Original Paper

Journal of Biomedical Science

J Biomed Sci 2001;8:77–82

P_{300} Event-Related Potential Amplitude as an Endophenotype of Alcoholism – Evidence from the Collaborative Study on the Genetics of Alcoholism

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Key Words
Alcohol dependence · Event-related potentials · Endophenotype · Genetics · Electrophysiology

Abstract
There is substantial information supporting the role of genetic factors in the susceptibility for alcohol dependence. However, the identification of specific genes that contribute to this predisposition has proven elusive, although several theoretically relevant candidates, e.g. DRD2 or 5-HT_{1B}, have been considered. The difficulty in identifying specific genes may be related to the clinical heterogeneity of the disorder resulting in a poorly defined phenotype for genetic analysis. An alternative approach to the use of a diagnostic phenotype for identifying alcoholism susceptibility genes may lie in the examination of the neurobiological correlates of the disorder, the so-called endophenotypes. One possible endophenotype of alcohol dependence may be related to the P_{300} waveform of the event-related brain potential (ERP). Using data obtained from the Collaborative Study on the Genetics of Alcoholism (COGA), a multi-site family-based study, the utility of P_{300} amplitude as an endophentype was examined. Differences in P_{300} amplitude were found between alcoholics and nonalcoholics, between unaffected relatives of alcoholics and relatives of controls, as well as between unaffected offspring of alcoholic fathers and offspring of controls. A genetic analysis indicated that attributes of the P_3 ERP waveform are heritable, and a quantitative trait locus analysis found linkage to several chromosomal regions. These data provide significant support for P_{300} as an endophenotype for alcohol dependence.

An increasing number of studies have pointed to the importance of genetic factors in the vulnerability for developing alcohol problems, including alcohol dependence [28, 38]. Family pedigree studies [22, 23], twin studies [37] and adoption studies [9, 11] all provide supporting data implicating the role of genes in alcoholism susceptibility. It has been suggested that as much as 40–60% of the variance in liability for developing alcoholism may be due to genetic effects [24, 28]. However, the early promise of identifying specific genes that contribute to this vulnerability has not yet been fulfilled. Initial reports of finding the genetic bases of alcoholism [7] have not stood the test of replication [20]. This is not to say that progress in the search for susceptibility genes contributing to alcohol dependence has not been made. Several investi-

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gative teams using both animal models [14, 15] and studies of affected populations [17, 18, 32, 38] have identified chromosomal regions that show considerable promise for containing susceptibility genes. While some medical disorders appear to result from a single gene and follow Mendelian patterns of inheritance (cf. Huntington's disease), others do not. Hypertension, diabetes and many cancers, for example, do not show typical Mendelian inheritance patterns. Such traits or conditions are called 'complex', as they do not follow the classic Mendelian transmission patterns of recessive or dominant inheritance [31]. Consequently, the direct relationship between phenotype and genotype is disrupted, i.e. the same genotype may result in different phenotypes or different genotypes may result in the same phenotype. Such may be the case with alcohol dependence.

There has been considerable work to identify 'subtypes' of alcoholism and alcohol dependence. Unfortunately, many of the resulting findings appear to be unreliable due to small sample sizes and do not replicate across studies [25]. Further, the clinical features of the disorder frequently fluctuate over time, suggesting different diagnostic phenotypes within the same individual for different stages of the illness. To avoid the problems that may be inherent in using clinical diagnosis or clinical phenotypes for detecting susceptibility genes, Gottesman and Shields [21] have suggested the use of intermediate or endophenotypes. In their conceptualization, the manifestations of endophenotypes would be closely linked to gene expression and highly heritable. These characteristics thus allow for endophenotypes to be used to identify persons at genetic risk for the disorder even in the absence of symptoms. Gottesman and Shields specified six criteria that must be satisfied for a trait to be identified as an endophenotype. These criteria include: (1) the trait must be present in affected individuals, in both the well state and during the course of the illness; (2) the trait must be present in unaffected biological relatives; (3) the trait must be present in individuals known to be at high risk for developing the disorder; (4) the trait must be predictive of an increased likelihood for developing the disorder; (5) the trait must be heritable, and (6) the trait should have biological manifestations closely linked to gene expression.

Since many traits and symptoms are shared across different psychiatric disorders, an endophenotype may not be specific for a particular diagnosis. Thus, disorders sharing a common genetic diathesis may also share the same endophenotype. Further, the presence of an endophenotype could serve as an indicator of increased risk for a disorder or a set of disorders, and assist in the identification of susceptibility genes.

