ELSEVIER

Biological Psychology 61 (2002) 229–248

BIOLOGICAL PSYCHOLOGY

www.elsevier.com/locate/biopsycho

Linkage and linkage disequilibrium mapping of ERP and EEG phenotypes

Bernice Porjesz [a,*], Henri Begleiter [a], Kongming Wang [a], Laura Almasy [f], David B. Chorlian [a], Arthur T. Stimus [a], Samuel Kuperman [b], Sean J. O'Connor [c], John Rohrbaugh [d], Lance O. Bauer [e], Howard J. Edenberg [c], Alison Goate [d], John P. Rice [d], Theodore Reich [d]

[a] *Department of Psychiatry, State University of New York, Health Science Center at Brooklyn, Box 1203, HSCB, 450 Clarkson Avenue, Brooklyn, NY 11203-2098, USA*
[b] *University of Iowa, Psychiatry Research, Iowa City, IA 52242, USA*
[c] *Indiana University School of Medicine, Indianapolis, IN 46202, USA*
[d] *Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA*
[e] *Department of Psychiatry, University of Connecticut Health Center, Farmington, CT 06030, USA*
[f] *Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio, TX 78245, USA*

Abstract

Linkage analyses of highly heritable electrophysiological phenotypes (EEG, ERP) that can potentially identify individuals at risk for alcoholism were performed on a large sample of families with a high density of alcohol dependence as part of the Collaborative Study on the Genetics of Alcoholism (COGA); these genetic findings are summarized. Quantitative trait loci (QTLs) were identified for several ERP characteristics (P300, N100, N400) and for the beta frequencies of the EEG where we report linkage and linkage disequilibrium at a $GABA_A$ receptor gene on chromosome 4. Genetic analyses of ERPs suggest that several regions of the human genome contain genetic loci related to the generation of N100, N400 and P300, which are possible candidate loci underlying the functional organization of human neuroelectric activity. The advent of genomics and proteomics and a fuller understanding of gene regulation, will open new horizons on the critical electrical events so essential for human brain function.

Keywords: P300; ERP; EEG; Genetics

* Corresponding author. Tel.: +1-718-270-2024; fax: +1-718-270-4081
E-mail address: bp@cns.hscbklyn.edu (B. Porjesz).

0301-0511/02/$ - see front matter
PII: S0301-0511(02)00060-1

1. Introduction

In order to identify novel genetic loci contributing to alcoholism susceptibility, recent studies have focused on a genome-wide approach. Such a strategy was employed by the Collaborative Study of the Genetics of Alcoholism (COGA), a multi-site family study designed to include both alcoholic and community control probands and their biological relatives. As psychiatric diagnoses are not unitary entities, but the consequence of several interacting traits, understanding the genetics of alcohol dependence requires correct identification of inherited phenotypes. The COGA study focused on endophenotypes, or covariates that correlate with alcohol dependence, to better define that trait or its underlying genetic mechanism. In COGA, we focused on elecrophysiological measures as biological endophenotypes, in order to identify relatives (including offspring) of affected individuals who would be considered unaffected with typical diagnostic systems. This manuscript is divided into two sections: the first part reviews the COGA genetic findings that are related to electrophysiology (EEG and ERP) and the second part presents new data relating to the genetics of the P3(00) and N1(00) components of the event related potential (ERP).

2. ERP and alcohol dependence

There are a number of problems in studying psychiatric genetics, including the genetic predisposition for alcoholism. Psychiatric illnesses are complex disorders, which can manifest low penetrance, clinical heterogeneity, variable expressivity, phenocopies, involve joint action of several disease loci, and have problems of stability of diagnoses over time. It has been suggested that diagnostic categories, along with their symptoms, reflect distal and variable effects of genes that increase vulnerability to the psychiatric disorders. In contrast, neurobiological dysfunctions reflect more proximal effects of such genes (Tsuang and Faraone, 2000). Because of the various problems with uncertainty of diagnosis in complex diseases, it is critical to find biological markers and use them instead of, or in addition to affected status. These biological markers (endophenotypes) serve as covariates that correlate with the main trait of interest and serve to better define that trait or its underlying genetic mechanism. Endophenotypes represent the genetic liability of the disorder among non-affected relatives of affected individuals. These biological endophenotypes need not be disease specific.

Biological endophenotypes are important in that they can: (1) identify relatives of affected individuals who would be considered unaffected with typical diagnostic systems, (2) identify individuals at risk before the development of the disease, and (3) help identify a candidate location for illness-susceptibility loci. Ideally, molecular genetic studies should be performed not on psychiatric diagnosis but on biological measures of the genetic predisposition involved in psychiatric disorders (Tsuang and Faraone, 2000).

Human ERPs provide a rich source of potentially useful endophenotypes for psychiatric genetics. These voltage deflections represent the amalgam of several overlapping components emanating from specific brain generators. These components can be divided into exogenous potentials, primarily influenced by the physical characteristics of the eliciting stimulus (Jewett et al., 1970; Cracco and Cracco, 1976) and endogenous potentials, which are primarily influenced by cognitive processes (Sutton et al., 1965; Donchin et al., 1978; Hillyard et al., 1978). While the spatial resolution of these potentials recorded at the scalp is relatively low, the temporal resolution is extremely high, providing a unique window on the millisecond transactions that take place in the human brain.

In 1965, Sutton and his colleagues first observed the P3(00) component in the human ERP. This endogenous component is the third positive component maximal at the parietal midline, and occurs in response to an infrequent task-relevant event. The voltage of the P3 component is significantly low in a variety of psychiatric disorders including schizophrenia (Roth et al., 1980; Brecher and Begleiter, 1983; McCarley et al., 1993; Ford et al., 1994), attention deficit disorder (Klorman et al., 1979), and alcoholism (Porjesz et al., 1980, 1987; Emmerson et al., 1987; Patterson et al., 1987; Pfefferbaum et al., 1991; Cohen et al., 1995; Prabhu et al., 2001). It was assumed that the P3 deficit in alcoholism was the consequence of the deleterious effects of alcohol on the brain; however, after a sufficient period of abstinence, many of the clinical abnormalities characteristic of alcohol dependence as well as sensory evoked potential deficits (e.g. brainstem potential) return to normal, while the P3 amplitude abnormality persists (Porjesz and Begleiter, 1985). This protracted deficit in long-term abstinent alcoholics suggested the possibility that P3 deficits may antecede alcohol use and dependence, and therefore be found in young individuals at high risk to develop alcoholism, such as young sons of alcoholic fathers.

Begleiter et al. (1984) reported that significantly lower P3 amplitudes could be observed in pre-adolescent sons of alcoholics who were naive to alcohol use or other illicit drugs. This was in contrast to control boys matched on a number of demographic variables to the boys at high risk for developing alcoholism. These significant differences were obtained without the administration of alcohol or placebo. While these findings have been replicated by many laboratories (O'Connor et al., 1987; Whipple et al., 1988; Porjesz and Begleiter, 1990; Hill et al., 1990; Whipple et al., 1991; Hill and Steinhauer, 1993; Berman et al., 1993; Benegal et al., 1995; Ramachandran et al., 1996; van der Stelt et al., 1998; van Der Stelt, 1999), a few studies failed to replicate the initial results (Polich and Bloom, 1987; Polich et al., 1988a,b). However, this same group performed a meta-analysis of all the published studies, and concluded that the low P3 observed in high-risk individuals may have predictive value as an index of vulnerability for alcoholism (Polich et al., 1994); the strongest findings were obtained for difficult visual tasks in young males. The use of low P3 voltage as a potential phenotypic marker was strengthened by studies suggesting that the reduced P3 found in alcoholics (Pfefferbaum et al., 1991) and in high-risk males (Benegal et al., 1995) was highly correlated with the number of dependent individuals in the family. In a well-designed study, Pfefferbaum et al. (1991) demonstrated that the amplitude of P3 in abstinent alcoholics was not related

to alcohol intake but was significantly related to the number of affected relatives in the family. While over the last few decades the P3 component of the ERP has been found to be of limited clinical use, its utility in the study of the pathogenesis of alcohol dependence appears to be quite promising.

