract grant sponsor: National Institutes of Health; Contract grant number: GM18897.

*Correspondence to: Laura Almasy, Department of Genetics, Southwest Foundation for Biomedical Research, PO Box 760549, San Antonio, TX 78245-0549. E-mail: almasy@darwin.sfbr.org

Received 30 September 1997; Accepted 2 November 1998

tients and their first degree relatives [Blackwood et al., 1991]. Because these ERP phenomena occur in psychiatric patients themselves and often in their close relatives, the neuroelectric abnormalities may reflect processes that underlie liability to these complex, multifactorial disorders, rather than functional changes caused by disease progression. Thus, an assessment of the genetics of ERPs may provide insight into the underlying neuropathology involved in liability to various psychiatric conditions.

Previous studies of ERP familiality have generally been limited to small to moderately sized samples of twin pairs. Surwillo [1980] and Polich and Burns [1987] compared N1 and P3 latencies in response to an infrequent auditory target stimulus in small samples of monozygotic (MZ) twins and age and sex matched pairs of unrelated controls. Both groups found that P3, but not N1, latency was more similar in the MZ twins than in the unrelated control pairs. Polich and Burns [1987] also assessed N1 and P3 amplitudes and reported that MZ twins showed significant correlations for both these traits although control pairs did not. Eischen and Polich [1994] compared correlations for ERPs from auditory and visual target stimuli among the members of 10 nuclear families with those across families and found that P3 and N1 amplitude and latency all were more highly correlated between family members than between nonrelatives. However, the conclusions that can be drawn from these three studies are somewhat limited as increased similarity among immediate family members could be due to shared environmental factors as well as shared genetic influences.

Rogers and Deary [1991] examined P3 amplitude and latency in response to an infrequent auditory stimulus in 10 MZ and 11 dizygotic (DZ) twin pairs; within-pair similarity was found to be greater for MZ twins than for DZ twins for P3 latency but not amplitude. O'Connor et al. [1994] compared 59 MZ and 39 same-sex DZ twin pairs for measurements of N1 and P3 amplitude and latency made at 17 electrodes in response to auditory target and non-target stimuli. P3 results were reported only for target stimuli and N1 results only for non-target stimuli. Heritability of N1 amplitude was significant only for the Cz electrode, whereas N1 latency showed significant heritabilities at a number of electrodes in the frontotemporal region. Contrary to the findings of Rogers and Deary [1991], O'Connor et al. [1994] found that P3 amplitude demonstrated heritabilities of 0.41 to 0.60 at caudal leads whereas P3 latency evinced no significant heritability.

In the largest study of ERP familiality to date, van Beijsterveldt and colleagues [1996] assessed 213 twin pairs at eight posterior electrodes in response to target and non-target stimuli in a visual oddball paradigm. Male and female twin pairs were analyzed separately, thereby permitting assessment of possible sex-specific influences. For males, P3 amplitude was more highly correlated in MZ twins than in DZ twins for both target and non-target stimuli, suggesting genetic effects on these traits. A similar result was obtained for female twins for nontarget P3 amplitude at the central and parietal leads. In contrast, MZ and DZ correlations in females were very similar for target P3 amplitude, providing no evidence for a genetic effect. However, these sex-specific analyses were based on less than half the data set. When twin correlations were calculated using both male and female twin pairs, resulting in a much larger and therefore more powerful sample, MZ correlations were substantially higher than DZ correlations for both target and non-target P3 amplitude. P3 latency yielded no consistent differences between MZ and DZ twins in either sex-specific or pooled samples.

Katsanis et al. [1997] assayed 30 MZ and 34 DZ twin pairs using a visual stimulus head-orientation ERP paradigm. Subjects were presented with a neutral stimulus and two types of response stimuli, one "easy" and one "difficult." P3 amplitude was heritable for both the easy and difficult tasks, whereas P3 latency was heritable only for the difficult stimulus condition. N1 latency was not heritable for either task, whereas N1 amplitude showed high heritability for both.

Because these studies have used differing sets of electrodes and a variety of stimulus tasks in two sensory modalities, the discrepancies across studies are difficult to evaluate. Only two of these reports [O'Connor et al., 1994; van Beijsterveldt et al., 1996] obtained ERP data from across the whole scalp, whereas others dealt with measurements at only one or a few electrodes. Previous reports of ERP familiality have generally reported correlations, rather than heritability; have lacked standard errors on these estimates; have been of modest statistical significance; and have largely been unable to address questions regarding differences in heritability across scalp locations or sensory modality. In an attempt to address more comprehensively the issue of genetic studies of ERP in families ascertained through an associated disease phenotype, ERP heritability was estimated in a large, pedigree-based sample selected on the basis of multiple alcoholic family members. Heritabilities are reported for N1 and P3 amplitude and latency at 19 scalp locations in response to visual target, non-target, and novel stimuli and auditory target stimuli. Because the auditory nontarget stimuli do not elicit P3, heritabilities are reported for N1 and P2 amplitude and latency for the auditory non-target condition.

