

Visual P3 as a potential phenotypic marker for alcoholism: evidence from the COGA national project

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Abstract. Recent data from the large national multisite Collaborative Study on the Genetics of Alcoholism (COGA) provide evidence for considering P3 amplitude as a phenotypic marker for alcoholism. Distributions of visual P3 amplitude at the Pz electrode to target stimuli in various samples of the COGA project were derived and compared based on data collected at six identical electrophysiological laboratories using identical procedures. The distribution of P3 amplitude in individuals over 16 years of age from randomly ascertained control families was compared to those from densely affected stage II alcoholic families in which three first degree relatives met criteria of alcohol dependence by DSM-III-R and Feighner definite based on direct interview (Semistructured Assessment for the Genetics of Alcoholism). The control distributions are based on 687 individuals from 163 randomly ascertained families and do not exclude individuals for psychiatric illness including alcoholism, so that the prevalence rates can be considered to be those of the general population. The stage II distributions are based on 1,276 individuals from 219 densely affected families. Z-transforms were performed on all P3 amplitude data, and a P3 amplitude beyond 2 SD below the mean was considered an "abnormal trait". It was found that 10% of stage II family members manifested P3s 2 SD below the mean compared to only 1.1% of controls. Twenty-two percent of affected stage II individuals manifested P3 amplitudes beyond 2 SD below the mean, compared to only 2.9% of affected controls, despite the fact that all of these individuals were alcohol dependent by DSM-III-R and Feighner definite criteria. Furthermore, among unaffected members of stage II families, 2.9% manifested P3 amplitudes < 2 SD below the mean compared to only 1.1% of unaffected controls. This suggests that family density for alcoholism is an important determinant of P3 amplitude. 17.5% of offspring of male probands fell beyond 2 SD below the mean compared to 2.5% in the controls. All comparisons of these age- and sex-matched distributions between groups were significant by chi-square at $p < 0.00001$. P3 amplitude means were significantly lower in stage II family members compared to 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 stage II individuals had significantly lower P3 amplitudes than unaffected individuals ($p < 0.001$), while there were no significant differences between affected and unaffected controls. Furthermore, affected stage II males had significantly lower P3 amplitudes than affected females ($p < 0.001$). The utility of P3 amplitude as a phenotypic marker for alcoholism risk, in conjunction with other ERP features is discussed to provide specificity.

Key words: alcoholism, ERPs, genetics, phenotypic markers.

Introduction

Electrophysiological aberrations have been reported in abstinent alcoholics with the use of ERPs (for review see [1]). We and others have reported that the P3 component is reduced in amplitude or absent in abstinent alcoholics [1–5]. 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 [3].

While P3 amplitude decrements had been thought 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. Furthermore, population genetic studies indicated that sons of alcoholic fathers were four times more likely to become alcoholic even if separated from their biological fathers at birth [6,7]. Therefore, the low P3 voltages should be apparent in subjects at risk for alcoholism, namely sons of alcoholic fathers, even prior to alcohol exposure.

The finding of low voltage P3 amplitudes in sons of alcoholic fathers compared to boys without first or second degree alcoholic relatives without the administration of alcohol was first reported by Begleiter et al. [8]. Since this original study, this finding has been replicated in several laboratories including our own [9–16]. It has been found under many different experimental conditions (easy and difficult tasks, speed and accuracy conditions, auditory and visual paradigms) with and without alcohol administration, in both older and younger subjects at risk. This finding is supported by a recent meta-analysis of the entire P3-high risk literature, undertaken by Polich et al. [17]. They conclude that: “Thus it is reasonable to conclude not only that the P3 component is a useful investigative tool in this context but also that it may have predictive value as an index of vulnerability for alcoholism when well-designed paradigms are used to elicit ERPs.”

Evidence that P3 is heritable comes from twin studies which indicate that identical twins manifest more similar P3s than unrelated individuals [18]; a study of MZ/DZ twin pairs recently reported that heritability of P3 amplitude ranges approximately between 0.49–0.60 at posterior leads [19]. In addition, there is evidence that P3 amplitude is directly related to the number of first degree alcoholic relatives and not the drinking history of an individual [5]. Furthermore, low P3 amplitudes in prepubescent children are predictive of later substance abuse in adolescence [16,20].