3. Collaborative Study on the Genetics of Alcoholism (COGA)

In 1989, a large national study known as the Collaborative Study on the Genetics of Alcoholism (COGA) was implemented with the express purpose of identifying genetic loci linked with the predisposition to develop alcoholism. A comprehensive review of the literature on the genetic epidemiology of alcoholism from twin studies, family studies and adoption studies concluded that the genetic effects account for 40–60% of the variance in the liability for alcoholism (Hesselbrock, 1995). The search for genes influencing the predisposition toward alcoholism is extremely arduous because it is difficult to understand how genetic risk is transmitted. Furthermore, psychiatric diagnosis is not informative regarding the underlying biological mechanisms. These problems lead to both false positives and false negatives, resulting in loss in statistical power when conducting linkage analysis. Thus, an alternative approach to the use of clinical phenotypes is to identify the fundamental neurobiological characteristics associated with alcoholism, the so-called endophenotypes or intermediate phenotypes, whose manifestation may be more closely linked to gene expression (Gottesman and Shields, 1972). Using heritable biological endophenotypes that could identify individuals at genetic risk in the absence of overt symptoms can alleviate many of the problems mentioned above. Endophenotypes represent the genetic liability of the disorder among non-affected relatives of affected individuals and need not be disease specific. This approach can also help identify a candidate location for the illness-susceptibility loci. Thus the COGA project has focused on the use of correlated quantitative biological endophenotypes, specifically electrophysiological measures such as EEG and ERP characteristics in conducting genetic analyses.

One of the basic criteria which must be met in order to consider a variable as a phenotypic marker or endophenotype, is to establish the heritability of that particular variable (Begleiter and Porjesz, 1995). Twin studies provide compelling evidence for the heritability of the P3 amplitude of the ERP. A large twin study (O'Connor et al., 1994) recorded P3 amplitude in monozygotic and dizygotic twins. The authors report that the estimate of heritability ranges between 0.49 and 0.60 at posterior leads. Similar heritabilities have been reported for P3 amplitude in the largest Mz–Dz twin studies to date in Holland (van Beijsterveldt, 1996; van Beijsterveldt et al., 1998), and in Australia (Wright et al., 2001). Even higher heritabilities (0.79) have been reported from the Minnesota Twin sample (Katsanis et al., 1997). Genetic correlations between P300 and the EEG power spectrum were examined (Anokhin et al., 2001). A substantial proportion of genetic influences on P3 amplitude were explained by strong heritability of slow EEG rhythms. A recent meta-analysis across five P300 twin studies (van Beijsterveldt and van Baal, 2002a,b)

estimated the heritability of P300 amplitude to be 60% (95% CI: 54–64%). Almasy et al. (1999) have recently reported significant heritabilities for P3 and N1 amplitudes based on 604 individuals from 100 families in the COGA family study. For visual target stimuli, there was significant heritability for P3 across the scalp that was somewhat higher parietal-occipitally; for N1, heritabilities were only significant at posterior leads, with a large anterior–posterior differential. Heritabilities for P3 to targets were similar but weaker for the auditory modality compared to the visual modality. On the other hand, the N1 heritabilities to targets differed markedly between visual and auditory stimulus conditions; auditory N1 heritabilities did not show the anterior–posterior differential. These strong heritability findings encouraged us to identify possible genetic loci related to the amplitude of the P3 and N1 components of the ERP.

In addition to heritability, there are a number of additional criteria that must be met in order for a variable to be considered as a phenotypic marker or endophenotype (Begleiter and Porjesz, 1995). In the general population, the trait must be reliable and stable, have a low base rate, and must identify individuals at risk. In the patient population, the trait should be prevalent, present during symptom remission (i.e. trait not state-related), present in first degree relatives of the index case at a rate higher than the normal population, and it should segregate with the illness in the affected relatives.

Using these criteria, we compared the distribution of P3 amplitude in individuals over 16 years of age from randomly ascertained control families (to obtain population base rates) to age and gender matched distributions from densely affected alcoholic families in the COGA project (Porjesz et al., 1996, 1998). The control distributions were based on 687 individuals from 163 randomly ascertained families and the distributions from the alcoholic families were based on 1276 individuals from 219 densely affected families. The control sample did not exclude individuals with psychiatric illness or alcoholism to obtain incidence rates of psychiatric disorders similar to those of the general population. P3 amplitude data was converted to z-scores, and a P3 amplitude beyond 2 SDs below the mean was considered an "abnormal trait". When age- and gender-matched distributions of P3 amplitude were compared, members of densely affected COGA families were more likely to manifest low P3 amplitudes (2 SD below the mean) than members of random control families. Not only did alcohol-dependent individuals from dense alcoholic families have significantly lower P3 amplitudes than alcohol dependent individuals from random control families, but significantly more alcoholics (22.1%) from the dense families were 2 SD below the mean compared to alcoholics from control families (2.9%) ($P < 0.00001$). Both sons and daughters of alcoholic male probands manifested significantly lower P3 amplitudes compared to age and gender matched offspring of control male probands, with significantly more of them in the "abnormal" range (15.7% vs. 2.5%, $P < 0.00001$). In addition, the unaffected members of alcoholic families had significantly lower P3 amplitudes compared to age and gender matched unaffected members of control families, with 6.8% of them in the range 2 SD below the mean compared to 0.1% from the normal population ($P < 0.00001$). Furthermore, alcoholic members of dense alcoholic families had signifi-

cantly lower P3 amplitudes than unaffected members of dense alcoholic families. These findings in both the general population and patient population indicate that P3 amplitude meets all the criteria listed above, further establishing the P3 component of the ERP as a good putative phenotypic marker (Porjesz et al., 1996, 1998).

4. Previous linkage findings from the COGA project

Linkage analysis was performed on the age-regressed visual P3 (VP3) target (607 individuals in 103 dense alcoholic families) dataset implementing the Sequential Oligogenic Linkage Analysis Routines (SOLAR) method, a multivariate, multipoint quantitative linkage package using variance components (Almasy and Blangero, 1998). A likelihood of odds ratio (LOD) score greater than 3.0 is considered to be significant for linkage. The SOLAR analysis found a significant linkage for the P300 amplitude at the O2 electrode on chromosome 2 (D2S434, 218 cM) (LOD = 3.28; $P < 0.0299$) and on chromosome 6 (D6S495, 213 cM) (LOD = 3.41; $P < 0.0219$) for the Cz electrode. LOD scores greater than 2.0, suggestive of linkage were also found for the T8 electrode on chromosomes 5 (D5S1501, 76 cM) and 13 (D13S321, 45 cM). These first electrophysiological genetic findings from the COGA project of several Quantitative Trait Loci (QTLs) influencing visual target P3 amplitude were published (Begleiter et al., 1998).

Given the strong evidence for several QTLs influencing VP3 amplitude, it was important to determine whether these loci also influence the risk for alcoholism. Using the SOLAR suite of programs, COGA performed a bivariate analysis, a method that allows for joint consideration of both the disease (alcoholism) and quantitative precursors/correlates (P3 amplitude) in pedigrees of arbitrary size and complexity (Williams et al., 1999). For the qualitative disease outcome, a continuous underlying liability distribution is assumed from which disease is determined by a threshold process. This procedure can assess whether correlations between P3 amplitude and alcoholism stem from shared genetic influences. We performed bivariate linkage screens of the three diagnoses (DSM-IIIR, DSM-IV, ICD-10) with P3 amplitude at Cz. The pattern of results was similar between diagnoses, but the strongest evidence for linkage was obtained with DSM-IV. Joint consideration of the DSM-IV diagnosis of alcoholism and the amplitude of the P300 component of the Cz event-related potential significantly increased the evidence for linkage of these traits to a chromosome 4 region near the class I alcohol dehydrogenase locus ADH3 (D4S250). A likelihood-ratio test for complete pleiotropy was significant, suggesting that the same quantitative-trait locus influences both risk of alcoholism and the amplitude of the P300 component.

