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Amplitude of Visual P3 Event-Related Potential as a Phenotypic Marker for a Predisposition to Alcoholism: Preliminary Results from the COGA Project

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Recent data collected at six identical electrophysiological laboratories from the large national multisite Collaborative Study on the Genetics of Alcoholism provide evidence for considering the P3 amplitude of the event-related potential as a phenotypic marker for the risk of alcoholism. The distribution of P3 amplitude to target stimuli at the Pz electrode in individuals 16 years of age and over from 163 randomly ascertained control families (n = 687) was compared with those from 219 densely affected alcoholic families (n = 1276) in which three directly interviewed first-degree relatives met both DSM-III-R and Feighner criteria at the definite level for alcohol dependence (stage II). 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 from control families was converted to Z-scores, and a P3 amplitude beyond 2 SD's below the mean was considered an "abnormal trait." When age- and sex-matched distributions of P3 amplitude were compared, members of densely affected stage II families were more likely to manifest low P3 amplitudes (2 SD below the mean) than members of control families, comparing affected and unaffected offspring, and all individuals; all comparisons of these distributions between groups were significant ($p < 0.00001$). P3 amplitude means were also significantly lower in stage II family members, compared with control family members for all comparisons, namely probands, affected and unaffected individuals ($p < 0.0001$), and offspring ($p < 0.01$). Furthermore, affected individuals from stage II families, but not control families, had significantly lower P3 amplitudes than unaffected individuals ($p < 0.001$). Affected males from stage II families had significantly lower P3 amplitudes than affected females ($p < 0.001$). Recent linkage analyses indicate that visual P3 amplitude provides a biological phenotypic marker that has genetic underpinnings.

Key Words: Phenotypic Markers, ERPs, Alcoholism, Genetics.

ELECTROPHYSIOLOGICAL ABERRATIONS as measured by event-related potentials (ERPs) have been reported in abstinent alcoholics (for review, see Porjesz and Begleiter[1,2]). We and others have reported that the P3 component is reduced in amplitude in abstinent alcoholics.[1,3–6] Despite the reversibility of latency delays in earlier, sensory-evoked potentials [e.g., brainstem auditory-evoked responses (BAERs)] with prolonged abstinence, the P3 amplitude decrements do not recover.[4] Although P3 amplitude decrements had been assumed to be due to the neurotoxic effects of alcohol on the brain, these findings suggested that low P3 amplitude may antecede the development of alcoholism.

The finding of low voltage P3 amplitudes in prepubescent sons of alcoholic fathers, compared with boys without first- or second-degree alcoholic relatives in experiments without the administration of alcohol, was first reported by Begleiter et al.[7] This finding has been replicated in several laboratories[8–17] under many different experimental conditions with and without alcohol administration, in both older and younger subjects at risk. This finding is supported by a recent meta-analysis of the P3 high-risk literature, undertaken by Polich et al.,[18] who conclude that the P3 may have predictive value as an index of vulnerability for alcoholism.

The low P3 amplitude is a robust finding that seems to characterize individuals at risk for alcoholism and may provide a phenotypic marker for alcoholism. This paper deals with the evidence supporting P3 amplitude as a phenotypic marker for alcoholism, based on data from the large national multisite Collaborative Study on the Genetics of Alcoholism (COGA) Project.

METHODS

The COGA Project is a multisite national consortium designed to study the genetics of alcoholism. The collaborative sites are located at: SUNY

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

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Health Science Center at Brooklyn, University of Connecticut Health Center, Washington University School of Medicine, University of California at San Diego, University of Iowa, and Indiana University Medical School. Alcoholic probands are initially recruited from inpatient and outpatient treatment facilities. Ascertained families contain a proband and two additional first-degree relatives who meet criteria of alcohol dependence by both DSM-III-R and Feighner at the definite level on direct interview. Psychiatric status including alcohol dependence is determined via the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a polydiagnostic instrument that was designed by COGA.[19] Once a family meets these criteria, it is considered to be a stage II family, and all family members are interviewed using the SSAGA. Blood is drawn for establishing lymphoblastoid cell lines and biochemical analyses, and neuropsychological and neurophysiological assessments are obtained.

