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Quantitative trait loci analysis of human event-related brain potentials: P3 voltage

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Abstract

The P3 event-related brain potential (ERP) is a positive-going voltage change of scalp-recorded electroencephalographic activity that occurs between 300–500 ms after stimulus onset. It is elicited when a stimulus is perceived, memory operations are engaged, and attentional resources are allocated toward its processing. Because this ERP component reflects fundamental cognitive processing, it has found wide utility as an assessment of human mental function in basic and clinical studies. In particular, P3 attributes are heritable and have demonstrated considerable promise as a means to identify individuals at genetic risk for alcoholism. We have conducted a quantitative linkage analysis on a large sample from families with a high density of affected individuals. The analyses suggest that several regions of the human genome contain genetic loci related to the generation of the P3 component of the ERP, which are possible candidate loci underlying the functional organization of human neuroelectric activity. © 1998 Elsevier Science Ireland Ltd.

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1. Introduction

The advent of human event-related potentials (ERP) has provided a set of non-invasive techniques recorded from the scalp. 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 the 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 scalp potentials recorded at the scalp is relatively low, the temporal resolution is quite high, providing a unique window on the millisecond to millisecond transactions which take place in the human brain.

In 1965, Sutton and his colleagues first observed the P3 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 (Klor-

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man 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). In alcoholism, it was assumed that the P3 deficit was the consequence of the deleterious effects of alcohol on the brain. After a sufficient period of abstinence many of the clinical abnormalities characteristic of alcohol dependence 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 naïve 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), 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 was primarily obtained with difficult visual tasks, and may have predictive value as an index of vulnerability for alcoholism (Polich et al., 1994). The use of low P3 voltage as a potential phenotypic marker was greatly strengthened by recent studies suggesting that the reduction in the P3 component of the ERP found in alcoholics (Pfefferbaum et al., 1991), and in high risk males (Benegal et al., 1995) was highly correlated with the number of alcohol 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 past 20 years, 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 quite promising.

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. As an integral part of this study, identical neurophysiology laboratories were established at all 6 sites (California, Connecticut, Indiana, Iowa, Missouri, and New York) for the purpose of collecting electroencephalographic (EEG) and event-related potential (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 was 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 and Feighner definite criteria for alcohol dependence. In addition to the proband, the study required two additional first degree relatives who were alcohol dependent by the same criteria. Individuals with comorbidity 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 EEG/ERP were recorded. The control families were randomly ascertained, and included individuals with psychiatric disorders 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 distribution of P3 amplitude in individuals over 16 years of age from randomly ascertained control families were compared to age and sex matched distributions from densely affected alcoholic families. The control distributions are based on 687 individuals from 163 randomly ascertained families and the distributions from the alcoholic families are based on 1276 individuals from 219 densely affected families. Alcoholic dependent individuals from dense alcoholic families had significantly lower P3s than alcohol dependent individuals from random control families. Both sons and daughters of alcoholic male probands manifest significantly lower P3 amplitudes compared to age and sex matched offspring of control male probands. In addition, the unaffected members of alcoholic families had a significantly lower P3 amplitude compared to age and sex matched unaffected members of control families. Alcoholic members of dense alcoholic families had significantly lower P3 amplitudes than unaffected members of dense alcoholic families. These findings certainly establish the P3 component of the ERP as a good putative phenotypic marker (Porjesz et al., 1996).

One of the basic criterion which must be met in order to use a variable as a phenotypic marker is to establish the heritability of that particular variable (Begleiter and Porjesz, 1995). Three recent 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 recently been reported for P3 amplitude in the largest twin study to date (Van Beijsterveldt, 1996). The most recent study (Katsanis et al., 1997) with monozygotic and dizygotic twins corroborated the findings that the P3 component of

the ERP is significantly heritable. Almasy et al. (1998) have recently reported similar heritabilities for P3 amplitude based on 604 individuals from 100 families in the COGA family study. These heritability findings encouraged us to identify possible genetic loci related to the amplitude of the P3 component of the ERP.