A semantic priming paradigm was used to elicit the N4(00) component, a negative component occurring approximately 400–600 ms after an incongruent (unprimed) word among contextually related (primed) words. While N4 is obtained to unprimed but not primed words in normal subjects, alcoholics manifest N4s to both primed and unprimed words. A genomewide linkage screen was performed on the amplitude

of the N4 and P3 components of the ERP, measured at 19 scalp locations in response to a semantic priming task for 604 individuals in 100 pedigrees ascertained as part of the COGA (Almasy et al., 2001). N4 and P3 amplitudes in response to three stimuli (nonwords, primed words [i.e. antonyms], and unprimed words) all showed significant heritabilities, the highest being 0.54. Both N4 and P3 showed significant genetic correlations across stimulus type at a given lead and across leads within a stimulus, indicating shared genetic influences among the traits. There were also substantial genetic correlations between the N4 and P3 amplitudes for a given lead, even across stimulus type. N4 amplitudes showed suggestive evidence of linkage in several chromosomal regions, and P3 amplitudes showed significant evidence of linkage to chromosome 5 (D5S1501, 90 cM), and suggestive evidence of linkage to chromosome 4 (D4S2374, 172 cM).

Eyes closed EEG data were also examined in the COGA project. The data from 19 leads were transformed into bipolar values and the EEG power spectrum was divided into the following beta frequency bands: slow beta 1 (12.5–16.0 Hz), beta 2 (16.5–20.0 Hz), and fast beta 3 (20.5–28.0 Hz). The EEG power in these spectral bands was compared between an age and gender matched sample of alcoholics and controls in the 18–50 year age range, after log transformation to a normal distribution. Bipolar pairs were analyzed overall and according to topographical region (frontal, central, and parietal). Significant differences were found between alcoholics and controls for all beta spectral bands (Rangaswamy et al., in press). Alcoholics manifested significantly more beta power, with the most significant differences occurring over central-frontal regions for all three beta bands.

COGA has performed SOLAR linkage analyses for eyes-closed EEG (Porjesz et al., 2002) from 1553 COGA family members from 250 families, using the fitting coefficients obtained from a singular value decomposition procedure, namely trilinear analysis (Wang et al., 2000). Applying this method to the horizontal bipolar pairs for beta 1, beta 2, and beta 3 absolute power, we extracted the first component for each of the three frequency bands. This method greatly reduces the number of variables to be used in subsequent analyses. The spectral values from bipolar leads were first regressed on age and gender, spectral distributions were examined, and values above 4 standard deviations were eliminated. We then ran the t-distribution option of the SOLAR variance component linkage analysis at 1 cM intervals across all chromosomes.

The first component for beta 1 accounted for 54% of the spatial variance and 73% of the spectral variance. The first component for beta 2 accounted for 52% of the spatial variance and 78% of the spectral variance. The first component for beta 3 accounted for 46% of the spatial variance and 70% of the spectral variance. We obtained significant linkage on chromosome 4 at 56 cM for beta 1 (LOD = 3.39) and more strikingly for beta 2 (LOD = 5.01) at the same locus. Suggestive linkage was obtained for beta 3 (LOD = 2.17) at the same locus. It should be noted that for all three beta frequency bands, the EEG linkage results were obtained at the same locus (56 cM) on chromosome 4, the locus of the microsatellite marker in *GABRB1*, which is at or near a cluster of $GABA_A$ receptor genes. Combined linkage/linkage disequilibrium analysis of the beta 2 horizontal trilinear phenotype with this

microsatellite marker yielded a significant LOD score of 6.53 and a P-value of 0.004 for association between beta 2 EEG phenotype and the *GABRB1* marker. The disequilibrium parameter (rho_d = 0.57) also became stronger. These results provide evidence for disequilibrium between the *GABRB1* microsatellite marker and the functional QTL. This significant linkage/linkage disequilibrium for the beta EEG is situated within a cluster of $GABA_A$ receptor genes on chromosome 4 including *GABARA2*, *GABARA4*, *GABARB1*, and *GABARG1*.

5. New linkage findings from the COGA project

We report here the results of linkage analysis based on a larger sample of subjects from the COGA project for the visual P3 paradigm initially reported by Begleiter et al. (1998). However, the current study is not simply a replication study; rather than being based on traditional methodology of averaged ERPs, we have based our analysis on a novel nonlinear method developed in our laboratory, namely, nonlinear dynamic warping (Wang et al., 2001). This new analysis has corroborated the initial findings of genetic signals on chromosomes 2, 5, 6, and 13, and has also identified additional chromosomal regions that may be involved in the P3 component of the ERP. Furthermore, we have also included a linkage analysis of the N1(00) component of the visual ERP using these methods.

6. Materials and methods

As an integral part of the COGA study, identical neurophysiology laboratories were established at all six of the original participating sites (SUNY Health Science Center at Brooklyn, University of Connecticut Health Center, Washington University School of Medicine in St. Louis, University of California at San Diego, University of Iowa, and Indiana University Medical School) for the purpose of collecting electroencephalographic (EEG) and ERP data from both dense alcoholic families and random control families.

Multiplex families with alcoholism were initially recruited from alcoholic probands who were in treatment facilities. Psychiatric diagnoses in all family members were obtained by administering a polydiagnostic instrument designed by COGA (Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994). All probands met DSM-IIIR criteria for alcohol dependence and Feighner definite criteria (COGA criteria). In addition to the proband, the study required two additional first-degree relatives who were alcohol dependent by the same COGA criteria on direct interview. Individuals with co-morbidity were included, with mortal illness as the sole exclusionary criterion. In addition, family members completed a neuropsychological battery and Family History questionnaire, blood was collected for various biochemical assays and DNA, and EEGs/ERPs were recorded. The control families were randomly ascertained, and included individuals with psychiatric disorders (including alcohol dependence), to reflect the prevalence

of such disorders in the general population. The protocol for the control families was otherwise identical to that of the families with alcohol dependence. At present, the COGA sample includes 10,216 individual members of alcoholic families and 1273 individual members of control families.

The genetic analysis of the COGA sample reported here is based on 1334 individuals from 253 dense alcoholic families. All individuals participated in several neurophysiological experiments. Each subject wore a fitted electrode cap containing the 19 leads of the 10/20 international system. The tip of the nose served as reference and the forehead as ground. Vertical and horizontal eye movements were monitored. Artifact rejection (>73.3 μV) was performed on line. Electrical activity was amplified 10K (Sensorium EPA-2 Electrophysiology Amplifiers) and recorded over a bandwidth of 0.02–50 Hz. Brain activity was sampled continuously at a rate of 256 Hz. Digital low pass filtering (32 Hz) of the raw data was performed off-line.

The COGA visual P3 paradigm has been described elsewhere (Cohen et al., 1994) in an intersite consistency study that indicated that there were no significant differences among the sites. There were three classes of visual stimuli: target (the letter X), non-target (squares), and novel (a different colored geometric figure on each trial), with the following probabilities of occurrence: target (0.125), non-target (0.75), and novel (0.125). Each stimulus subtended a visual angle of 2.5°. Stimulus duration was 60 ms, and the interstimulus interval was 1.6 s. When the subject detected the target stimulus, he or she responded with the right or left index finger and depressed a button on a modified computer mouse as quickly as possible; designation to right or left hand was alternated across subjects. Response speed was emphasized, but not at the cost of accuracy. The experiment terminated automatically after a minimum of 25 target stimuli, 150 non-target stimuli, and 25 novel, artifact-free trials had been acquired. Trials with response times (RT) >1000 ms were rejected. The number of response errors for the entire sample was $<1\%$.