The control families are "randomly" ascertained to be representative of the general population at each of the six sites. Subjects were recruited from HMOs, motor vehicle bureaus, and dental clinics. Individuals are not excluded for psychiatric illness or alcoholism to obtain prevalence rates that are similar to those of the population at large. In this ERP study, the control group consisted of 687 individuals 16 years of age and older from 163 families, and the stage II families included 1276 individuals 16 years of age and older from 219 families.

The COGA Neurophysiology component consists of identical electrophysiological laboratories at each of the six collaborative sites in which EEG and ERPs from various paradigms are collected. The same experimental procedure and data acquisition hardware and software are used in each laboratory.

The subject was seated in a dimly lit sound-attenuated chamber (IAC) focusing on a fixation point in the center of the screen. Subjects wore a fitted electrode cap (Electro-Cap International, Inc.) containing the 19 leads of the 10/20 International System. The tip of the nose, a relatively electrically inactive cephalic location, served as the reference, and the forehead as ground. Vertical and horizontal eye movements were monitored, and ocular artifact rejection (>73.3 μV) was performed online. Electrical activity was amplified 10K (Sensorium EPA-2 Electrophysiology Amplifiers) and sampled continuously at a rate of 256 Hz (bandwidth: 0.02 to 50 Hz). Digital filtering (32-Hz low-pass filter) of the raw data was performed offline.

The COGA Visual P3 paradigm consisted of the presentation of three types of visual stimuli (n = 280), 60 msec duration, subtending a visual angle of 2.5 degrees, with an interstimulus of 1.6 sec. The rare target stimulus (n = 35) was the letter X, to which the subject pressed a button with his or her right or left hand, as quickly as possible; the responding hand was alternated across subjects within each site to counterbalance any laterality effects due to responding. Speed was emphasized, but not at the expense of accuracy. The frequently occurring nontargets (n = 210) were squares, whereas the rare novel stimuli (n = 35) consisted of colored geometric polygons that were different on each trial; the subject did not respond to the nontarget and novel stimuli. The stimuli were pseudorandomly presented, with the constraint that neither targets nor novels could be repeated consecutively.

To determine whether the data collected at the six COGA sites could be pooled, an intersite consistency study was conducted.[20] Data from the COGA Visual P3 paradigm were collected from 16 healthy right-handed males between the ages of 18 to 29 at each center. The waveforms were found to be remarkably similar to each other in all three stimulus categories, and P3 amplitudes were not found to be significantly different across sites.[20] The absence of site effects allowed the data from all sites to be pooled.

Data in the present paper come from Visual P3 recordings obtained at all six COGA laboratories. The analyses were limited to only the P3s recorded to the target stimulus at the Pz electrode, because this is the lead at which P3 is maximum, and measurement of P3 is optimal under these conditions. ERPs were averaged, including only correct trials. P3 amplitude was measured as the voltage difference from the baseline (187 msec of EEG prior to stimulus onset) to the largest positive peak in the latency window 250 to 600 msec after the stimulus.

P3 amplitude data was converted to z-scores to better understand the deviance of the experimental sample in comparison with the control sample.

Table 1. Demographic Characteristics of Members of 219 Stage II (n = 1276) and 163 Control Families (n = 687)

	Stage II	Control
Sex (%)		
Male	47.7	48.0
Female	52.3	52.0
Age		
Mean age	36.7	33.5
Site (%)		
UCONN	19.4	22.8
INDIANA	12.2	18.2
IOWA	9.0	18.1
SUNY	20.0	14.5
WASHU	24.6	11.8
UCSD	14.6	14.6
Ethnic (%)		
White Non-Hispanic	77.8	86.1
Black Non-Hispanic	14.8	4.0
White Hispanic	4.6	4.2
Black Hispanic	1.0	1.0
American Indian	0.8	1.0
Asian/Pacific Islander	0.4	1.8
Education		
No. of years	12.6	14.1
Socioeconomic		
Income level		
1,000–29,999	49.1	29.4
30,000–74,999	41.5	52.0
75,000–150,000	9.3	18.6

UCONN, University of Connecticut; INDIANA, Indiana University; IOWA, University of Iowa; SUNY, State University of New York; WASHU, Washington University in St. Louis; and UCSD, University of California at San Diego.