The low P3 component 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 for considering P3 as a phenotypic marker for alcoholism, presenting data from the large national multisite Collaborative Study on the Genetics of Alcoholism (COGA) project. In order to be considered as a phenotypic marker, there are certain criteria that must be met (Table 1). This paper considers how low P3 amplitude meets each of these criteria for a phenotypic marker for alcoholism, providing data that comes predominantly from the large national multisite COGA project.

Table 1. P3 amplitude as phenotypic marker.

A. Studies of subjects in the general population should show that the trait:

1. can be reliably measured and is stable over time.
 2. is genetically transmitted.
 3. the "abnormal" trait has a low base rate.
 4. identifies individuals at risk.
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B. Studies in patient populations should show that the trait:

1. is prevalent in the patient population.
 2. is present during symptom remission.
 3. occurs among first degree relatives of the index case at a rate higher than that of the normal population.
 4. segregation with the illness in affected relatives.
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Methods

COGA is a multisite national consortium designed to study the genetics of alcoholism. The collaborative sites are located at: SUNY Health Science Center, University of Connecticut Health Center, Washington University School of Medicine, University of California at San Diego, University of Iowa and Indiana University Medical School. It is a family study that ascertains families in which the proband and two additional first degree relatives meet criteria of alcohol dependence by both DSM-III-R and Feighner definite on direct interview with the SSAGA (Semistructured Assessment for the Genetics of Alcoholism), a polydiagnostic instrument that was designed by COGA. 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 COGA neurophysiology component consists of six identical electrophysiological laboratories, at each of the six collaborative sites, in which EEG and ERPs from various paradigms including the visual P3 are collected. The same experimental procedure and data acquisition hardware and software are used in each laboratory.

The control families are randomly ascertained to be representative of the general population at each of the six sites. Individuals are not excluded for psychiatric illness or alcoholism, and the prevalence rates can be considered those of the population at large. In this ERP study, the control group consisted of 687 individuals from 163 families with offspring over 16 years of age. The stage II families in this study included 1,276 individuals from 219 families with offspring over 16 years of age.

The subject was seated in a dimly lit sound attenuated chamber (IAC) focusing on a fixation point in the center of the screen. The paradigm consists of the presentation of three types of visual stimuli ($n = 280$), 60 ms duration, subtending a visual angle of 2.5° namely frequently occurring nontargets ($n = 210$), rare Targets ($n = 35$) and rare Novels ($n = 35$). The stimuli are randomly presented at an ISI of 1.6 s apart. The Target stimulus is the letter X, to which the subject presses a button in his right or

left hand, as quickly as possible. Speed is emphasized, but not at the expense of accuracy. The hand is alternated across subjects. The Novel stimuli consist of colored geometric polygons that are different on each trial.

Subjects wore a fitted electrode cap (Electro-Cap International, Inc.) containing the 21 leads of the 10-20 international system. The tip of the nose served as the reference and the forehead as ground. Vertical and horizontal eye movements were monitored, and artifact rejection ($> 73.3 \mu\text{V}$) was performed on-line. Electrical activity was amplified 10 K (Sensorium EPA-2 Electrophysiology Amplifiers) at a rate of 256 Hz (bandwidth 0.02–50 Hz). Digital filtering (32 Hz low pass filter) of the raw data was performed off-line.

In order to pool the data collected at the six COGA sites, an intersite consistency study was conducted. Data were collected from 16 healthy right-handed males between the ages of 18–29 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 [21]. The absence of site effects allowed the data from all sites to be pooled.

The COGA data in the present paper come from Visual P3 data obtained at all six laboratories. P3 amplitude is measured as the voltage from the baseline to the peak.

Results and Discussion

The data were reviewed in relation to each criterion in Table 1 to consider P3 amplitude as a phenotypic marker for alcoholism. These criteria include the following aspects:

General population

Studies should show that the trait can be reliably measured and is stable over time
The test-retest reliability of the visual target P3 amplitude = 0.71–0.86, indicating that it is reliable and stable over time.

Studies should show that the trait is genetically transmitted

Evidence that the trait is genetically transmitted comes from both twin studies and family studies. O'Connor et al. [19] performed Mz/Dz twin studies and reported auditory P3 amplitude heritability to range between 0.49–0.60 at posterior leads. Family studies from the COGA project estimate heritability between 0.50–0.60. Based on a large sample of 163 randomly ascertained control families with offspring over 16 years of age (687 individuals), Rice and Daw (Washington University) most recently performed a commingling analysis on the amplitude of the visual P3 component to target stimuli recorded at the Pz lead (the condition under which P3 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.