MATERIALS AND METHODS

The families in this study were ascertained through six separate sites as part of the Collaborative Study on the Genetics of Alcoholism (COGA). Probands met both *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) criteria for alcohol dependence [American Psychiatric Association, 1987] and Feighner definite criteria for alcoholism, [Feighner et al., 1972] and were also required to have two additional first-degree relatives who were alcohol dependent by the same criteria for a family to enter the study. In 100 families meeting these criteria, 604 individuals were examined in identical electrophysiological laboratories at the six COGA data collection sites. Although family members provided a detailed psychiatric history, no one was excluded on this basis. Mortal illness was the only exclusionary criterion. Family members also completed a neuropsychological battery and a family history ques-

tionnaire, with EEG/ERP data and blood samples collected for subsequent analyses. These procedures were approved by the institutional review boards of all six COGA sites and all participants gave informed consent. Subjects ranged in age from 16 to 70 years old and included approximately equal numbers of males and females (51 versus 49%).

The COGA experimental designs for visual and auditory ERP studies have previously been described in detail in studies documenting the consistency of measurements across the six COGA laboratories [Alexander et al., 1994; Cohen et al., 1994] and the protocols will only briefly be reviewed here. Subjects were seated in a dimly lit sound-attenuated chamber (Industrial Acoustics Corp.) and wore a fitted electrode cap (Electro-Cap International, Inc.) containing the 21 leads of the 10–20 international system. The tip of the nose served as the reference and the forehead as ground. Electrical activity was amplified 10 K (Sensorium EPA-2 Electrophysiology Amplifier) over a bandwidth of 0.02–50 Hz and continuously sampled (Concurrent 5550 computer) at a rate of 256 Hz. Vertical and horizontal eye movements were monitored and artifact rejection was performed on-line. Digital filtering (32 Hz low-pass filter) of the accumulated data was performed off-line.

The visual paradigm consisted of the presentation of three types of stimuli, each of 60 ms duration and subtending a visual angle of 2.5°. Non-target stimuli occurred frequently ($p = 0.75$), whereas novel and target stimuli occurred rarely ($p = 0.125$ each). The three types of stimuli were presented in random order at an interval of 1.6 sec. The target stimulus was the letter X, to which the subject was instructed to press a button as quickly as possible with either the right or left hand, which was counterbalanced across subjects. Squares were used for the non-target stimulus, and novel stimuli consisted of a set of nonrepeating colored geometric polygons. The experiment terminated when a minimum of 25 target, 150 non-target, and 25 novel artifact free trials had been achieved.

In the auditory paradigm, subjects were instructed to keep their eyes focused on a fixation target displayed on the computer monitor. Two types of stimuli were presented binaurally, a low tone (600 Hz) and a high tone (1600 Hz), with a stimulus duration of 60 ms (10 ms rise and fall time, 40 ms plateau) and an intensity of 60 dB SPL. Subjects were required to press a button as quickly as possible in response to the rare ($p = 0.125$) target stimulus, which alternated between the high and low tone across subjects. A total of 25 target and 75 non-target artifact free trials were acquired.

In both the visual and auditory paradigms, target trials with a response time of greater than 1,000 ms were rejected. Speed of response was emphasized, but not at the expense of accuracy. ERPs were averaged across trials for each type of stimulus and a semiautomatic peak picking procedure was used. For all visual stimuli, the P3 component of the response was selected as the largest positive peak within a time window of 250 to 600 ms. For the auditory oddball paradigm, P3 components were selected for target stimuli and P2 for non-target stimuli, with the non-target P2 peak being the largest positive peak prior to the P3 for the target. In both the auditory and visual paradigms, the N1 component was selected as the most negative component within the 75 to 180 ms interval post-stimulus. Peak amplitude was measured relative to the pre-stimulus baseline (187 ms of EEG prior to stimulus onset) and peak latency was taken as the time point with the maximum positive or negative amplitude within the specified time window.

The 100 families examined ranged in size from 2 to 20 phenotyped individuals, with most pedigrees having two generations of family members examined and a few having three generations. The complexity of these pedigrees and their information content are illustrated by the number and variety of pairwise relationships within the families. These pedigrees encompass 1759 phenotyped relative pairs, including 497 parent-child pairs, 758 sibling pairs, 335 avuncular pairs, and 104 first cousin pairs, as well as a number of grandparent-grandchild, half-sibling, half-avuncular, and half-cousin pairs. It should be noted that these relative pair counts are provided to illustrate the complexity of the COGA pedigrees as the maximum likelihood analyses employed utilize entire pedigrees simultaneously.

Additive genetic heritabilities and their standard errors were calculated using standard maximum likelihood variance decomposition techniques, implemented in SOLAR [Almasy and Blangero, 1998], with phenotypes regressed for age and sex prior to analyses. The phenotypic covariance matrix for a pedigree can be written as

$$\Omega = 2\Phi\sigma_g^2 + \mathbf{I}\sigma_e^2$$

where σ_g^2 is the variance due to additive genetic factors, Φ is the kinship matrix, σ_e^2 is the variance resulting from individual-specific environmental effects, and I is an identity matrix. To incorporate dominance effects (nonadditive allelic effects within a locus), an additional variance term is added to this formula, structured by a matrix of Jacquard's Δ_7 coefficients, which reflect the probability of a relative pair sharing two alleles identical by descent from a common ancestor. *P*-values were obtained by comparing a model in which additive genetic heritability was estimated with one in which that parameter was fixed at zero. The difference in $\log_e$ likelihood between these two models is distributed as a mixture of a chi-square distribution with one degree of freedom and a point mass at zero [Self and Liang, 1987]. A similar comparison of nested models was used to assess the significance of dominance effects.