2. Materials and methods

The genetic analysis of the COGA sample is based on 607 individuals from 103 families, comprising about 758 sib-pairs. All individuals participated in several neurophysiological experiments. Each subject wore a fitted electrode cap containing the 21 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 ($>73.3\ \mu V$) was performed on line. Electrical activity was amplified 10 K (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 filter (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 3 classes of visual stimuli: target (the letter X), non-target (squares), and novel (a set of completely different colored geometric figures and polygons that changed 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; hands were 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 $<1\%$.

For each subject, the average ERPs to the target were measured with a semi-automatic computer peak detection program and were independently assessed by two experienced investigators with high reliability (>0.96). The P3 component was selected at each electrode as the highest positive peak within a time window of 275–575 ms. The amplitude of the P3 component to the target stimulus was measured at all scalp leads as the difference in peak voltage relative to the prestimulus baseline (187 ms of EEG prior to stimulus onset). P3 amplitudes were regressed for age and gender before the linkage analysis.

A whole genome screen was initially conducted using highly polymorphic microsatellite markers with an inter-marker spacing of 20 cM. Genotyping was performed by both manual methods (incorporation of radioactivity and detection of allele sizes by denturing gel electrophoresis) and semi-automated methods (fluorescent labeling and detection on the ABI model 373). Data were checked for non-inheritances using 3 separate programs, Genemaster (John Rice), after which questionable alleles were reexamined by the original autoradiogram, CRIMAP, and USERM 13. Incompatible data were deleted within each family. The genotyping and data cleaning were done without knowledge of the phenotype for any individual. Allele frequency estimates were obtained using the maximum likelihood methods (Boehnke, 1991) and implemented on the program USERM 13. The marker order and distances were calculated from these data using CRIMAP. In total, 286 markers were used. Regions of interest were identified, and flanking markers were placed at an average distance of 10 cM or less.

For the quantitative trait linkage analysis, we used a newly developed package of variance component-based linkage programs (SOLAR) (Blangero and Almasy, 1996, 1997) to test for quantitative trait loci (QTLs). The suggested benefit of the variance component approach over formal linkage analysis lies in its parsimony, and in the well known consistency of its estimators even in the presence of distributional violations. This multipoint linkage analysis is an extension of the strategy developed by Goldgar (1990), Schork (1993) and Amos (1994) to estimate the genetic variance attributable to the region around a genetic marker. This method has recently been extended from sibships to pedigrees of arbitrary complexity (Comuzzie et al., 1997) and has been used to map genes contributing to risk of non-insulin dependent diabetes (Stern et al., 1996), and obesity (Duggirala et al., 1996). This approach is based on specifying the expected genetic covariances between arbitrary relatives as a function of the identity-by-descent relationships at a given marker locus. For the nuclear family-based multipoint linkage screening we used the program MAPMAKER/SIBS (Kruglyak and Lander, 1995) to obtain the maximum likelihood estimates of the identity by descent probability matrices for each nuclear family evaluated at every cM on every chromosome. These estimates were then used in our variance component linkage analyses. For the current data set, multipoint linkage analysis was performed for the P3 amplitude 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 1.9 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.

3. Results

Heritabilities at each electrode position were estimated

Table 1

Maximum likelihood estimates of heritabilities (h2) of P3 amplitude to target stimuli for each scalp electrode

Trait	Target		
	h^2	SE	*P*
01	0.416	0.074	0.000002
02	0.505	0.076	<0.000001
P7	0.374	0.077	0.000024
P3	0.403	0.074	0.000002
FP1	0.324	0.075	0.000047
Pz	0.469	0.075	<0.000001
FP2	0.294	0.073	0.000193
P4	0.491	0.076	<0.000001
P8	0.442	0.080	0.000003
T7	0.349	0.075	0.000035
C3	0.391	0.079	0.000011
Cz	0.419	0.077	0.000003
Cz	0.419	0.077	0.000003
C4	0.448	0.075	<0.00001
T8	0.371	0.076	0.000014
F7	0.280	0.073	0.000460
F3	0.476	0.081	<0.000001
Fz	0.472	0.082	<0.000001
F4	0.393	0.078	0.000003
F8	0.290	0.072	0.000260

SE represents the standard error and *P* the probability (significance level).