Single trials from each subject were processed by applying the trilinear modeling method (Wang et al., 2000) to improve the signal to noise ratio. The processed trials were then aligned by dynamic time warping for each channel (Wang et al., 2001). Dynamic time warping is a nonlinear method to eliminate the timing differences of the features (e.g. peaks, such as P3 and N1) of single trials. A warping function (timing change) is computed for each trial based on all the trials and their estimated derivatives. With this timing change, all the trials would develop at an average pace and have features at the same latency. For each subject, the estimate of the ERP signal at the channel is the average of the aligned single trials, using the 800 ms post-stimulus. The P3 and N1 amplitudes were picked from fixed intervals, namely: 289–600 ms for P3, and 113–222 ms for N1. These intervals were determined by inspecting the grand mean of the estimated ERP signals from all channels and all subjects. Age and gender were used as covariates in the linkage analysis.

A whole genome screen was conducted using 351 highly polymorphic microsatellite markers. Marker genotyping and Mendelian error-detection have been previously described (Reich et al., 1998). Maximum likelihood estimates of marker allele frequencies were obtained from data on all genotyped individuals in the

COGA dataset using the USERM13 program (Boehnke, 1991). CRIMAP (Green, 1990) was used to calculate marker order and distances. Regions of interest were identified, and flanking markers were placed at an average distance of 10 cM or less.

The quantitative ERP phenotypes (P3, N1 amplitudes) were used in a variance component linkage analysis using SOLAR (Almasy and Blangero, 1998; Blangero et al., 2001); SOLAR uses all relative pairs by constructing likelihood functions for whole pedigrees. The appropriate variance–covariance matrix for a pedigree depends on the predicted proportion of genes shared identical by descent (i.b.d.) at a hypothesized QTL; this proportion depends in turn on the proportion shared i.b.d. at genotyped markers and on the type of relative pair. Maximum likelihood estimates for the variance component parameters were obtained, and a LOD score was computed as log 10 of the likelihood ratio comparing two models: a model where the additive genetic variance $\sigma^2 a$ for the QTL is estimated versus a model where $\sigma^2 a$ is constrained to be 0 (no linkage). Variance component analyses were carried out at 1 cM intervals across all chromosomes using SOLAR (Blangero et al., 2001). While the variance component method generally assumes multivariate normality within pedigrees, the method is quite robust to distributional violations (Beaty and Liang, 1987; Beaty et al., 1987; Amos et al., 1996; Allison et al., 1999). Because of slight kurtosis in the distributions of the ERP traits, analyses were performed using the multivariate t-distribution rather than the multivariate normal distribution option of SOLAR (Blangero et al., 2001). For the current data set, multipoint linkage analysis was performed for the P3 and N1 amplitudes of the ERP by testing for linkage at 1 cM intervals across all chromosomes. The resultant LOD functions were then drawn and areas with LODs greater than 2.0 further scrutinized. At significant peaks, we then examined the proportion of variance attributable to the QTL, and estimated its standard error using standard likelihood methods.

7. Results

LOD scores greater than 1.0 are presented in Table 1 for the target visual P3 component and in Table 2 for the N1 component.

LOD scores greater than 2.0 were found for several different chromosomes for P3 (Fig. 1). For P3, there was significant linkage (LOD = 3.0) on chromosome 2 for both the P4 and C4 electrodes at 241 and 242 cM, respectively, between the markers D2S425 and D2S434. There was suggestive linkage on chromosome 5 for a number of primarily frontal leads at 135–146 cM, between the markers D5S1501 and D5S641 (LOD = 2.3–2.64). There was also suggestive linkage (LOD = 2.3) on chromosome 6 for the P4 lead at 150 cM at the marker D6S495. Suggestive linkage was also found on chromosome 17 for P7 (LOD = 2.6) and T7 (LOD = 2.4) at 55 and 53 cM, respectively.

LOD scores greater than 2.0 were also found on a number of chromosomes for the N1 component of the ERP (Fig. 2). There was significant linkage (LOD = 3.85) on chromosome 16 for the FP1 electrode at 36 cM peaking between markers D16S675 and D16S406, and suggestive linkage for the P8 lead at 45 cM peaking at marker

Table 1
Lod scores > 1.0 on chromosomes with significant (> 3.0) or suggestive (> 2.0) linkage for the visual P3 component

CHROM	LOC (cM)	LEAD	LOD
2	170	CZ	1.0603
2	240	F4	1.0230
2	241	P4	2.9870
2	242	P8	1.7214
2	243	T8	1.6152
2	242	C4	2.9628
5	135	FP2	2.4061
5	140	FP1	2.6404
5	140	CZ	1.4769
5	140	F3	2.3060
5	140	C4	2.5147
5	141	P4	1.9929
5	141	T8	1.6202
5	141	FZ	2.4928
5	142	F4	2.5294
5	146	F8	2.2577
5	146	PZ	2.0532
5	148	P3	1.8039
5	150	C3	1.3372
5	150	O1	1.1019
6	130	P3	1.1900
6	140	CZ	1.1356
6	140	PZ	1.0731
6	150	P4	2.2915
6	150	T7	1.1199
6	151	C3	1.7692
17	53	T7	2.3879
17	56	O1	1.6841
17	56	P3	2.0708
17	55	P7	2.5846
17	110	F4	1.0783

D16S687. There was suggestive linkage on chromosome 3 for the P4 lead (LOD = 2.6) at 113 cM, and for the P3 lead (LOD = 2.1) at 112 cM, both between the markers D3S2406 and WATA128; suggestive linkage was also obtained for the T8 lead (LOD = 2.4) at 117 cM and the C4 lead (LOD = 2.3) at 120 cM, both between WATA128 and D3S2459 markers. Suggestive linkage was also seen on chromosome 7 for the P8 electrode at 160 cM (LOD = 2.4) between markers D7S1817 and D7S2847, and for the O2 electrode at 153 cM (LOD = 2.4) between markers D7S2847 and D7S1809; LOD scores of 2.11 were also found for electrode P7 at 155

Table 2
Lod scores > 1.0 on chromosomes with significant (> 3.0) or suggestive (> 2.0) linkage for the visual N1 component

CHROM	LOC (cM)	LEAD	LOD
3	110	F3	1.3327
3	110	P8	1.0797
3	112	P3	2.0876
3	113	P4	2.5893
3	116	PZ	1.7379
3	117	C3	1.9768
3	117	T8	2.3775
3	120	C4	2.2872
3	120	F4	1.1315
3	120	F8	1.0870
7	150	P4	1.4905
7	153	O2	2.3936
7	155	P7	2.1062
7	160	P8	2.4015
7	160	P3	1.3634
7	168	T7	2.1092
13	42	T8	2.3502
13	45	FP2	2.0632
13	50	O2	1.4855
13	76	F8	1.8828
13	80	C4	1.0454
13	98	P3	1.8181
13	100	P7	1.1562
16	11	O1	1.6164
16	12	PZ	1.8317
16	17	F8	1.8990
16	19	P4	1.8727
16	20	C4	1.3477
16	20	F4	1.0187
16	20	T8	1.9431
16	36	FP1	3.8458
16	40	F3	1.0493
16	40	FP2	1.3698
16	45	P8	2.1607

cM in the same region and electrode T7 at 168 cM. On chromosome 13, there was suggestive linkage for electrode T8 at 42 cM (LOD = 2.4) and for electrode FP2 at 45 cM (LOD = 2.1), both between D13S325 and D13S321. Small linkage signals (LOD = 2.0) were also noted on chromosomes 5 (P8, 200 cM), 10 (F4, 66cM) and 11 (T7, 78 cM).