For the purposes of this paper, a P3 amplitude beyond 2 SDs below the control mean was considered an "abnormal trait." Comparisons of age- and sex-matched P3 amplitude means and distributions were made between members of stage II densely affected families and members of control families.

RESULTS

The demographic characteristics of the 219 densely affected stage II families (n = 1276) and the 163 random control families (n = 687) making up the COGA sample are presented in Table 1. Comorbidity with respect to other psychiatric disorders of the COGA stage II and control samples are presented in Table 2.

There were no significant differences in P3 amplitude among the sites in the pooled dataset. The percentage of individuals in each group contributed by each site is in Table 1. Whereas there were unequal numbers of individuals included from each site, the amplitude of P3 was significantly lower for stage II, compared with control family members at each site.

When age- and sex-matched distributions of P3 amplitudes from the COGA sample were compared, members of densely affected stage II families were more likely to manifest low P3 amplitudes (2 SD below the mean) than members of control families, comparing affected and unaffected offspring and all individuals (Table 3). It was found that 10% of family members from stage II families manifested P3 amplitudes 2 SDs below the mean, compared with only 1.1% of control family members (Fig. 1 and Table 3). Twenty-two per-

Table 2. Co-morbidity Characteristics (DSM-III-R) of Members of 219 Stage II (n = 1276) and 163 Control Families (n = 687)

	Stage II	Control
ASP	10.6	2.4
ASP (conduct)	17.1	6.1
Cocaine		
Abuse	0.3	0.0
Dependence	16.8	1.4
Major depressive episode		
Current	1.4	1.0
Lifetime	36.0	22.7
Marijuana		
Abuse	1.1	0.6
Dependence	24.7	6.3
Mania		
Current	1.1	0.3
Lifetime	4.0	1.3
Obsessive/compulsive	2.2	0.6
Opioid		
Abuse	0.1	0.0
Dependence	4.6	0.2
Panic disorder	3.6	1.1
Sedative		
Abuse	0.6	0.0
Dependence	5.4	0.2
Somatization disorder	0.0	0.0
Stimulant		
Abuse	0.4	0.2
Dependence	8.2	0.6

ASP, antisocial personality.

cent of alcohol-dependent individuals from stage II families, compared with only 2.9% of affected individuals from control families, manifested P3 amplitudes beyond 2 SDs below the mean (Fig. 2 and Table 3). Furthermore, among nonalcoholic members of stage II families, 6.8% manifested P3 amplitudes beyond 2 SDs below the mean, compared with only 0.1% of nonalcoholic members of control families (Fig. 3 and Table 3). Among offspring of male stage II probands, 17.5% fell beyond 2 SDs below the mean, compared with 2.5% in the control families (Table 3). As Table 3 indicates, all comparisons of these age- and sex-matched distributions between groups were significant by χ^2 at $p < 0.00001$. Furthermore, P3 amplitude means were significantly lower in stage II family members, compared with control family members for all comparisons between groups, namely probands, affected and unaffected individuals ($p < 0.0001$), and offspring ($p < 0.01$). Within-group comparisons indicated that affected individuals from stage II families had significantly lower P3 amplitudes than unaffected individuals ($p < 0.001$), whereas there were no significant differences between affected and unaffected members of control families. Furthermore, affected males from stage II families had significantly lower P3 amplitudes than affected females ($p < 0.001$). These various comparisons indicate that members of stage II families show significantly lower P3 amplitudes than members of control families.