Studies should show that 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 frequency 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 are randomly ascertained to be representative of the population. Individuals are not excluded due to a history of psychiatric illness or alcoholism, and the prevalence rates can be considered those of the population at large. The P3 amplitude data were transformed into z-scores. As can be seen in Fig. 1, 1.1% of the control population had a P3 amplitude beyond 2 SD below the mean. For the purposes of this paper, an "abnormal trait" is a P3 amplitude beyond 2 SD below the mean.

Studies should show that the trait identifies individuals at risk

As reviewed in the introduction, low P3 amplitudes are prevalent in sons of alcoholic fathers. In the COGA project, both sons and daughters of stage II alcoholic fathers manifest significantly lower P3 amplitudes ($23.6 \mu\text{V}$) compared to matched offspring of control probands ($27.6 \mu\text{V}$, $p < 0.01$). In the COGA database, the z-transformed

Z Statistic Percentages

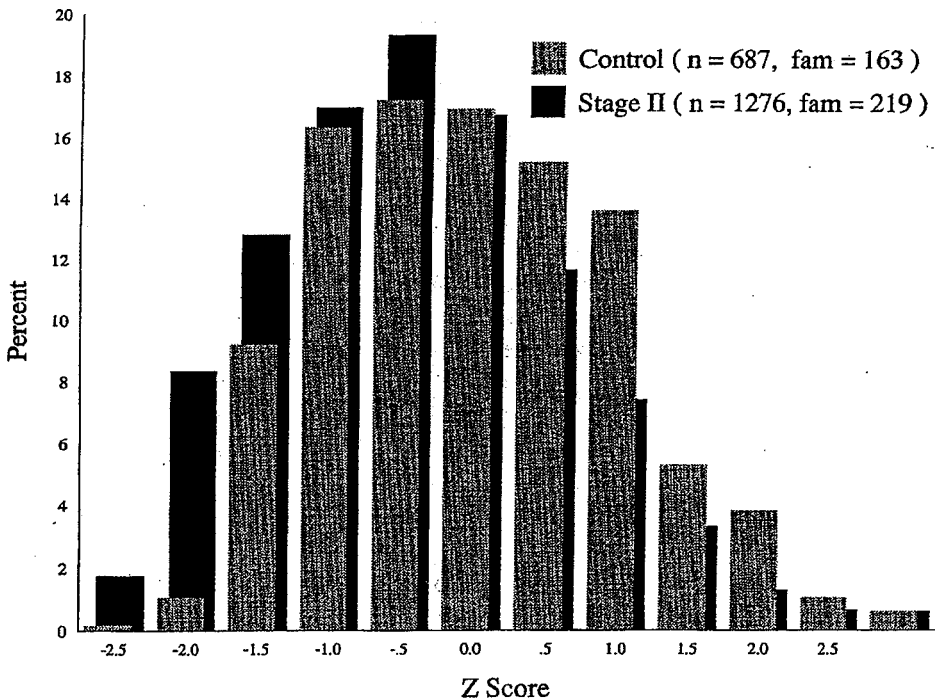


Fig. 1. Z-transformation of P3 amplitudes (abscissa) in randomly ascertained control families (light gray) and densely affected stage II COGA families (black). Along the ordinate are the percentages of individuals with these z-scores. These distributions are based on 687 individuals from 163 control families and 1,276 individuals from 219 stage II families.

P3 amplitudes of 16–25-year-old offspring of male probands were compared to matched offspring of male probands of control families. Offspring of female probands were not included in this analysis because of the effects of FAS and FAE. 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 to offspring in control families (2.5%) (χ^2 $p < 0.00001$). Ten percent of offspring of stage II male probands had amplitudes $< 12 \mu\text{V}$, while none of the control family offspring did. Similar results are currently being obtained with younger offspring in the COGA project.

Patient population

Studies should show that the trait is prevalent in the patient population

As discussed in the introduction, low P3 amplitudes characterize male alcoholics. The COGA project has provided us with the opportunity to investigate electrophysiological measures in female as well as male probands and family members. As this is such a large project, it allows us to examine large samples of subgroups of alcoholics, including females. While reduced P3 amplitudes have been frequently reported in male alcoholics, female alcoholics have 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 stage II alcoholics have significantly lower P3 amplitudes than female stage II alcoholics (17.3 vs. 15.1 μV , $p < 0.001$). A z-transform of the P3 amplitude in stage II alcoholic probands indicates that a large percentage of them have low P3 amplitudes. Twenty-two percent of affected stage II individuals have low P3 amplitudes beyond 2 SD below the mean. Therefore, low P3 amplitude characterizes alcoholics.