under an additive polygenic model using maximum likelihood methods. The results are statistically significant (see Table 1). Using standard maximum likelihood methods implemented in SOLAR, we computed genetic, environmental, and phenotypic correlations for all possible combinations of the 19 traits (see Table 2). We noticed a strong spatial pattern in the correlations among the phenotypes with 5 clusters from posterior to anterior scalp locations: (O1, O2), (P7, P3, Pz, P4, P8), (T7, C3, Cz, C4, T8), (F7, F3, Fz, F4, F8), and (Fp1, Fp2). We have focused on the genetic correlations, which represent a measure of pleiotropy (i.e. shared genetic influences) and have a similar interpretation as standard phenotypic correlations. Within clusters, we find that 81% of the genetic variation in P3 amplitude at the various scalp electrodes is shared in common. Similarly, for adjacent clusters approximately 64% of the genetic variation is due to shared genetic influences, while separation of two clusters yields 30%, 3 clusters 7%, and the occipital versus frontal measures share 0% (i.e. no common genetic influences).

Given the high degree of genetic correlation between these traits, we objectively reduced the number of linkage scans to be considered while maintaining the full range of genetic variability contained in the data. We performed a Principal Component Analysis (PCA) on the 19×19 matrix of genetic correlations in order to select a subset of phenotypes which minimized the amount of redundant information contained in the data while maximizing the range of genetic variation represented. After an initial PCA, using all 19 phenotypes, we performed a varimax rotation. The first 3 eigenvectors accounted for 97.9% of the genetic covariation. For each of these factors, we selected the trait phenotype with the highest loading to represent the specific factor. The 3 electrodes best representing the 3 major factors were Cz, O2, and T8.

In order to evaluate the potential false positive rate in a multivariate genomic scan, we repeatedly ($n = 502$) simulated 3 new phenotypes given the observed family structure, missing data structure, phenotypic standard deviations, heritabilities for each trait, and the observed genetic and environmental correlations between traits. Taking the marker data as fixed, we performed a complete multipoint genomic

Table 2

Genetic correlations (above diagonal) and enviromental correlations (below diagonal) between P3 amplitude at the various leads

	C3	C4	CZ	F3	F4	F7	F8	Fp1	Fp2	FZ	O1	O2	P3	P4	P7	P8	PZ	T7	T8
C3		0.89	0.98	0.86	0.87	0.74	0.65	0.47	0.47	0.87	0.62	0.57	0.85	0.81	0.71	0.66	0.85	0.87	0.76
C4	0.82		0.95	0.74	0.85	0.61	0.64	0.41	0.43	0.80	0.72	0.65	0.93	0.92	0.78	0.71	0.93	0.88	0.87
CZ	0.90	0.92		0.79	0.83	0.68	0.59	0.43	0.42	0.83	0.66	0.58	0.88	0.84	0.74	0.65	0.88	0.88	0.78
F3	0.79	0.77	0.82		0.95	0.96	0.81	0.84	0.85	0.99	0.41	0.35	0.65	0.62	0.49	0.45	0.61	0.74	0.65
F4	0.66	0.82	0.77	0.88		0.86	0.87	0.87	0.82	0.98	0.52	0.47	0.76	0.76	0.57	0.54	0.73	0.78	0.77
F7	0.69	0.64	0.63	0.83	0.73		0.82	0.75	0.81	0.93	0.29	0.27	0.49	0.49	0.43	0.41	0.46	0.71	0.63
F8	0.55	0.73	0.61	0.70	0.82	0.71		0.77	0.84	0.83	0.27	0.26	0.50	0.53	0.42	0.45	0.46	0.71	0.76
Fp1	0.58	0.64	0.60	0.79	0.77	0.81	0.73		0.98	0.86	0.02	0.05	0.22	0.25	0.02	0.05	0.20	0.36	0.32
Fp2	0.55	0.65	0.59	0.75	0.82	0.74	0.82	0.91		0.85	–0.01	0.02	0.22	0.25	0.06	0.06	0.20	0.42	0.39
FZ	0.75	0.81	0.85	0.92	0.91	0.72	0.7	0.75	0.75		0.42	0.36	0.69	0.64	0.51	0.45	0.65	0.79	0.73
O1	0.60	0.55	0.57	0.33	0.31	0.33	0.29	0.27	0.26	0.37		0.99	0.90	0.92	0.94	0.91	0.84	0.76	0.72
O2	0.61	0.61	0.60	0.38	0.34	0.35	0.35	0.28	0.29	0.42	0.88		0.84	0.87	0.92	0.92	0.77	0.69	0.68
P3	0.87	0.77	0.81	0.60	0.54	0.54	0.47	0.46	0.46	0.60	0.83	0.78		0.99	0.89	0.83	0.99	0.84	0.81
P4	0.77	0.84	0.82	0.60	0.58	0.51	0.54	0.48	0.48	0.64	0.78	0.85	0.87		0.92	0.88	0.95	0.86	0.86
P7	0.72	0.62	0.62	0.43	0.38	0.41	0.31	0.33	0.30	0.43	0.88	0.79	0.90	0.76		0.97	0.85	0.86	0.86
P8	0.64	0.71	0.64	0.43	0.44	0.38	0.44	0.36	0.36	0.47	0.80	0.88	0.77	0.89	0.76		0.74	0.82	0.84
PZ	0.83	0.84	0.87	0.66	0.63	0.57	0.57	0.54	0.55	0.68	0.76	0.78	0.92	0.94	0.76	0.79		0.82	0.76
T7	0.86	0.70	0.74	0.75	0.62	0.77	0.54	0.61	0.54	0.65	0.62	0.59	0.83	0.69	0.78	0.61	0.74		0.95
T8	0.70	0.84	0.73	0.69	0.74	0.62	0.8	0.64	0.66	0.68	0.53	0.61	0.69	0.77	0.55	0.74	0.76	0.65	