To be considered as a phenotypic marker, there are certain criteria that must be met. This paper considers how low P3 amplitude meets each of these criteria for a phenotypic marker for alcoholism, using data that come predominantly from the large national multisite COGA Project described herein. These criteria include:

A. Studies in the general population should show:

1. *The trait can be reliably measured and is stable over time:* The test-retest reliability of the target P3 amplitude has been reported to be between 0.62 to 0.93, indicating that it is reliable and stable over time.[21]

2. *The trait is genetically transmitted:* Evidence that the trait is genetically transmitted comes from both twin studies and family studies. O'Connor et al.[22] reported auditory P3 amplitude Mz twin heritability to range between 0.49 to 0.60 at posterior leads. Similar heritabilities based on a large twin study have been recently reported for visual P3 amplitude.[23] Family data from the COGA Project estimated heritability of visual P3 amplitude to be between 0.43 to 0.60.[24,25] Based on a large sample of 163 randomly ascertained COGA control families with offspring 16 years old and over (687 individuals), Daw et al.[24] performed a co-mingling analysis on the amplitude of the visual P3 component to target stimuli recorded at the Pz lead (the condition under which measurement of P3 amplitude is optimal). Testing for admixture, the P3 amplitude was found not to be due to a major gene, but could be accounted for by a single skewed distribution with an estimated heritability at 0.50 in the general population. More recently, Almasy et al.[25] have estimated the heritability of P3 amplitude in 604 individuals from 100 stage II pedigrees ascertained as part of the COGA Project. They report significant heritabilities for both visual and auditory P3 amplitudes to target stimuli, with higher heritabilities for visual than auditory P3 amplitudes.

3. *The "abnormal" trait has a low base rate:* Evidence that the "abnormal trait" has a low base rate is found by examining the P3 amplitude distribution in control families (n = 687 from 163 families) (Fig. 1). In contrast to most standard ERP studies that use "squeaky clean" controls, these control families were randomly ascertained to be representative of the general population. As indicated in Table 3, the mean P3 amplitude in the control sample was 21.2 μV (SD 8.5), whereas the amplitude was higher in our "squeaky clean" controls (24.3 μV) with a narrower range (SD 6.6). Based on the distributions of P3 amplitude from control families that were converted to z-scores, only 1.1% of the control population had a P3 amplitude lower than 2 SD

Table 3. P300 Amplitude Characteristics of Stage II and Control Subjects in the COGA Study

	Mean (SD) P300 amplitude in μV			% of subjects with P300 ≥2 SDs below the mean		
	Stage II	Control [mean (SD)]	p	Stage II	Control	p
All	17.4 (8.6)	21.2 (8.5)	0.0001	10.0	1.1	0.00001
Alcoholic	15.9 (7.8)	21.2 (6.8)	0.0001	22.1	2.9	0.00001
Nonalcoholic	17.5 (8.6)	20.4 (8.4)	0.0001	6.8	0.1	0.00001
Offspring	23.6 (7.3)	27.6 (6.8)	0.01	17.5	2.5	0.00001