Studies should show that the trait is present during symptom remission

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

Studies should show that the trait occurs among first degree relatives of the index case at rate higher than that of the normal population

A z-transform of P3 amplitudes from 1,276 individuals from 219 stages II families compared to z-transforms of P3 amplitudes of 687 individuals from 163 control families is illustrated in Fig. 1. Ten percent of stage II family members have low P3 amplitudes beyond 2 SD below the mean, compared to only 1.1% of controls, regardless of their affected status (χ^2 $p < 0.00001$). Therefore, it seems that a much larger percentage of stage II family members manifest low P3 amplitudes than is found in the general population.

Studies should show that there is segregation with illness in affected relatives

Affected members ($n = 610$) of stage II families (by DSM III-R and Feighner criteria) manifested significantly lower P3 amplitudes than unaffected ($n = 405$) stage II family members ($15.9 \mu\text{V}$ and $17.5 \mu\text{V}$, respectively, $p < 0.001$). A formal segregation analysis is currently underway in the stage II families. However, P3 amplitudes between affected ($n = 68$) and unaffected ($n = 428$) 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 stage II individuals ($n = 610$) compared to matched affected members of control families ($n = 68$), despite the fact that in both cases they were alcohol dependent by both DSM III-R and Feighner criteria (15.9 vs. $21.2 \mu\text{V}$, respectively, $p < 0.0001$).

The distributions of P3 amplitudes from stage II affected individuals compared to matched affected controls was significantly different ($\chi^2 p < 0.00001$); P3 amplitude falls beyond 2 SD below the mean were found in 22% of affected stage II family members compared to only 2.9% in affected controls (Fig. 2). This indicates that low

Z Statistics of Affected Individuals

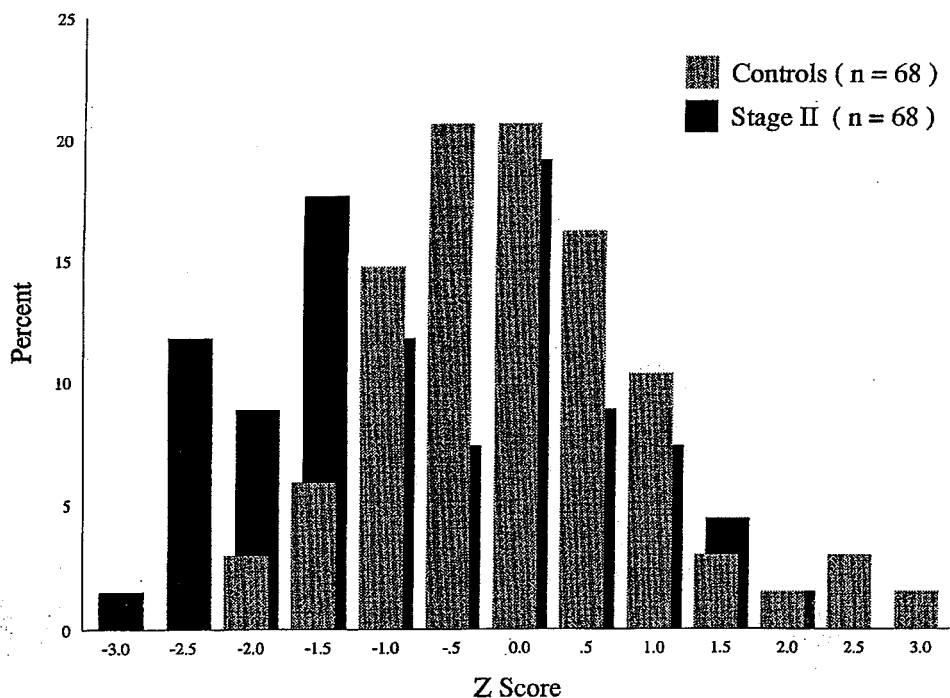


Fig. 2. Z-transformation of P3 amplitudes (abscissa) in age- and sex-matched affected individuals from randomly ascertained control families (light gray) and densely affected stage II COGA families (black) ($n = 68/\text{group}$). Along the ordinate are the percentage of individuals with these z-scores.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

P3 amplitude is more prevalent in affected relatives in dense stage II alcoholic families (i.e., with at least three affected first-degree relatives), while in the control groups, these alcoholics could represent sporadic cases. These data suggest that family density is an important variable in determining P3 amplitude. While P3 amplitudes are significantly lower in affected stage II males compared to unaffected stage II males, stage II females do not differ significantly based on affected status, although there is a trend in the expected direction.