RESULTS

Table I summarizes the visual P3 amplitude and latency results. P3 amplitude evinced highly significant heritabilities across most scalp locations for all three types of visual stimuli. Although heritabilities for visual target stimuli were uniform across the scalp ($h^2 = 0.30$ to 0.53), non-target and novel stimuli tended to show moderate heritabilities at frontal and central leads ($h^2 = 0.15$ to 0.32) and higher heritabilities at parietal and occipital leads ($h^2 = 0.24$ to 0.40). P3 la-

TABLE I. Heritabilities (± Standard Error) for Visual P3 Phenotypes Measured at 19 Scalp Positions

	Amplitude			Latency		
Lead	Target	Non-target	Novel	Target	Non-target	Novel
FP1	0.32 ± 0.08******	0.17 ± 0.06***	0.20 ± 0.07***	0.27 ± 0.07*****	0.02 ± 0.05	0.18 ± 0.06***
FP2	0.30 ± 0.08******	0.15 ± 0.06**	0.21 ± 0.07***	0.34 ± 0.08******	0.03 ± 0.06	0.19 ± 0.06***
F7	0.30 ± 0.07******	0.24 ± 0.07****	0.15 ± 0.07**	0.30 ± 0.07******	0.06 ± 0.08	0.23 ± 0.06******
F3	0.48 ± 0.08******	0.26 ± 0.07*****	0.26 ± 0.07*****	0.39 ± 0.08******	0.07 ± 0.06	0.24 ± 0.06*****
Fz	0.48 ± 0.09******	0.28 ± 0.07******	0.29 ± 0.07******	0.41 ± 0.08******	0.06 ± 0.06	0.23 ± 0.06*****
F4	0.40 ± 0.08******	0.26 ± 0.07*****	0.25 ± 0.07*****	0.38 ± 0.08******	0.07 ± 0.06	0.24 ± 0.06*****
F8	0.30 ± 0.07******	0.18 ± 0.07**	0.19 ± 0.07***	0.33 ± 0.08******	0.12 ± 0.06*	0.23 ± 0.06*****
T7	0.35 ± 0.08******	0.27 ± 0.07*****	0.15 ± 0.07**	0.33 ± 0.07******	0.00 ± 0.00	0.24 ± 0.06*****
C3	0.39 ± 0.08******	0.29 ± 0.07******	0.21 ± 0.07***	0.35 ± 0.07******	0.09 ± 0.06*	0.22 ± 0.06*****
Cz	0.44 ± 0.08******	0.29 ± 0.07******	0.24 ± 0.07****	0.39 ± 0.08******	0.12 ± 0.06*	0.21 ± 0.06*****
C4	0.49 ± 0.08******	0.32 ± 0.08******	0.26 ± 0.07*****	0.45 ± 0.08******	0.12 ± 0.06*	0.22 ± 0.06*****
T8	0.38 ± 0.08******	0.29 ± 0.07******	0.26 ± 0.08****	0.38 ± 0.08******	0.13 ± 0.06**	0.19 ± 0.06****
P7	0.37 ± 0.08******	0.29 ± 0.08*****	0.24 ± 0.08****	0.42 ± 0.08******	0.09 ± 0.06*	0.27 ± 0.06******
P3	0.42 ± 0.08******	0.33 ± 0.07******	0.30 ± 0.07******	0.43 ± 0.08******	0.10 ± 0.06*	0.22 ± 0.06*****
Pz	0.51 ± 0.08******	0.32 ± 0.07******	0.32 ± 0.08******	0.42 ± 0.08******	0.12 ± 0.06*	0.21 ± 0.06****
P4	0.52 ± 0.08******	0.37 ± 0.08******	0.38 ± 0.08******	0.44 ± 0.08******	0.13 ± 0.06**	0.21 ± 0.06*****
P8	0.44 ± 0.08******	0.38 ± 0.08******	0.36 ± 0.08******	0.44 ± 0.09******	0.08 ± 0.06	0.24 ± 0.06*****
O1	0.42 ± 0.08******	0.34 ± 0.08******	0.28 ± 0.07*****	0.46 ± 0.09******	0.07 ± 0.06	0.26 ± 0.06*****
O2	0.53 ± 0.08******	0.39 ± 0.08******	0.40 ± 0.08******	0.49 ± 0.09******	0.09 ± 0.06	0.23 ± 0.06*****

* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$
**** = $p < 0.0001$
***** = $p < 0.00001$
****** = $p < 0.000001$

tency also yielded highly significant heritabilities with a uniform distribution across the leads for visual target and novel stimuli ($h^2 = 0.18$ to 0.49), but very low heritability in response to visual non-target stimuli ($h^2 \leq 0.13$).