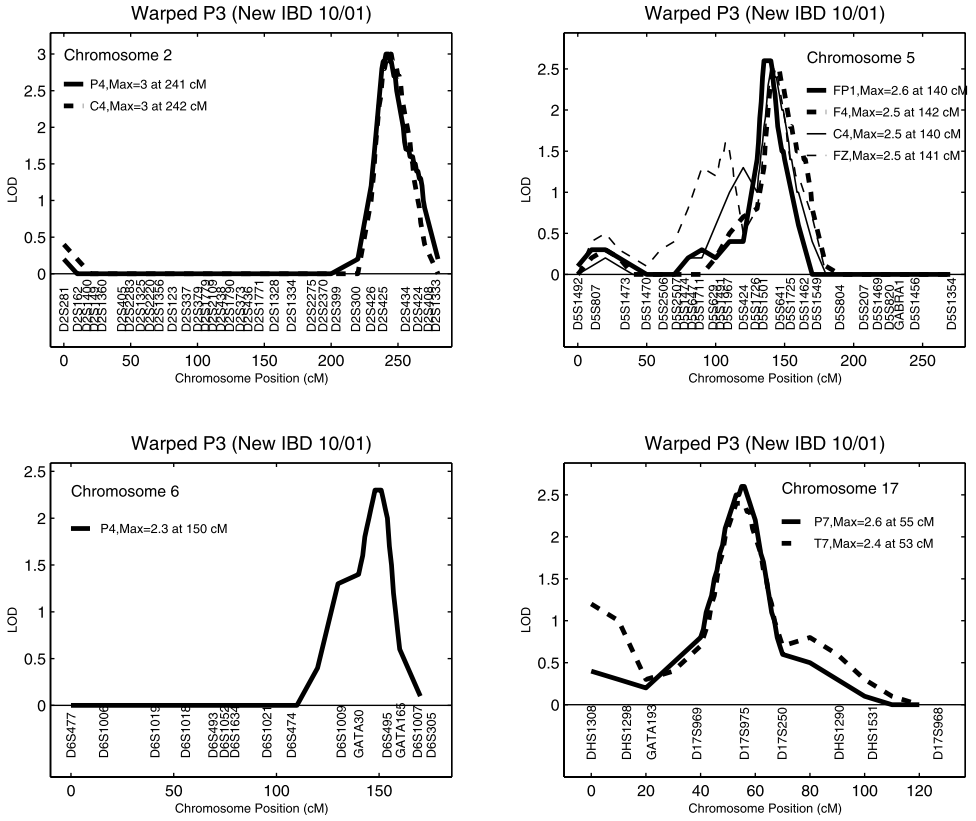

Fig. 1. Linkage of P300 amplitude for four chromosomes with LOD scores >2.3 (chromosomes 2, 5, 6, 17) based on ERPs subjected to dynamic warping of single trials. The x-axis indicates the markers used in the genomic screen and the virtual distances in centimorgans (cM). The y-axis indicates the LOD scores.

8. Discussion

The results indicated that there were significant or suggestive linkage for VP3 at the same chromosomal regions as reported in our initial analysis on a smaller sample (Begleiter et al., 1998), namely chromosomes 2, 5, and 6, and now also suggestive linkage for chromosome 17. While chromosome 2 was still significant for linkage with P3 amplitude in the current analysis, as it was in the initial analysis, the significant finding on chromosome 6 in the initial analysis now manifested suggestive linkage at the same locus. Chromosome 5 showed suggestive linkage at the same location in both analyses. Interestingly, this is the same location on chromosome 5 (D5S1501) where there was significant linkage for a visual P3 in a semantic priming paradigm (Almasy et al., 2001). While there was still a signal on chromosome 13, it was now below 2.0. It should be noted that the current analysis differed from the initial analysis in a number of ways. In the current analysis, we used the more stringent t-distribution option than in the original analysis (that was based on the

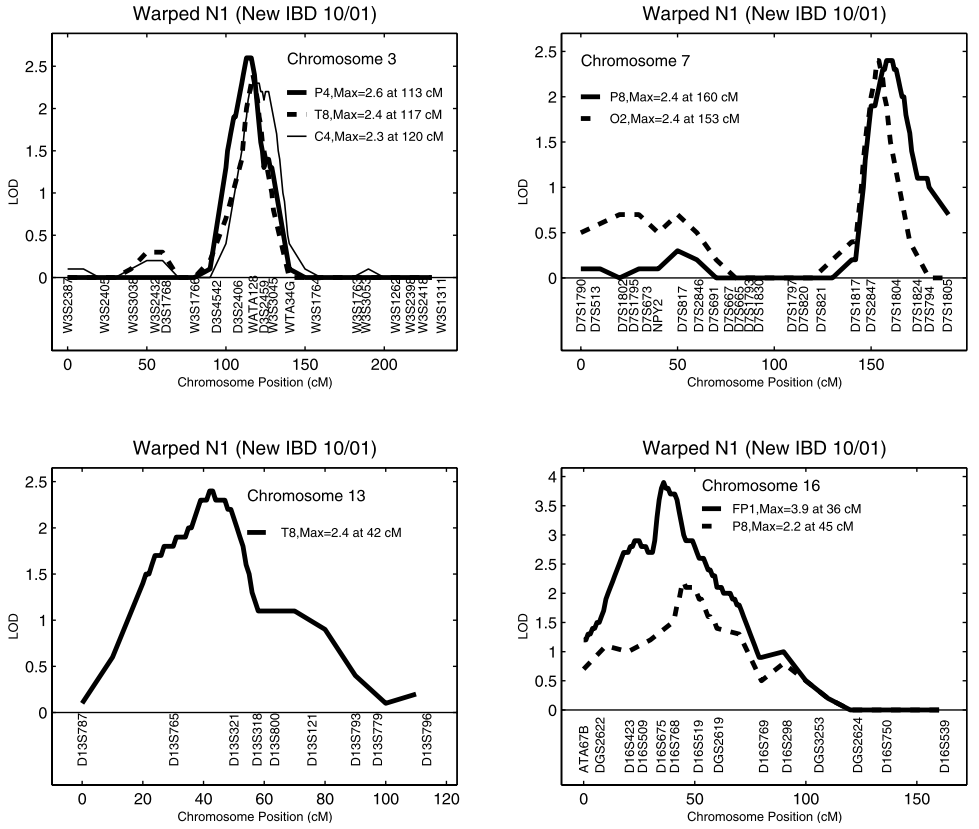

Fig. 2. Linkage of N100 amplitude for chromosomes with LOD scores >2.4 (chromosomes 3, 7, 13, 16) based on ERPs subjected to dynamic warping of single trials. The x-axis indicates the markers used in the genomic screen and the virtual distances in centimorgans (cM). The y-axis indicates the LOD scores.

assumption of a normal distribution); the t-distribution option is insensitive to outliers. Furthermore, we used non-linear dynamic warping in the current analysis, which uses data from individual trials, while the initial analysis was based on averaged ERPs. The linkage analyses were also based on different genetic maps. Finally, the results were based on different samples. Despite these differences in analytic technique, the results were at the same chromosomal loci as the original findings, with only the strength of the signals varying in these new analyses compared to the original published results.