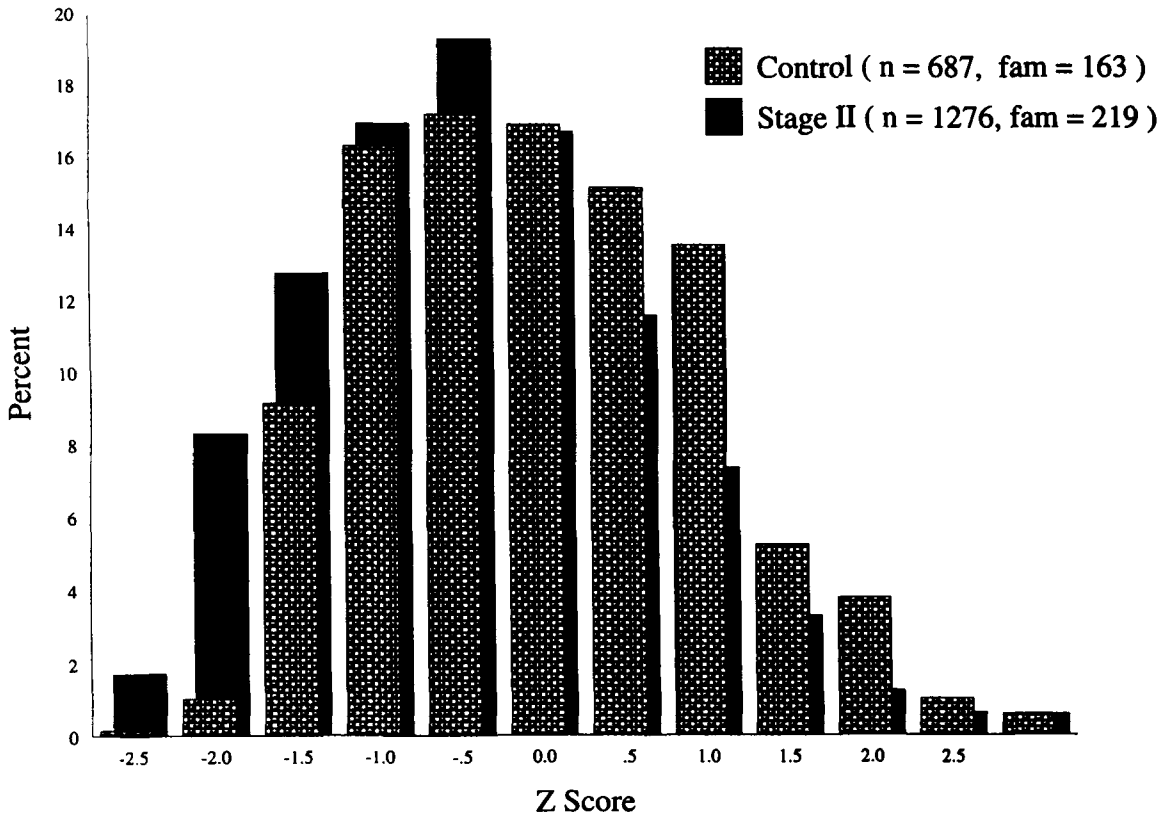

Fig. 1. Z-scores of P3 amplitudes (abscissa) in randomly ascertained control families (black and white pattern) and densely affected stage II COGA families (solid black) (three or more alcohol dependent first-degree relatives). Along the ordinate are the percentage of individuals with these z-scores. These distributions are based on 687 individuals from 163 control families and 1276 individuals from 219 stage II families.

below the mean, as can be seen in Table 3 and Fig. 1. As an "abnormal trait" is defined as a P3 amplitude beyond 2 SDs below the control mean in this paper, it can be concluded that the "abnormal trait" (low P3) has a low base rate.

4. *The trait identifies individuals at risk for the disorder:* As reviewed herein, low P3 amplitudes are prevalent in sons of alcoholic fathers. In the COGA Project, both sons and daughters of alcoholic fathers from stage II families manifest significantly lower P3 amplitudes (23.6 μV), compared with age- and sex-matched offspring of control probands (27.6 μV, $p < 0.01$) (Table 3). As Table 3 indicates, the P3 amplitudes are larger in this younger subset of both groups than the rest of the sample, because age has a direct effect on P3; nevertheless, the P3 amplitude is significantly higher in the offspring of age- and sex-matched control probands, compared with offspring of alcoholics. The z-score distributions of P3 amplitudes of 16- to 25-year-old offspring of male probands from stage II families were compared with age- and sex-matched offspring of male probands of control families. Offspring of female probands were not included in this analysis because of the potential effects of fetal alcohol syndrome and fetal alcohol effect. Based on these matched distributions, the offspring of stage II families manifested a significantly larger percentage of offspring with P3 amplitudes beyond 2 SD below the mean (17.5%), compared with offspring in control families (2.5%) (χ^2, $p < 0.00001$, $df = 3$) (Table 3).