Table II presents heritability of visual N1 amplitude and latency. N1 amplitude was highly significant at parietal and occipital leads under all three visual stimulus conditions ($h^2 \geq 0.27$). In contrast, frontal and central leads demonstrated significant heritability of N1 amplitude only in response to the non-target stimuli, although isolated central and temporal leads had moderately significant heritability in the target and novel conditions. Visual N1 latency yielded weak to moderate heritability ($h^2 = 0.00$ to 0.20) under all three stimulus conditions.

Heritability of P3 or P2 amplitude and latency in response to auditory stimuli are presented in Table III.

TABLE II. Heritabilities (± Standard Error) for Visual N1 Phenotypes Measured at 19 Scalp Positions

	Amplitude			Latency		
Lead	Target	Non-target	Novel	Target	Non-target	Novel
FP1	0.00 ± 0.00	0.20 ± 0.07***	0.03 ± 0.06	0.16 ± 0.07**	0.15 ± 0.07**	0.15 ± 0.07**
FP2	0.06 ± 0.06	0.24 ± 0.07****	0.05 ± 0.06	0.17 ± 0.07**	0.13 ± 0.06**	0.16 ± 0.07**
F7	0.00 ± 0.00	0.19 ± 0.07***	0.04 ± 0.06	0.12 ± 0.07*	0.11 ± 0.06*	0.17 ± 0.07**
F3	0.01 ± 0.05	0.24 ± 0.07****	0.04 ± 0.06	0.06 ± 0.06	0.10 ± 0.06*	0.13 ± 0.07**
Fz	0.04 ± 0.06	0.23 ± 0.07****	0.05 ± 0.06	0.09 ± 0.06	0.16 ± 0.07**	0.19 ± 0.07***
F4	0.09 ± 0.06	0.31 ± 0.08******	0.01 ± 0.05	0.11 ± 0.06*	0.14 ± 0.07**	0.16 ± 0.07**
F8	0.05 ± 0.06	0.24 ± 0.07***	0.07 ± 0.06	0.00 ± 0.00	0.11 ± 0.07*	0.15 ± 0.07**
T7	0.14 ± 0.07*	0.34 ± 0.08******	0.12 ± 0.06*	0.10 ± 0.07*	0.07 ± 0.06	0.03 ± 0.05
C3	0.14 ± 0.07*	0.32 ± 0.08******	0.20 ± 0.07***	0.09 ± 0.06	0.15 ± 0.07**	0.16 ± 0.06**
Cz	0.10 ± 0.06*	0.25 ± 0.07****	0.13 ± 0.07*	0.11 ± 0.09*	0.10 ± 0.06*	0.20 ± 0.07***
C4	0.22 ± 0.07***	0.40 ± 0.08******	0.12 ± 0.06*	0.07 ± 0.06	0.17 ± 0.06***	0.12 ± 0.06*
T8	0.21 ± 0.07***	0.30 ± 0.08*****	0.11 ± 0.07*	0.04 ± 0.06	0.12 ± 0.06**	0.02 ± 0.05
P7	0.45 ± 0.09******	0.53 ± 0.08******	0.34 ± 0.08******	0.17 ± 0.07**	0.03 ± 0.05	0.05 ± 0.05
P3	0.43 ± 0.08******	0.49 ± 0.09******	0.38 ± 0.08******	0.09 ± 0.06*	0.12 ± 0.06*	0.11 ± 0.06*
Pz	0.27 ± 0.07*****	0.28 ± 0.08*****	0.32 ± 0.07******	0.10 ± 0.06*	0.19 ± 0.07***	0.15 ± 0.06**
P4	0.40 ± 0.08******	0.47 ± 0.08******	0.35 ± 0.07******	0.09 ± 0.06	0.14 ± 0.06**	0.08 ± 0.06
P8	0.51 ± 0.09******	0.46 ± 0.08******	0.45 ± 0.08******	0.14 ± 0.07**	0.09 ± 0.06*	0.00 ± 0.05
O1	0.49 ± 0.08******	0.37 ± 0.07******	0.43 ± 0.07******	0.13 ± 0.06**	0.10 ± 0.06*	0.07 ± 0.05
O2	0.54 ± 0.08******	0.40 ± 0.07******	0.49 ± 0.07******	0.11 ± 0.06*	0.12 ± 0.06*	0.11 ± 0.06*

* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$
**** = $p < 0.0001$
***** = $p < 0.00001$
****** = $p < 0.000001$

TABLE III. Heritabilities (± Standard Error) for Auditory P3 (Target) and P2 (Non-target) Phenotypes Measured at 19 Scalp Positions