In addition, unaffected stage II family members ($n = 405$) had significantly lower P3 amplitudes than unaffected controls ($n = 428$) (17.5 vs. $20.3 \mu\text{V}$, respectively, $p < 0.0001$) (Fig. 3). The z-transformations of the P3 amplitudes in the unaffected matched groups indicated that 6.8% of unaffected stage II family members had P3s < 2 SD below the mean compared to 1.1% of the unaffected controls ($\chi^2 p < 0.00001$).

These findings are in keeping with those of Pfefferbaum et al. [5], who reported that P3 amplitude in alcoholics is a function of the number of first degree alcoholic relatives. Using a PATH analysis, he found that P3 amplitude was directly related to the number of first degree alcoholic relatives, not any drinking history variables.

Z Statistics of Unaffected Individuals

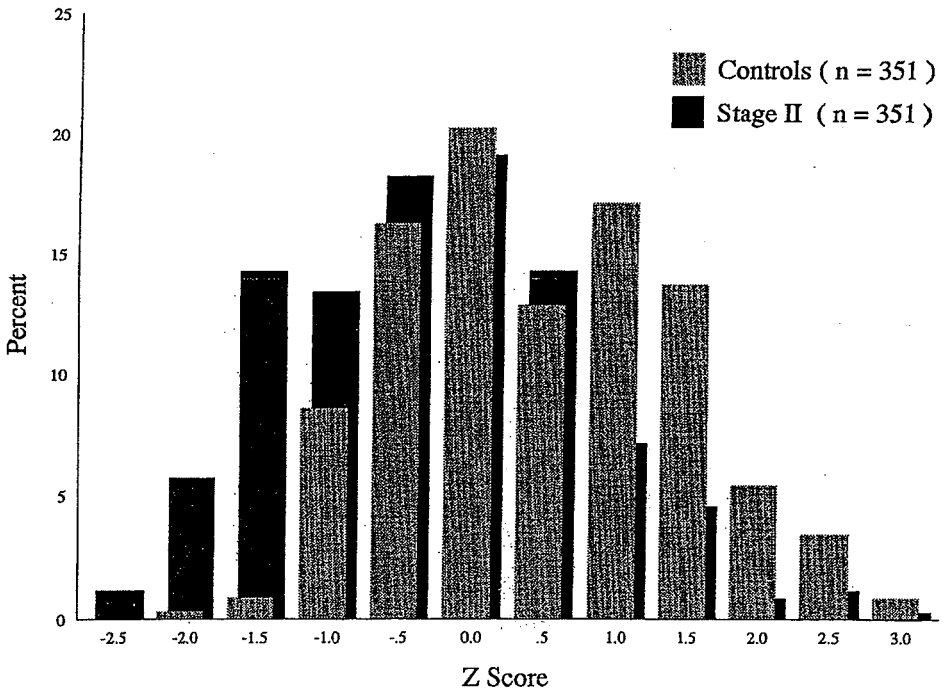


Fig. 3. Z-transformation of P3 amplitudes (abscissa) in unaffected individuals from randomly ascertained control families (light gray) and densely affected stage II COGA families (black). Along the ordinate are the percentage of individuals with these z-scores. These distributions are based on age- and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

Therefore family history of alcoholism, not alcohol history determines P3 amplitude.

Figure 4 summarizes the visual P3 amplitude means of various subgroups of the COGA project. Notice that P3 amplitudes are significantly lower in stage II family members compared to Control family members for all comparisons between groups, namely probands, affected and unaffected individuals ($p < 0.0001$). P3 mean amplitudes in the adult control family members are in the low 20 μV range, whereas the stage II families manifest P3s in the mid teens. P3 amplitudes are higher in both offspring groups, due to their age, but are significantly lower in the stage II offspring compared to control offspring ($p < 0.01$). Within group comparisons indicate that affected stage II individuals have significantly lower P3 amplitudes than unaffected individuals ($p < 0.001$), while there are no significant differences between affected and unaffected controls. Furthermore, affected stage II males manifest significantly lower P3 amplitudes than affected females ($p < 0.001$). All comparisons of distributions between groups were significant by chi-square analysis at $p < 0.00001$.