Because of multiple overlapping generators involved in the production of the P3 component of the ERP, the identification of specific generators has been elusive and inconclusive. Although the present quantitative trait analysis was derived from scalp recordings, it may provide fundamental information on genetic determinants of the multiple brain mechanisms that contribute to the amalgam of neuroelectric activity known as P3. The QTL analysis we employed has identified various genetic loci that may eventually lead to candidate genes. The region on chromosome 2 with

significant linkage (between D2S425 and D2S434) most likely maps around 2q35-qter, a region syntenic with mouse chromosome 1 (40–50 cM). The region on chromosome 6 with suggestive linkage at the marker D6S495, is a marker which maps to 6q22.3, a region syntenic with mouse chromosome 10 (0–20 cM) and 17 (1–10 cM). Several neurotransmitter receptors do map within the linkage hotspots, and may be plausible candidate genes: the ionotropic glutamate receptor (GRIK2) maps to 6q21–23.2, and the acetylcholine receptor d (CHRND) and g (CHRNG) chains map to chromosome 2q32-qter.

In addition to these linkage results for P3, we have also examined the N1(00) component obtained in the same VP3 paradigm using the SOLAR methods described above. Again using the t-distribution option with warped ERPs, we found significant linkage on chromosome 16 and suggestive linkage on chromosomes 3, 7 and 13.

For several decades several investigators have used neurophysiological features obtained from EEG/ERP to study cognitive processes in humans (Sutton et al., 1965, 1967; Gevins et al., 1997; Hillyard et al., 1978; Donchin et al., 1978; Donchin, 1979; Polich and Kok, 1995; Naatanen, 1992, 1996). The initial discovery of the P300 component by Sutton and his colleagues (1965, 1967) was a watershed of research for the next three decades. Other investigators have attempted, with some degree of success, to use similar features to inform us about the nature of various clinical conditions (John et al., 1988; McCarley et al., 1993; Ford et al., 1994, 2001; Pfefferbaum et al., 1995; Roth et al., 1980; Porjesz et al., 1998). Most of the EEG/ERP features used yield outstanding temporal resolution, and provide a modicum of reliable and valid information. However it should be noted that the spatial resolution of EEG/ERP, and our understanding of possible generators and physiological mechanisms are currently inadequate. Indeed, for most ERP features, the biological underpinnings remain unknown and need to be elucidated in order to provide critical information about possible pathophysiological mechanisms.

To date, a number of researchers have reported preliminary advances in elucidating possible mechanisms of brain EEG oscillations (Lopes da Silva, 1993; Steriade et al., 1990, 1993; Llinas and Ribary, 1993; Llinas, 2001; McCormick et al., 1995; Basar et al., 2001a,b; Freeman, 1985; Traub et al., 1999; Whittington et al., 1996). Understanding the mechanisms of brain oscillations may be achieved through the study of networks in slice preparations as well as in vivo recordings. This is best illustrated in recent books by Lopes da Silva (1993), Traub et al. (1999), Llinas (2001) and Steriade (2001).

Because these neuroelectric features are in large measure under genetic control (O'Connor et al., 1994; van Beijsterveldt, 1996; Katsanis et al., 1997; Almasy et al., 1999; van Beijsterveldt and van Baal, 2002a,b), it is now possible to identify genes and their functions, which are primarily responsible for the production of these neurophysiological phenomena. In this report we summarize our past QTLs findings involving a genetic analysis of the visual P3 (Begleiter et al., 1998), an additional genetic study in which we identified QTLs resulting from an N400 semantic study, as well as confirming evidence of P3 QTLs obtained in the same N400 paradigm (Almasy et al., 1999). In addition, we report findings from a bivariate analysis in

which we jointly examine diagnosis together with P3 amplitude (Williams et al., 1999). Furthermore, we discuss recent exciting findings of linkage and linkage disequilibrium for the beta EEG frequency and a $GABA_A$ receptor gene cluster (Porjesz et al., 2002). In addition, we focused on new genetic results obtained from a significantly larger sample in which we collected N1 and P3 from a visual paradigm. It is obvious from past and present results that some components of the visual ERP are not only heritable but have allowed us to identify chromosomal loci (QTLs). The replicable QTLs need to be pursued in order to further identify specific genes. This may be achieved by selecting candidate genes within a QTL and conducting association studies, such as linkage disequilibrium. The identification of a specific allele should naturally lead to the isolation of a specific protein, and thus to a better understanding of the molecular biology involved in the electrical activity in the human brain. With the advent of genomics and proteomics and a fuller understanding of gene regulation, the next decade appears to open new horizons on the critical electrical events so essential for the human brain.

Acknowledgements

The Collaborative Study on the Genetics of Alcoholism (COGA) (H. Begleiter, SUNY HSCB Principal Investigator, T. Reich, Washington University, Co-Principal Investigator) includes nine different centers where data collection, analysis, and/or storage takes place. The nine sites and Principal Investigators and Co-Investigators are: Indiana University (T.-K. Li, J. Nurnberger Jr., P.M. Conneally, H. Edenberg); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego (M. Schuckit); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (B. Porjesz, H. Begleiter); Washington University in St. Louis (T. Reich, C.R. Cloninger, J. Rice, A. Goate); Howard University (R. Taylor); Rutgers University (J. Tischfield); and Southwest Foundation (L. Almasy). This national collaborative study is supported by the NIH Grant U10AA08403 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

References

Allison, D.B., Neale, M.C., Zannolli, R., Schork, N.J., Amos, C.I., Blangero, J., 1999. Testing the robustness of the likelihood-ratio test in a variance-component quantitative-trait loci-mapping procedure. Am. J. Hum. Genet. 65, 531–544.

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

Almasy, L., Porjesz, B., Blangero, J., Begleiter, H., Chorlian, D.B., O'Connor, S.J., Polich, J., Kuperman, S., Rohrbaugh, J., Bauer, L.O., Reich, T., 1999. Heritability of the P300 and N100 components of the event-related brain potentials in families with a history of alcoholism. Neuropsychiatr. 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., Polich, J., Bauer, L.O., Rice, J., Reich, T., 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.

Amos, C.I., Zhu, D.K., Boerwinkle, E., 1996. Assessing genetic linkage and association with robust components of variance approaches. Ann. Hum. Genet. 60, 143–160.

Anokhin, A.P., van Baal, G.C., van Beijsterveldt, C.E., de Geus, E.J., Grant, J., Boomsma, D.I., 2001. Genetic correlation between the P300 event-related brain potential and the EEG power spectrum. Behav. Genet. 31, 545–554.

Basar, E., Basar-Eroglu, C., Karakas, S., Schurmann, M., 2001. Gamma, alpha, delta, and theta oscillations govern cognitive processes. Int. J. Psychophysiol. 39, 241–248.

Basar, E., Schurmann, M., Demiralp, T., Basar-Eroglu, C., Ademoglu, A., 2001. Event-related oscillations are 'real brain responses'—wavelet analysis and new strategies. Int. J. Psychophysiol. 39, 91–127.

Beaty, T.H., Liang, K.Y., 1987. Robust inference for variance components models in families ascertained through probands: I. Conditioning on proband's phenotype. Genet. Epidemiol. 4, 203–210.

Beaty, T.H., Liang, K.Y., Seery, S., Cohen, B.H., 1987. Robust inference for variance components models in families ascertained through probands: II. Analysis of spirometric measures. Genet. Epidemiol. 4, 211–221.

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

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

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

Benegal, V., Jain, S., Subbukrishna, D.K., Channabasavanna, S.M., 1995. P300 amplitudes vary inversely with continuum of risk in first degree male relatives of alcoholics. Psychiatr. Genet. 5, 1–8.

Berman, M.S., Whipple, S.C., Fitch, R.J., Noble, E.P., 1993. P3 in young boys as a predictor of adolescent substance abuse. Alcohol 10, 69–76.

Blangero, J., Williams, J.T., Almasy, L., 2001. Variance component methods for detecting complex trait loci. Adv. Genet. 42, 151–181.

Boehnke, M., 1991. Allele frequency estimation from pedigree data. Am. J. Hum. Genet. 48, 22–25.