	Amplitude		Latency	
Lead	Target	Non-target	Target	Non-target
FP1	0.34 ± 0.09******	0.27 ± 0.08*****	0.22 ± 0.09**	0.16 ± 0.08*
FP2	0.36 ± 0.08******	0.28 ± 0.08****	0.23 ± 0.08***	0.16 ± 0.08*
F7	0.27 ± 0.07*****	0.27 ± 0.07*****	0.29 ± 0.08****	0.18 ± 0.08**
F3	0.38 ± 0.08******	0.46 ± 0.08******	0.25 ± 0.08***	0.31 ± 0.09****
Fz	0.40 ± 0.08******	0.49 ± 0.09******	0.29 ± 0.09****	0.23 ± 0.09**
F4	0.35 ± 0.08******	0.44 ± 0.09******	0.27 ± 0.08****	0.18 ± 0.08**
F8	0.26 ± 0.08****	0.31 ± 0.08******	0.20 ± 0.08**	0.20 ± 0.07**
T7	0.35 ± 0.08******	0.47 ± 0.08******	0.24 ± 0.08***	0.17 ± 0.07**
C3	0.35 ± 0.07******	0.50 ± 0.09******	0.31 ± 0.09****	0.09 ± 0.07
Cz	0.39 ± 0.07******	0.56 ± 0.09******	0.25 ± 0.08***	0.17 ± 0.08**
C4	0.40 ± 0.07******	0.44 ± 0.08******	0.29 ± 0.09****	0.13 ± 0.08*
T8	0.29 ± 0.08*****	0.39 ± 0.08******	0.20 ± 0.08**	0.10 ± 0.07*
P7	0.28 ± 0.07*****	0.40 ± 0.08******	0.14 ± 0.07*	0.12 ± 0.07*
P3	0.32 ± 0.07******	0.48 ± 0.08******	0.25 ± 0.08***	0.08 ± 0.07
Pz	0.36 ± 0.07******	0.47 ± 0.08******	0.25 ± 0.08***	0.10 ± 0.07
P4	0.36 ± 0.07******	0.44 ± 0.09******	0.24 ± 0.08***	0.06 ± 0.06
P8	0.32 ± 0.07******	0.36 ± 0.08******	0.20 ± 0.08**	0.11 ± 0.07*
O1	0.31 ± 0.07******	0.38 ± 0.08******	0.19 ± 0.07**	0.15 ± 0.07*
O2	0.34 ± 0.07******	0.33 ± 0.08******	0.22 ± 0.08***	0.18 ± 0.07**

* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$
**** = $p < 0.0001$
***** = $p < 0.00001$
****** = $p < 0.000001$

Auditory amplitude and latency demonstrated a pattern similar to that found for visual stimuli. Target P3 and nontarget P2 amplitudes were both highly heritable ($h^2 = 0.27$ to 0.56). Target P3 latency had moderate heritability ($h^2 = 0.14$ to 0.31), but non-target P2 latency produced weak heritabilities, with the exception of a cluster of frontal electrodes demonstrating moderate P2 heritability ($h^2 = 0.18$ to 0.31).

Table IV presents heritability of auditory N1 amplitude and latency. Unlike target P3, the N1 component differed markedly between the visual and auditory stimulus conditions. N1 amplitude heritability was moderate to high ($h^2 = 0.16$ to 0.52) in response to both auditory target and non-target stimuli (Table IV). However, the anterior/posterior heritability differential for visual N1 target and novel amplitudes was not ob-

TABLE IV. Heritabilities (± Standard Error) for Auditory N1 Phenotypes Measured at 19 Scalp Positions

	Amplitude		Latency	
Lead	Target	Non-target	Target	Non-target
FP1	0.22 ± 0.08***	0.31 ± 0.09*****	0.24 ± 0.08***	0.14 ± 0.08*
FP2	0.23 ± 0.08****	0.37 ± 0.09******	0.24 ± 0.08***	0.22 ± 0.08***
F7	0.18 ± 0.08**	0.40 ± 0.08******	0.19 ± 0.08**	0.22 ± 0.08***
F3	0.25 ± 0.08***	0.46 ± 0.08******	0.30 ± 0.09*****	0.40 ± 0.09******
Fz	0.26 ± 0.08****	0.45 ± 0.08******	0.21 ± 0.08***	0.32 ± 0.09*****
F4	0.27 ± 0.08****	0.45 ± 0.08******	0.21 ± 0.08***	0.32 ± 0.10*****
F8	0.17 ± 0.08**	0.39 ± 0.08******	0.26 ± 0.08****	0.22 ± 0.08***
T7	0.12 ± 0.07*	0.25 ± 0.07****	0.20 ± 0.08**	0.21 ± 0.07***
C3	0.33 ± 0.09******	0.47 ± 0.08******	0.32 ± 0.09*****	0.30 ± 0.08******
Cz	0.32 ± 0.09*****	0.52 ± 0.07******	0.32 ± 0.09*****	0.28 ± 0.07******
C4	0.29 ± 0.08****	0.47 ± 0.07******	0.22 ± 0.08***	0.36 ± 0.08******
T8	0.19 ± 0.08**	0.25 ± 0.07****	0.19 ± 0.07**	0.20 ± 0.07***
P7	0.12 ± 0.07*	0.16 ± 0.08**	0.13 ± 0.08*	0.19 ± 0.07***
P3	0.19 ± 0.08**	0.36 ± 0.08******	0.27 ± 0.09***	0.16 ± 0.07**
Pz	0.22 ± 0.08***	0.50 ± 0.08******	0.18 ± 0.08**	0.23 ± 0.07****
P4	0.24 ± 0.08****	0.37 ± 0.08******	0.21 ± 0.08***	0.19 ± 0.07***
P8	0.19 ± 0.08**	0.24 ± 0.08****	0.17 ± 0.07**	0.24 ± 0.07*****
O1	0.17 ± 0.07**	0.28 ± 0.08****	0.19 ± 0.08**	0.17 ± 0.07**
O2	0.21 ± 0.08***	0.33 ± 0.08******	0.18 ± 0.08**	0.16 ± 0.07**