B. Studies in patients should show that:

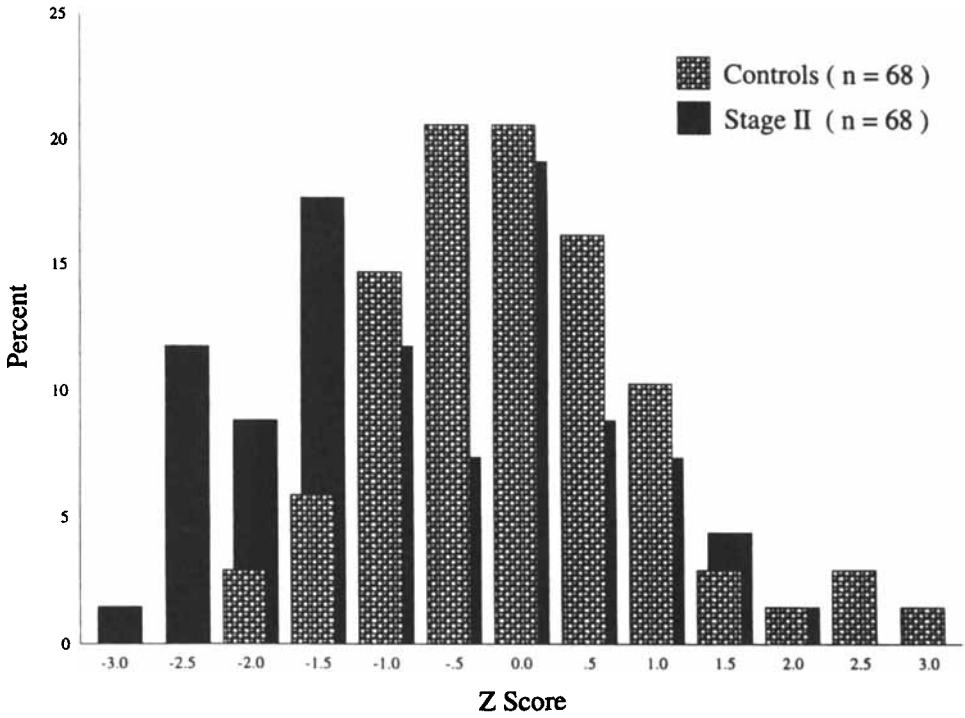

Fig. 2. Z-scores of P3 amplitudes (abscissa) in age- and sex-matched affected individuals from randomly ascertained control families (pattern) and densely affected stage II COGA families (solid black) (n = 68/group). Along the ordinate are the percentage of individuals with these z-scores. These distributions are based on alcohol-dependent individuals, assessed by SSAGA (both DSM-III-R alcohol-dependent and Feighner definite) from control families and densely affected stage II families.

1. *The trait is prevalent in the patient population:* Low P3 amplitudes have frequently been reported in male alcoholics (for review, see Porjesz and Begleiter[1,2]). The magnitude of the COGA Project provides the opportunity to investigate electrophysiological measures in large samples of female, as well as male, probands and among family members, an area that has not been adequately studied. Data from the COGA Project indicate that female alcoholics also manifest a diminution in P3 amplitude, but not to the same degree as male alcoholics. Male alcoholics from stage II families have significantly lower P3 amplitudes than female alcoholics from stage II families (15.1 μV vs. 17.3 μV, respectively; $p < 0.001$). P3 amplitude z-scores in stage II alcoholic probands indicate that 22% of affected individuals from stage II families have low P3 amplitudes beyond 2 SD below the mean (Table 3). Therefore, low P3 amplitude characterizes many alcoholics.

2. *The trait is present during symptom remission:* P3 does not recover with prolonged abstinence, despite reversibility of BAER.[4] Alcoholics in a long-term recovery program (4 months) do not show reversibility of P3 deficits; members of Alcoholics Anonymous abstinent from 3 to 10 years still manifest low P3 amplitudes.[4] Therefore, P3 amplitudes remain depressed during abstinence, despite symptom remission, indicating that low P3 amplitude is a trait rather than a state characteristic.