scan for each trait. We then quantified the distribution of LOD score peaks which provided us with empirical genome-wise *P*-values for the simultaneous analysis of the 3 phenotypes.

The results of the quantitative trait analysis yielded significant linkage on chromosomes 2 (LOD = 3.28) and 6 (LOD = 3.41). Analysis of chromosome 6 provided significant linkage at the Cz electrode. The significant findings for chromosome 2 indicate the importance of the right hemisphere occipital electrode (O2) for the visual stimuli of the ERP. Two other chromosomes yielded LOD scores above 2.0: chromosome 5 and 13. Fig. 1 represents all the LOD scores over 1.5 from the genomic screens.

We evaluated genome-wise and experiment-wise significance for a number of LOD score cutoff points. For example, for a LOD score of 3.41 (chromosome 6) the genome-wise *P*-value is 0.0073 with an experiment-wise *P*-value of 0.0219 (i.e. one would expect to see one such LOD score in an analysis of these 3 traits every 1/0.0219 = 45.7 genome scans). For a LOD score of 3.28 (chromosome 2), the empirical genome-wise *P*-value is 0.0099 and the experiment-wise *P*-value is 0.0299 (i.e. we would expect to see one such LOD score in an analysis of these 3 traits every 1/0.0299 = 33.4 genome scans). These empirical experiment-wise *P*-values would be expected from a Bonferroni correction of the empirical genome-wise *P*-values. This suggests that the choice of 3 minimally redundant phenotypes from among the original group of 19 traits was indeed successful.

4. Discussion

We have identified for the first time a number of genetic loci which are related to the P3 voltage of the ERP. Because of the 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 the genetic determinants of the multiple brain mechanisms that contribute to the amalgam of neuroelectric activity known as P3. The quantitative trait linkage analysis we employed has identified various genetic loci that may,