* = $p < 0.05$
** = $p < 0.01$
*** = $p < 0.001$
**** = $p < 0.0001$
***** = $p < 0.00001$
****** = $p < 0.000001$

served in response to the auditory target stimuli, although two isolated electrodes did have weaker heritabilities ($h^2 = 0.12$). Again in contrast to the results found for visual stimuli, N1 latency from target and nontarget auditory stimuli was moderately to highly heritable ($h^2 = 0.13$ to 0.40), with the largest heritability values occurring at the F3, Fz, F4, C3, Cz, and C4 electrodes.

DISCUSSION

The present study assessed ERP heritability in a large pedigree-based sample ascertained through alcoholic probands at 19 electrodes to compare heritabilities across scalp positions, stimulus response tasks (target versus non-target), and stimulus modalities. Use of multiple electrodes and stimulus conditions implies an increased likelihood of observing false positive results. However, traditional corrections for multiple tests would be overly conservative since the present study employs suites of correlated phenotypes. Measurements at nearby scalp locations are highly correlated such that phenotypic correlations among all combinations of the 19 electrodes range from 0.16 to 0.63 for visual target P3 amplitude, from 0.15 to 0.66 for auditory target P3 amplitude, from 0 to 0.74 for auditory target N1 amplitude, and from 0.10 to 0.96 for visual non-target P3 amplitude. Auditory and visual P3 target amplitude are also highly correlated, with phenotypic correlations at the 19 electrodes ranging from 0.46 to 0.61. In contrast, auditory and visual P3 latency and N1 amplitude and latency demonstrate phenotypic correlations around zero. Peak amplitude and latency also yield similarly low phenotypic correlations for both N1 and P3. However, amplitudes are correlated across stimulus type, with correlations between visual target and non-target amplitudes ranging between 0.16 and 0.28 for P3 and between 0.23 and 0.50 for N1.

The complicated pattern of correlations among ERP measurements makes it difficult to determine the effective number of independent statistical tests performed. A total of 380 heritabilities were calculated. Even if a Bonferroni correction were applied, which would be unduly conservative, the 158 heritabilities described as strong (uncorrected $p < 0.0001$) would remain statistically significant with p-values less than 0.05 and almost all (89%) would still have p-values under 0.01. Thus, no corrections have been made to the significance values reported in Tables I–IV.

P3 Amplitude and Latency

P3 amplitude was strongly heritable across all stimulus conditions for both the visual and auditory paradigms. These findings are in agreement with the pattern seen in most previous studies, with the exception of Rogers and Deary [1991], who found no difference in pairwise similarity of P3 amplitude in a small sample of MZ and DZ twins. The present results might most appropriately be compared with those of O'Connor et al. [1994] who also report heritabilities, whereas most other studies of ERP familiality reported correlation coefficients. The present study found heritabilities for P3 amplitude in response to auditory target stimuli that ranged from 0.27 to 0.40. These estimates are slightly lower than those obtained by O'Connor et al. [1994], which ranged from 0.45 to 0.60. However, the estimates from the twin study are broad sense heritability, including dominance effects, whereas the estimates reported here are narrow sense heritability, reflecting only additive genetic effects.

P3 latency demonstrated moderate to strong heritability in auditory target and visual target and novel conditions, but very low heritability in the visual nontarget condition. Although this is in contrast to the O'Connor et al. [1994] and van Beijsterveldt et al. [1996] studies, which found no significant heritability of P3 latency in response to target stimuli, the present findings are similar to other studies that found evidence for genetic influences on target P3 latency [Surwillo, 1980; Polich and Burns, 1987; Rogers and Deary, 1991; Eischen and Polich, 1994; Katsanis et al., 1997].

P2 Amplitude and Latency

P2 amplitude demonstrated strong heritabilities in the auditory non-target condition. Heritability of P2 latency was very low, with the exception of a single frontal lead at which heritability was 0.31 in response to auditory non-target stimuli. The present finding of significant heritability for P2 amplitude is in conflict with the results of Polich and Burns [1987], the only other group to examine familiality of P2 amplitude and latency in response to nontarget stimuli. In a sample of 10 MZ twins, correlations for both P2 amplitude and latency were not significantly different from zero. The present findings are similar to those of the Katsanis et al. [1997] study, which found that correlations in P2 amplitude were significantly higher in MZ than DZ twins in response to both their easy and difficult target conditions, even though correlations for P2 latency did not differ between MZ and DZ twins for either target condition.