Brecher, M., Begleiter, H., 1983. Event-related potentials to high incentive stimuli in unmedicated schizophrenic patients. Biol. Psychiatr. 18 (6), 661–674.

Bucholz, K.K., Cadoret, R., Cloninger, C.R., Dinwiddie, S.H., Hesselbrock, V.M., Nurnberger, J.I., Reich, T., Schmidt, I., Schuckit, M.A., 1994. A new semi-structured psychiatric interview for use in genetic linkage studies: A report of the reliability of the SSAGA. J. Stud. Alcohol 55, 149–158.

Cohen, H.L., Wang, W., Porjesz, B., Begleiter, H., 1995. Auditory P300 in young alcoholics: Regional response characteristics. Alcohol: Clin. Exp. Res. 19 (2), 469–475.

Cohen, H.L., Wang, W., Porjesz, B., Bauer, B.O., Kuperman, S., O'Connor, S.J., Rohrbaugh, J., Begleiter, H., 1994. Visual P300: An interlaboratory consistency study. Alcohol 11 (6), 583–587.

Cracco, R.Q., Cracco, J.B., 1976. Somatosensory evoked potentials in man: Far-field potentials. Electroencephalogr. Clin. Neurophysiol. 41, 460–466.

Donchin, E., 1979. Event-related brain potentials: A tool in the study of human information processing. In: Begleiter, H. (Ed.), Evoked Brain Potentials and Behavior. Plenum, New York, pp. 13–88.

Donchin, E., Ritter, W., McCallum, W.C., 1978. Cognitive psychophysiology: The endogenous components of the ERP. In: Callaway, E., Tueting, P., Koslow, S.H. (Eds.), Event-Related Brain Potentials in Man. Academic Press, New York, pp. 349–411.

Emmerson, R.Y., Dustman, R.E., Shearer, D.E., Chamberlin, H.M., 1987. Visually evoked and event related potentials in young abstinent alcoholics. Alcohol 4, 241–248.

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

Ford, J.M., Mathalon, D.H., Kalba, S., Marsh, L., Pfefferbaum, A., 2001. N1 and P300 abnormalities in patients with schizophrenia, epilepsy, and epilepsy with schizophrenia like features. Biol. Psychiatr. 49, 848–860.

Freeman, W.J., 1985. Analytic techniques used in search for the physiological basis of the EEG. Methods of analysis of brain electrical and magnetic signals. In: Gevins, A., Remond, A. (Eds.), Handbook of Electroencephalography and Clinical Neurophysiology (Chapter 18). Amsterdam, Elsevier Biomedical Press.

Gevins, A., Smith, M.E., McEvoy, L., Yu, D., 1997. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. Cereb. Cortex 7 (4), 374–385.

Gottesman, I., Shields, J., 1972. Schizophrenia and Genetics: A Twin Study Vantage Point. Academic Press, New York.

Green, P.H., 3/26/90. Documentation for CRI-MAP version 2.4

Hesselbrock, V.M., 1995. The genetic epidemiology of alcoholism. In: Begleiter, H. Kissin, B. (Eds.), Alcohol and Alcoholism, Vol. 1. The Genetics of Alcoholism, Oxford University Press, New York, pp. 17–39.

Hill, S.Y., Steinhauer, S.R., 1993. Assessment of prepubertal and post pubertal boys and girls at risk for developing alcoholism with P300 from a visual discrimination task. J. Stud. Alcohol. 54, 350–358.

Hill, S.Y., Steinhauer, S., Park, J., Zubin, J., 1990. Event-related potential characteristics in children of alcoholics from high density families. Alcohol: Clin. Exp. Res. 14, 6–16.

Hillyard, S.A., Picton, T.W., Regan, D., 1978. Sensation, perception and attention: Analysis using ERPs. In: Callaway, E., Tueting, P., Koslow, S.H. (Eds.), Event Related Brain Potentials in Man. Academic Press, New York, pp. 223–321.

Jewett, D.L., Romano, M.N., Williston, J.S., 1970. Human auditory evoked potentials: Possible brain stem components detected on the scalp. Science 167, 1517–1518.

John, E.R., Prichep, L.S., Friedman, J., Easton, P., 1988. Neurometrics: computer assisted differential diagnosis of brain dysfunctions. Science 293, 162–169.

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

Klorman, R., Salzman, L., Pass, H., Borgstedt, A.D., Dainer, K.B., 1979. Effects of methylphenidate on hyperactive children's evoked responses during passive and active attention. Psychophysiology 16 (1), 23–29.

Llinas, R., Ribary, U., 1993. Coherent 40 Hz oscillation characteristics dream state in humans. Proc. Natl. Acad. Sci. USA 90, 2078–2081.

Llinas, R.R., 2001. I of the Vortex. MIT press, Cambridge, MA.

Lopes da Silva, F.H., 1993. Computer-assisted EEG diagnosis: pattern recognition and brain mapping. In: Niedermeyer, W., Lopes da Silva, F. (Eds.), Electroencephalography: Basic Principles, Clinical Applications and Related Fields, vol. 3. Williams and Wilkins, Baltimore, pp. 1063–1086.

McCarley, R.W., Shenton, M.E., O'Donnell, B.F., Faux, S.F., Kikinis, R., Nestor, P.G., Jolesz, F.A., 1993. Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. Arch. Gen. Psychiatr. 50, 190–198.

McCormick, D.A., Trent, F., Ramoa, A.S., 1995. Postnatal development of synchronized network oscillations in the ferret dorsal lateral geniculate and perigeniculate nuclei. J. Neurosci. 15 (8), 5739–5752.

Naatanen, R., 1992. Attention and Brain Function. Lawrence Erlbaum Assoc, Hillsdale.

Naatanen, R., 1996. MMN as a measure of central auditory processing accuracy. In: Ogura, C., Koga, Y., Shimokochi, M. (Eds.), Recent Advances in Event-Related Brain Potential Research. Elsevier Science BV, Amsterdam, pp. 3–10.

O'Connor, S.J., Hesselbrock, V., Tasman, A., DePalma, N., 1987. P3 amplitudes in two distinct tasks are decreased in young men with a history of paternal alcoholism. Alcohol 4, 323–330.

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

Patterson, B.W., Williams, H.L., Mclean, G.A., Smith, L.T., Schaeffer, K.W., 1987. Alcoholism and family history of alcoholism: Effects on visual and auditory event-related potentials. Alcohol 4, 265–274.

Pfefferbaum, A., Ford, J.M., White, P.M., Mathalon, D., 1991. Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. Alcohol. Clin. Exp. Res. 15 (5), 839–850.

Pfefferbaum, A., Roth, W.T., Ford, J.M., 1995. Event-related potentials in the study of psychiatric disorders. Arch. Gen. Psychiatr. 52, 559–563.

Polich, J., Bloom, F.E., 1987. P300 from normals and adult children of alcoholics. Alcohol 4, 301–305.

Polich, J., Kok, A., 1995. Cognitive and biological determinants of P300: an integrative review. Biol. Psychol. 41, 103–146.

Polich, J., Burns, T., Bloom, F.E., 1988. P300 and the risk for alcoholism: Family history, task difficulty and gender. Alcohol: Clin. Exp. Res. 12, 248–254.

Polich, J., Haier, R.J., Buchsbaum, M., Bloom, F.E., 1988. Assessment of young men at risk for alcoholism with P300 from a visual discrimination task. J. Stud. Alcohol. 49, 186–190.

Polich, J., Pollock, V.E., Bloom, F.E., 1994. Meta-analysis of P300 amplitude from males at risk for alcoholism. Psychol. Bull. 115, 55–73.