3. *The trait occurs among first-degree relatives of the index case at a rate higher than that found in the normal population:* The z-scores of P3 amplitudes from 1276 individuals from 219 stage II families was compared with z-scores of P3 amplitudes of 687 individuals from 163 control families (Fig. 1). Ten percent of stage II family members have low P3 amplitudes beyond 2 SDs below the mean, compared with only 1.1% of controls, regardless of their affected status (χ^2, $p < 0.00001$, $df = 3$) (Table 3). Therefore, it seems that a much larger percentage of stage II family members manifest low P3 amplitudes than is found in the general population.

4. *The trait segregates with illness in affected relatives:* Affected members of stage II families (by DSM-III-R and Feighner criteria) manifested significantly lower P3 amplitudes than unaffected stage II family members (15.9 μV and 17.5 μV, respectively, $p < 0.001$). However, P3 amplitudes between affected and unaffected family members in control families did not differ significantly from each other. This indicates that affected relatives in dense alcoholic families manifest low P3 amplitudes. In addition, P3 amplitudes were significantly lower in affected individuals from stage II families, compared with age- and sex-matched affected members of control families, despite the fact that, in both cases, they were alcohol-dependent by both DSM-III-R and Feighner criteria (15.9 μV vs. 21.2 μV, respectively, $p < 0.0001$) (Table 3).

The distributions of P3 amplitudes from affected individuals in stage II families, compared with age- and sex-matched affected controls was significantly different (χ^2, $p < 0.00001$, $df = 3$); P3 amplitude values beyond 2 SDs below the mean were found in 22% of affected members of stage II families, compared with only 2.9% in affected controls (Fig. 2 and Table 3). This indicates that low P3 amplitude is more prevalent in affected relatives in dense stage II alcoholic families (i.e., with at least three affected

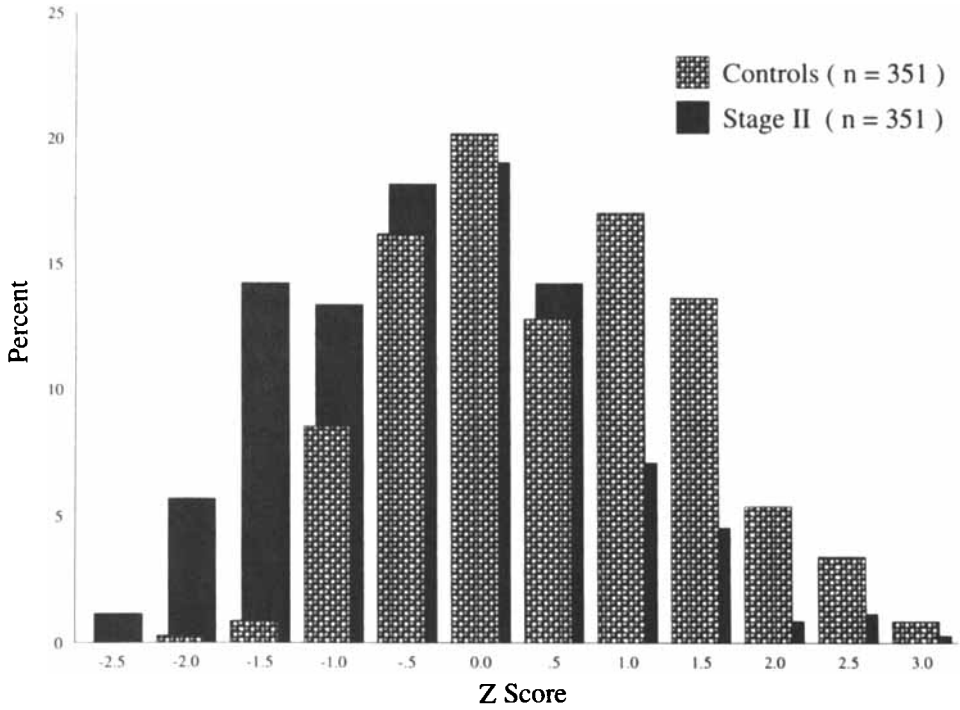

Fig. 3. Z-scores of P3 amplitudes (abscissa) in unaffected individuals from randomly ascertained control families (pattern) and densely affected stage II COGA families (solid black). Along the ordinate are the percentage of individuals with these z-scores. These distributions are based on age- and sex-matched unaffected individuals (n = 351/group) from control families and densely affected stage II families.