N1 Amplitude and Latency

N1 amplitude was heritable for all stimulus conditions in both the auditory and visual modalities. However, a pronounced increase in heritability from anterior to posterior electrodes was found only in response to visual target and novel stimuli. The three previous studies that addressed N1 amplitude also found evidence for genetic influences on this trait in both target [Polich and Burns, 1987; Katsanis et al., 1997] and non-target [O'Connor et al., 1994] stimulus conditions. O'Connor et al.[1994] found a significant heritability for N1 amplitude in response to an auditory nontarget stimulus only at the Cz electrode, the scalp location producing the highest heritability in the present sample.

Katsanis et al. [1997] found the best-fitting maximum likelihood model for N1 amplitude in response to a visual target stimulus was one that contained dominance, rather than additive, genetic effects. However, it is unclear whether they found models containing solely additive genetic effects to be significantly, or only marginally, worse fitting than the nonadditive models. In the present study, two maximum likelihood

models were tested that assessed dominance variance for each of the posterior leads with significant N1 amplitude heritability for the visual target condition. One model allowed dominance variance as the only genetic component and the other allowed both dominance and additive genetic variances. In all cases, the model including only dominance had a significantly worse fit to the data than a model that included additive genetic variance, and the model allowing both types of genetic variance was not significantly better than one allowing only additive genetic influences. Thus, no evidence of non-additive genetic effects on N1 amplitude was found.

N1 latency had very weak heritability in all visual stimulus conditions and moderate to strong heritability for auditory stimulus conditions. Katsanis et al. [1997] also observed no significant heritability of N1 latency for either the easy or difficult conditions in their visual target recognition task. In an auditory paradigm, O'Connor et al. [1994] found heritabilities ranging from 0.43 to 0.63 at frontotemporal electrodes for non-target stimuli. This result is also similar to the present study in which the strongest heritabilities for auditory non-target N1 latency were observed at frontal and central leads.

Environmental Influences

The use of extended families reduces the confounding of genetic influences with shared environmental influences that can be problematic when sibships or nuclear families are studied in isolation. The present sample includes many related individuals who were not raised in the same household and do not presently live in the same household, such as first cousins. To assess the extent to which environmental influences shared by family members residing in the same household might be inflating the observed ERP heritabilities, correlations were calculated for all stimulus conditions at all 19 electrodes in the 46 available phenotyped spouse pairs. Spouses in the COGA sample are unrelated and the correlations between them are most likely due to shared environmental factors, although it is possible that they are due to assortative mating. Only the visual P3 latencies demonstrated significant spousal correlations, indicating that the heritability figures reported for these traits may be overestimates. The mean spouse correlations for the visual P3 latencies taken over the 19 scalp positions were 0.44 for target stimuli, 0.27 for non-target, and 0.46 for novel. Spouse correlations were not different from zero for visual P3 amplitudes, visual N1 ERPs, or auditory ERPs, indicating that the heritabilities reported for these traits are unlikely to have been inflated by shared environmental factors.

CONCLUSION

The present study estimated the heritability of ERP response to a variety of visual and auditory stimuli measured at 19 scalp locations in 100 families with a history of alcoholism. P3 amplitude and latency and N1 amplitude and latency all had significant genetic components. However, heritabilities differed across stimulus modality, stimulus response task, and scalp location. These findings are generally in keeping with those of previous studies, despite the fact that families in this study were ascertained through individuals with alcoholism, a phenotype that has been shown to be correlated with certain ERP abnormalities [Begleiter et al., 1984; Porjesz and Begleiter, 1979, 1985]. To assess the extent to which the ascertainment of these families through alcoholic probands might be influencing the reported heritabilities, a conservative ascertainment correction strategy was employed, conditioning the likelihood of each pedigree on the ERP trait of the alcoholic proband through whom the family was identified. The effects of this ascertainment correction were assessed on target P3 amplitude, the trait with the strongest evidence of a relationship with alcoholism [Porjesz et al., 1996, 1998]. For both the visual and auditory modalities at each of the 19 electrodes, conditioning on the proband's P3 amplitude did not alter the reported heritabilities by more than ± 0.02 and all p-values remained unchanged.

Susceptibility to complex diseases such as alcoholism is primarily a quantitative process that reflects an unobservable continuous liability. In most cases, the underlying risk of disease cannot be assessed and only a dichotomy of affected and unaffected individuals can be evaluated. Moving from a continuous to a dichotomous scale reduces power to detect genetic effects [Wijsman and Amos, 1997]. Quantitative risk factors, such as may be reflected by some ERP paradigms, permit use of the continuous liability scale and thus contain additional genetic information that disease state by itself lacks. A linkage study to locate genes involved in a complex disease process through a correlated quantitative trait might take one of two approaches: (1) identify genes affecting ERPs through quantitative trait linkage analysis and then attempt to ascertain which of these loci is having pleiotropic effects on alcoholism; (2) utilize new methods for simultaneous linkage analysis of discrete and quantitative traits [Blangero et al., 1997]. This bivariate approach exploits pleiotropy between the disease phenotype and the correlated quantitative trait to increase the power to detect linkage over that provided by the discrete trait alone. The present findings suggest that ERP measures associated with risk for alcoholism, such as P3 amplitude, have a substantial and detectable genetic component in families with a history of alcoholism and may be suitable phenotypic markers for these types of quantitative trait and bivariate linkage analyses.