This paper has considered the P3 amplitude as a potential marker of risk for alcoholism in relation to the criteria for a phenotypic marker. Data from the COGA

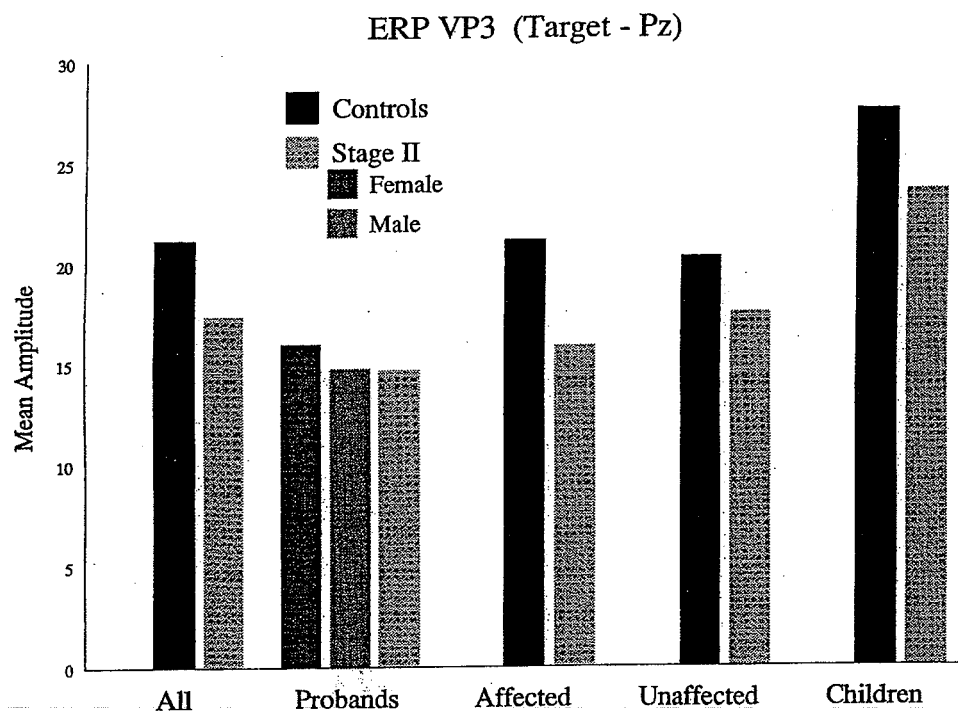


Fig. 4. Histogram of mean visual P3 amplitude (in μV) to target stimuli at Pz electrode, for groups from randomly ascertained control and densely affected stage II families, as follows: all (control = 21.2 μV vs. stage II = 17.4 μV , $p < 0.0001$), stage II probands (all 14.7 μV , female 17.3 μV , male 15.1 μV), affected individuals (control = 21.2 μV vs. stage II = 15.9 μV , $p < 0.0001$), unaffected individuals (control = 20.4 μV vs. stage II = 17.5 μV , $p < 0.0001$), and offspring (control = 27.6 μV vs. stage II = 23.6 μV , $p < 0.01$). Male stage II alcoholics have significantly lower P3 amplitudes than female stage II alcoholics (17.3 vs. 15.1 μV , $p < 0.001$).

project suggest that low P3 amplitude satisfies each of these criteria, supporting its utility as a potential phenotypic marker. Recent findings [16,20] 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 retesting the offspring of stage II alcoholics as they pass through the age of risk. The COGA data would predict that the offspring who manifest P3 amplitudes in the low range are most at risk for developing alcoholism.

While this paper has focused on P3 amplitude, low P3 amplitudes may not be specific to alcoholism. The COGA project consists of other paradigms which examine additional components such as N400, CNV, VMP. These other measures may add specificity to the electrophysiological measures as phenotypic markers. Recently, we have been finding that electrophysiological aberrations in alcoholics and subjects at risk are not limited to P3, but are apparent in these other ERP measures as well. This cluster of electrophysiological measures may represent a more specific phenotypic marker for a predisposition to alcoholism than reduced P3s alone.

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