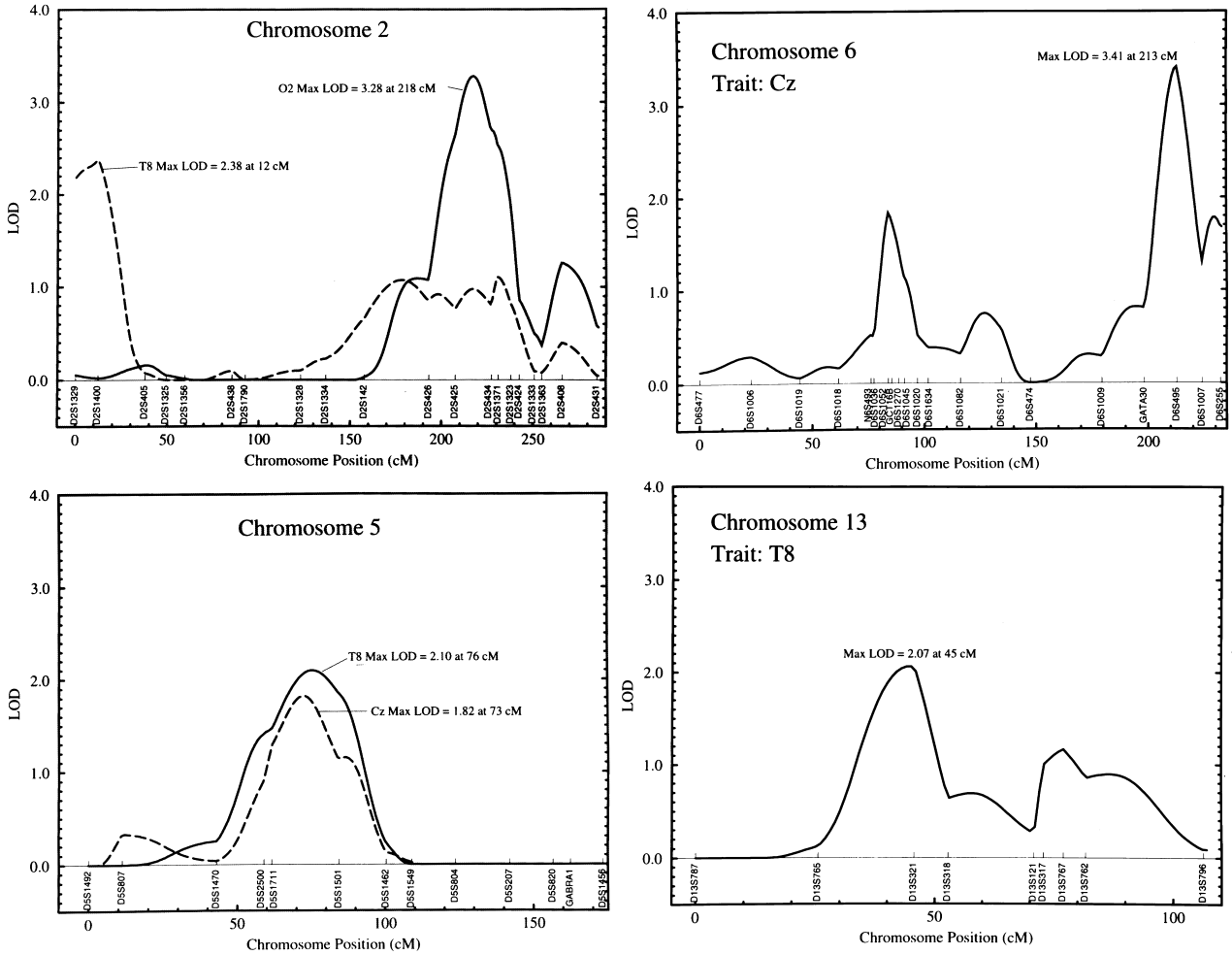

Fig. 1. LOD score over 1.5 from the 3 genomic screens for electrodes 01, Cz and T8. The *x* axis on each graph indicates the markers used and the virtual distance in centimorgans (cM) The *y*-axis indicates the LOD scores.

with the use of fine mapping, eventually yield candidate genes.

In our study, a region of 40 cM on chromosome 2 showed positive LOD scores with a peak multipoint LOD score of 3.28 between D2S425 and D2S434. These markers most likely map around 2q35-qter, a region syntenic with mouse chromosome 1 (40–50 cM). The second region showing significant LOD scores was a 10 cM region on chromosome 6 between GATA30 and D6S1007. There was a peak multipoint LOD score of 3.41 close to D6S495, a marker which maps to 6q22.3, a region syntenic with mouse chromosome 10 (0–20 cM) and 17 (0–10 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.