ACKNOWLEDGMENTS

COGA (H. Begleiter, SUNY-Health Science Center at Brooklyn, principal investigator; T. Reich, Washington University, co-principal investigator) includes six different centers where data collection takes place. The six sites and principal investigator and coinvestigators are: Indiana University (J. Nurnberger Jr., P.M. Conneally); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego and Scripps Institute (M. Schuckit, F. Bloom); University of Connecticut (V. Hesselbrock); State University of New York, Health Science Center at Brooklyn (H. Begleiter, B.

Porjesz); Washington University in St. Louis (T. Reich, C.R. Cloninger).

REFERENCES

Alexander JE, Polich J, Bloom FE, Bauer LO, Kuperman S, Rohrbaugh J, Morzorati S, O'Connor SJ, Porjesz B, Begleiter H. 1994. P300 from an auditory oddball task: inter-laboratory consistency. Int J Psychophysiol 17:35–46.

Almasy L, Blangero J. 1998. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Human Genet 62:1198–1211.

American Psychiatric Association. 1987. Diagnostic and statistical manual of mental disorders. Washington, DC.

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

Blackwood DHR, St. Clair DM, Muir WJ, Duffy JC. 1991. Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. Arch Gen Psychiatry 48:899–909.

Blangero J, Almasy L, Williams JT, Porjesz B, Reich T, Begleiter H, and COGA collaborators. 1997. Incorporating quantitative traits in genomic scans of psychiatric diseases: alcoholism and event-related potentials. Psychiatric Genet 74:602.

Cohen HL, Wang W, Porjesz B, Bauer L, Kuperman S, O'Connor SJ, Rohrbaugh J, Begleiter H. 1994. Visual P300: an interlaboratory consistency study. Alcohol 11:583–587.

Eischen SE, Polich J. 1994. P300 from families. Electroencephalography Clin Neurophysiol 92:369–372.

Feighner JF, Robins E, Guze S, Woodruff R, Winokur G, Munoz R. 1972. Diagnostic criteria for use in psychiatric research. Arch Gen Psychiatry 26:57–63.

Katsanis J, Iacono WG, McGue MK, Carlson SR. 1997. P300 event-related potential heritability in monozygotic and dizygotic twins. Psychophysiology 34:47–58.

O'Connor S, Morzorati S, Christian JC, Li T-K. 1994. Heritable features of the auditory oddball event-related potential: Peaks, latencies, morphology and topography. Electroencephalography Clin Neurophysiol 92: 115–125.

Polich J, Burns T. 1987. P300 from identical twins. Neuropsychologia 25: 299–304.

Polich J, Pollock VE, Boom FE. 1994. Meta-analysis of P300 amplitude from males at risk for alcoholism. Psychol Bull 115:55–73.

Porjesz B, Begleiter H. 1979. Visual evoked potentials and brain dysfunction in chronic alcoholics. In: Begleiter H., editor. Evoked brain potentials and behavior. New York: Plenum. p 277–302.

Porjesz B, Begleiter H. 1985. Human brain electrophysiology and alcoholism. In: Tarter DV, Thiel D, editors. Alcohol and the brain. New York: Plenum. p 139–182.

Porjesz B, Begleiter H, Litke A, Bauer LO, Kuperman S, O'Connor SJ, Rohrbaugh J. 1996. Visual P3 as a potential phenotypic marker for alcoholism: evidence from the COGA national project. In: Ogura C, Koga Y, Shimokochi M., editors. Recent advances in event-related brain potential research. New York: Elsevier Science. p 539–549.

Porjesz B, Begleiter H, Reich T, Van Eerdewegh P, Edenberg HJ, Foroud T, Goate A, Litke A, Chorlian DB, Stimus A, Rice J, Blangero J, Almasy L, Sorbell J, Bauer LO, Kuperman S, O'Connor SJ, 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. Alcoholism: Clin Exp Res 22:1317–1323.

Rogers TD, Deary I. 1991. The P300 component of the auditory event-related potential in monozygotic and dizygotic twins. Acta Psychiatr Scand 83:412–416.

Self SF, Liang K-Y. 1987. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. J Am Stat Assoc 82:605–610.

Surwillo WW. 1980. Cortical evoked potentials in monozygotic twins and unrelated subjects: comparisons of exogenous and endogenous components. Behavior Genet 10:201–209.

van Beijsterveldt CEM, Molenaar PCM, de Geus EJC, Boomsma DI. 1996. Individual differences in P300 amplitude: a genetic study in adolescent twins. In: van Beijsterveldt T. The genetics of electrophysiological indices of brain activity: An EEG study in adolescent twins. Amsterdam: Universiteit Van Amsterdam. p 51–68.

Wijsman EM, Amos CI. 1997. Genetic analysis of simulated oligogenic traits in nuclear and extended pedigrees: Summary of GAW10 contributions. Genet Epidemiol 14:719–735.