Porjesz, B., Almasy, L., Edenberg, H.J., Wang, K., Chorlian, D.B., Foroud, T., Goate, A., Rice, J.P., O'Connor, S.J., Rohrbaugh, J., Kuperman, S., Bauer, L.O., Crowe, R., Schuckit, M.A., Hesselbrock, V., Conneally, P.M., Tischfield, J.A., Li, T.K., Reich, T., Begleiter, H., 2002. Linkage disequilbrium between the beta frequency of the human EEG and a GABAA receptor gene locus. Proceedings of the National Academy of Science 99 (6), 3729–3733.

Porjesz, B., Begleiter, H., 1985. Human brain electrophysiology and alcoholism. In: Tarter, R., Thiel, D.V. (Eds.), Alcohol and the Brain. Plenum, New York, pp. 139–182.

Porjesz, B., Begleiter, H., 1990. Individuals at risk for alcoholism: Neurophysiologic processes. In: Cloninger, C.R., Begleiter, H. (Eds.), Banbury Report 33: Genetics and Biology of Alcoholism. Cold Spring Harbor Laboratory Press, New York, pp. 137–182.

Porjesz, B., Begleiter, H., Samuelly, I., 1980. Cognitive deficits in chronic alcoholics and elderly subjects assessed by evoked brain potentials. Acta Psychiatr. Scand. 62 (Suppl.286), 15–29.

Porjesz, B., Begleiter, H., Bihari, B., Kissin, B., 1987. Event-related brain potentials to high incentive stimuli in abstinent alcoholics. Alcohol 4, 283–287.

Porjesz, B., Begleiter, H., Litke, A., Bauer, L.O., Kuperman, S., O'Connor, S.J., 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. (Eds.), Recent Advances in Event-Related Brain Potential Research. Elsevier, Amsterdam, pp. 539–549.

Porjesz, B., Begleiter, H., Reich, T., Van Eerdewegh, P., Edenberg, H.J., Foroud, T., Goate, A., Rice, J., Litke, A., Chorlian, D., Blangero, J., Stimus, A.T., Sorbell, J., Bauer, L.O., Kuperman, S., O'Connor, S.J., Rohrbaugh, J., 1998. Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism. Alcohol: Clin. Exp. Res. 22 (6), 1317–1323.

Prabhu, V.R., Porjesz, B., Chorlian, D.B., Wang, K., Stimus, A., Begleiter, H., 2001. Visual P3 in female alcoholics. Alcohol: Clin. Exp. Res. 25 (4), 531–539.

Rangaswamy, M., Porjesz, B., Wang, K.M., Chorlian, D.B., Bauer, O., Rohrbaugh, J., O'Connor, J.S., Kuperman, S., Reich, T., Begleiter, H., Beta power in the EEG of alcoholics. Biol. Psychiatr., in press.

Ramachandran, G., Porjesz, B., Begleiter, H., Litke, A., 1996. A simple auditory oddball task in young adult males at high risk for alcoholism. Alcohol: Clin. Exp. Res. 20 (1), 9–15.

Reich, T., Edenberg, H.J., Goate, A., Williams, J.T., Rice, J.P., Van Eerdewegh, P., Foroud, T., Hesselbrock, V., Schuckit, M.A., Bucholz, K., Porjesz, B., Li, T.K., Conneally, P.M., Nurnberger, J.I., Jr., Tischfield, J.A., Crowe, R., Cloninger, C.R., Wu, W., Shears, S., Carr, K., Crose, C., Willig, C., Begleiter, H., 1998. A genome-wide search for genes affecting the risk for alcohol dependence. Am. J. Med. Genet. (Neuropsych. Genet.) 81 (3), 207–215.

Roth, W.T., Pfefferbaum, A., Horvath, T.B., Berger, P.A., Kopell, B.S., 1980. P3 reduction in auditory evoked potentials of schizophrenics. Electroencephalogr. Clin. Neurophysiol. 49, 497–505.

Steriade, M., Gloor, P., Llinas, R.R., Lopes de Silva, F.H., Mesulam, M.M., 1990. Report of IFCN Committee on basic mechanisms. Basic mechanisms of cerebral rhythm activities. Electroencephalogr. Clin. Neurophysiol. 76 (6), 481–508.

Steriade, M., McCormick, D.A., Sejnowski, T.J., 1993. Thalamocortical oscillations in the sleeping and aroused brain. Science 262 (5134), 679–685.

Steriade, M., 2001. The Intact and Sliced Brain. MIT Press, Cambridge, MA.

Sutton, S., Barren, M., Zubin, J., John, E.R., 1965. Evoked potential correlates of stimulus uncertainty. Science 150, 1187–1188.

Sutton, S., Tueting, P., Zubin, J., John, E.R., 1967. Information delivery and the sensory evoked potential. Science 155, 1436–1439.

Traub, R.D., Jefferys, J.G.R., Whittington, M.A., 1999. Fast Oscillations in Cortical Circuits. The MIT Press, Cambridge, Massachusetts.

Tsuang, M.T., Faraone, S.V., 2000. The future of psychiatric genetics. Curr. Psychiatric. Rep. 2, 133–136.

van Beijsterveldt, T., 1996. The Genetics of Electrophysiological Indices of Brain Activity: An EEG Study in Adolescent Twins. Universiteit Van Amsterdam, Amsterdam.

van Beijsterveldt, C.E.M., Molenaar, P.C.M., de Geus, E.J.C., Boomsma, D.I., 1998. Individual differences in P300 amplitude: A genetic study in adolescent twins. Biol. Psychol. 47, 97–120.

van Beijsterveldt, C.E.M., van Baal, G.C.M., 2002a. Twin and family studies of the human electroencephalogram: a review and a meta-analysis. Biol. Psychol. 61 (1–2), 111–138.

van Beijsterveldt, T., van Baal, C., 2002b. Review and meta-analysis of heritability studies in human electrophysiology. Biol. Psychol.

van der Stelt, O., Geesken, R., Gunning, W.B., Snel, J., Kok, A., 1998. P3 scalp topography to target and novel visual stimuli in children of alcoholics. Alcohol: Int. Biomed. J. 15 (2), 119–136.

van Der Stelt, O., 1999. Visual P3 as a potential vulnerability marker of alcoholism: Evidence from the Amsterdam Study of Children of Alcoholics. Alcohol Alcoholism 34 (3), 267–282.

Wang, K., Begleiter, H., Porjesz, B., 2000. Trilinear modeling of event-related potentials. Brain Topogr. 12 (4), 263–271.

Wang, K., Begleiter, H., Porjesz, B., 2001. Warp-averaging event-related potentials. Electroencephalogr. Clin. Neurophysiol. 112, 1917–1924.

Whipple, S.C., Berman, S.M., Noble, E.P., 1991. Event-related potentials in alcoholic fathers and their sons. Alcohol 8, 321–327.

Whipple, S.C., Parker, E.S., Nobel, E.P., 1988. An atypical neurocognitive profile in alcoholic fathers and their sons. J. Stud. Alcohol. 49, 240–244.

Whittington, M.A., Jeffreys, J.G.R., Traub, R.D., 1996. Effects of intravenous anaesthetic agents on fast inhibitory oscillations in the rat hippocampus in vitro. Br. J. Pharmacol. 118, 1977–1986.

Williams, J.T., Begleiter, H., Porjesz, B., Edenberg, H.J., Foroud, T., Reich, T., Goate, A., Van Eerdewegh, P., Almasy, L., Blangero, J., 1999. Joint multipoint linkage analysis of multivariate qualitative and quantitative traits. II. Alcoholism and event related potentials. Am. J. Hum. Genet. 65, 1148–1160.

Wright, M.J., Hansell, N.K., Geffen, G.M., Geffen, L.B., Smith, G.A., Martin, N.G., 2001. Genetic influence on the variance in P3 amplitude and latency. Behav. Genet. 31, 555–565.