The future identification and functions of genes responsible for the production of this important neuroelectric phenomenon will provide a unique opportunity to elucidate the biological substrate of the P3 component of the ERP. In addition to conducting quantitative trait linkage analyses of the P3 component of the visual ERP, we are also assessing QTLs related to a comprehensive set of neuroelectric features (ERP/EEG) collected in a large number of control and alcoholic families. These future results will contribute greatly to our understanding of the biological mechanisms involved in neuroelectric activity so essential in cognitive and clinical neuroscience.

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References

Almasy, L., Porjesz, B., Blangero, J., Chorlian, D.B., O'Connor, S.J., Polich, J., Kuperman, S., Rohrbaugh, J., Bauer, L.O., Reich, T. and Begleiter, H. Heritability of the P300 and N100 components of the event-related brain potential in families with a history of alcoholism. Neuropsych. Genet., 1998, in press.

Amos, C.I. Robust variance-components approach for assessing genetic linkage in pedigrees. Am. J. Hum. Genet., 1994, 54: 535–543.

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

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

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

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

Blangero, J. and Almasy, L. SOLAR: Sequential Oligogenic Linkage Analysis Routines. Technical Notes No. 6, Population Genetics Laboratory, Southwest Foundation for Biomedical Research, San Antonio, TX., 1996.

Blangero, J. and Almasy, L. Multipoint oligogenic linkage analysis of quantitative traits. Genet. Epidemiol., 1997, 14: 959–964.

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

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

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

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

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

Comuzzie, A.G., Hixson, J.E., Almasy, L., Mitchell, B.D., Mahoney, M.C., Dyer, T.D., Stern, M.P., MacCluer, J.W. and Blangerons, J. A major quantitative trait locus determining serum leptin levels and fat mass is located on human chromosome 2 (letter). Nat. Gen., 1997, 15: 273–275.

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

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

Duggirala, R., Stern, M.P., Mitchell, B.D., Reinhart, L.J., Shipman, P.A., Uresandi, O.C., Chung, W.K., Leibel, R.L., Hales, C.N., O'Connell, P. and Blangero, J. Quantitative variation in obesity-related traits and insulin precursers linked to the OB gene region on human chromosome 7. Am. J. Hum. Genet., 1996, 59: 694–703.

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

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

Goldgar, D.E. Multipoint analysis of human quantitative genetic variation. Am. J. Hum. Genet., 1990, 47: 957–967.

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

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

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

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

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

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

Kruglyak, L. and Lander, E.S. Complete multipoint sib-pair analysis of qualitative and quantitative traits. Am. J. Hum. Genet., 1995, 57: 439–454.

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

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

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

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

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

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

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

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

Polich, J., Pollock, V.E. and Bloom, F.E. Meta-analysis of P300 amplitude from males at risk for alcoholism. Psychol. Bull., 1991, 115: 55–73.

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

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

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

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

Porjesz, B., Begleiter, H., Litke, A., Bauer, L.O., Kuperman, S., O'Connor, S.J. and Rohrbaugh, J. Visual P3 as a potential phenotypic marker for alcoholism: Evidence from the COGA national project. In: C. Ogura, Y. Koga and M. Shimokochi (Eds.), Recent Advances in Event-Related Brain Potential Research, Elsevier, Amsterdam, 1996, pp 539–549.

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

Roth, W.T., Pfefferbaum, A., Horvath, T.B., Berger, P.A. and Kopell, B.S. P3 reductionin auditory evoked potentials of schizophrenics. Electroenceph. clin. Neurophysiol., 1980, 49: 497–505.

Schork, N.J. Extended multipoint identity-by-descent analysis of human quantitative traits: efficiency, power, and modeling considerations. Am. J. Hum. Genet., 1993, 53: 1306–1319.

Stern, M.P., Duggirala, R., Mitchell, B.D., Reinhart, L.J., Shivakumar, S., Shipman, P.A., Uresandi, O.C., Benavides, E., Blangero, J. and O'Connell, P. Evidence for linkage of regions on chromosomes 6 and 11 to plasma glucose concentrations in Mexican Americans. Genome Res., 1996, 6: 724–734.

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

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

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

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