first-degree relatives); whereas in the control groups, these alcoholics could represent sporadic cases. These data suggest that prevalence of alcoholism in the family is an important variable in determining P3 amplitude.

In addition, unaffected stage II family members had significantly lower P3 amplitudes than unaffected controls (17.5 μV vs. 20.4 μV, respectively, $p < 0.0001$) (Table 3). As Fig. 3 illustrates, the z-scores of the P3 amplitudes in the unaffected matched groups indicated that 6.8% of unaffected stage II family members had P3's beyond 2 SD below the mean, compared with 0.1% of the unaffected controls (χ^2, $p < 0.00001$, $df = 3$).

DISCUSSION

The P3 amplitude has been considered as a potential marker of risk for alcoholism in relation to each criterion for a phenotypic marker. Data from the COGA Project suggest that low P3 amplitude fulfills each of these criterion, supporting its utility as a potential phenotypic marker. These findings are consistent with those of Pfefferbaum et al.,[6] who reported that P3 amplitude in alcoholics is a function of the number of first-degree alcoholic relatives. Using a PATH analysis, they found that P3 amplitude was directly related to the number of first-degree alcoholic relatives, and not to any drinking history variables. Therefore, family history of alcoholism, not alcohol consumption, is correlated with P3 amplitude. Recent findings[15,26] indicate that low P3 amplitude in young children predicts future substance abuse in adolescents. Longitudinal studies are underway as part of the COGA Project to retest all family members. This will be particularly informative in assessing the offspring of alcoholics from stage II families as they pass through the age of risk for developing alcohol-related problems, including alcohol dependence. COGA data would predict that the offspring who manifest P3 amplitudes in the low range are most at risk for developing alcoholism.

Recently, the COGA Project has undertaken various linkage analyses, including studies to identify the genetic bases of ERP's.[27] Two methods were used: SAGE Sibpal,[28] a nonparametric method program using 2-point Identity by Descent methods, and SOLAR (Sequential Oligogenic Linkage Analysis Routines),[29] a multipoint quantitative linkage package using variance components. The genetic analysis of the COGA sample is based on 990 individuals from 105 densely affected families, comprising about 300 sibpairs. Approximately 291 highly polymorphic DNA markers were genotyped in these alcoholic families with a mean intermarker interval of 14 cM. The COGA visual P3 linkage analysis was based on 604 individuals from 100 pedigrees. Two "hotspots" of significant linkage were identified: one on chromosome 6 at Cz and related leads (LOD = 3.41) and the other on chromosome 2 at O2 (LOD = 3.28) and related posterior leads. Because these findings were apparent with both SAGE Sibpal and the SOLAR method, at adjacent markers and leads, they do not seem to represent spurious cases. Currently flanking markers are being placed in this region. A recent dissertation from Holland in Molenaar and Boomsma's group[23] studied the visual P3 in a large sample of twins using a multivariate genetic analysis approach. They reported two independent factors to account for visual P3 amplitude, namely: one factor that influences all electrodes and a

second factor that influences occipital leads. Perhaps these chromosome 2 findings for the posterior leads represent this second occipital factor.

The linkage analyses indicate that the visual P3 amplitude provides a biological phenotypic marker that has genetic underpinnings. Understanding the genetic control of brain electric activity may provide clues about cerebral function and shed light on pathogenic mechanisms of neurological and psychiatric disorders where impairment of brain electric activity is apparent (e.g., low P3 amplitude observed in alcoholism).

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