A biological trait that has received considerable attention by alcohol researchers and which appears to meet the criteria specified by Gottesman and Shields [21] is the amplitude of the P_{300} waveform, an evoked electroencephalographic (EEG) brain potential. The P_{300} waveform is identified as the largest positive peak voltage of the event-related potential (ERP) waveform occurring between 250 and 500 ms after presentation of a stimulus. This component is thought to index several aspects of cognitive functioning, including attention and the maintenance of working memory [34]. More recently, Begleiter and Porjesz [5] have also proposed that a low P_{300} amplitude may serve as an indicator of central nervous system disinhibition. However, the relationship between cortical disinhibition and disinhibitory behaviors (e.g. failure to obey rules, impulsivity, conduct problems) found in several psychiatric disorders, including alcohol dependence, remains to be tested.

This paper will examine the evidence supporting the use of P_{300} amplitude as an endophenotype for alcohol dependence. Each criterion specified by Gottesman and Shields [21] for the identification of an endophenotype will be addressed using data from the Collaborative Study on the Genetics of Alcoholism (COGA).

Methods

Data for this report were derived from the COGA, a 6-site family study of the genetics of alcohol dependence. To date, more than 1,800 families have been recruited, representing over 12,000 individuals. To be considered 'affected', probands were required to meet both DSM-III-R criteria for alcohol dependence [1] and the criteria of Feighner et al. [16] for definite alcoholism to be eligible for study. All probands were required to be in active treatment, with the majority being ascertained through inpatient treatment units. A multistage ascertainment procedure was used. Probands with no or only one additional first-degree relative affected with alcohol dependence were designated as stage I, while probands with at least two additional affected first-degree relatives were designated as stage II. Control families were recruited from the local communities of each site through a variety of recruiting schemes, and families were not excluded if a family member was found to have a history of alcohol dependence. All subjects provided a detailed psychiatric history via a structured interview, the Semistructured Assessment for the Genetics of Alcoholism. This is a polydiagnostic interview with good reliability [8] and validity [26]. A more detailed description of the study and assessment protocol can be found elsewhere [17, 38].

Only individuals from stage II families with a high risk for alcoholism provided a blood sample for genetic analysis and participated in an EEG/ERP assessment. For the EEG/ERP studies, each subject wore a fitted, 21-lead electrode cap following the 10/20 international

system. The reference electrode was placed on the tip of the nose, and a ground electrode was placed on the forehead. Three visual stimuli were presented: targets (probability = 0.125), nontargets (probability = 0.75) and novel infrequent nontargets (probability = 0.125). The experiment terminated automatically after a minimum of 25 target stimulus, 150 nontarget stimulus and 25 novel nontarget stimulus artifact-free trials had been acquired. Stimulus duration was 60 ms with an interstimulus interval of 1.6 s. Each stimulus subtended a visual arc of 2.5°. Trials with a response time greater than 1,000 ms were rejected. P_{300} amplitude was identified automatically and defined as the highest positive peak voltage within 275–575 ms after stimulus onset. P_{300} amplitude was measured at each lead as the difference in peak voltage relative to the prestimulus baseline. Data collection equipment and procedures are described in more detail elsewhere [12].

Table 1. P_{300} amplitudes (μV) and endophenotypic criteria: persons at high risk for alcoholism versus controls

		Family type	
		stage II	controls
Criterion 1	Alcoholics	15.9 ± 7.8	21.2 ± 6.8*
Criterion 2	Nonalcoholic relatives	17.5 ± 8.6	20.4 ± 8.4*
	Nonalcoholic offspring	23.6 ± 7.3	27.6 ± 6.8*

* $p < 0.01$.

Results

Each of the six criteria specified by Gottesman and Shields [21] that must be satisfied in order to consider P_{300} amplitude an endophenotype for alcohol dependence were examined.

(1) The trait must be present in affected individuals. This criterion has been directly addressed in the COGA in two separate studies. Porjesz et al. [36] compared the P_{300} amplitudes in response to a visual stimulus of alcoholics from COGA families with a high risk for alcoholism (designated as stage II) and of alcoholics identified in control families. The alcoholic subjects from stage II families were found to have significantly lower P_{300} amplitudes than the alcoholics from control families (table 1). Further, almost 25% of the stage II alcoholics had P_{300} amplitudes that were more than 2 standard deviations below the COGA adult sample average P_{300} voltage.

These data were re-examined in a slightly different way by Costa et al. [13], who compared P_{300} amplitudes in relation to a diagnosis of alcohol dependence and antisocial personality disorder. They also found reported reduced P_{300} amplitudes among persons with a lifetime diagnosis of alcohol dependence compared to nonalcoholics (9.5 vs. 11.4 μV; $p < 0.05$) in the anterior leads but not the posterior leads. However, Costa et al. also found that P_{300} amplitudes were reduced for younger (<30 years old) subjects with a diagnosis of antisocial personality disorder compared to those subjects without this diagnosis ($p < 0.01$), but only in the anterior leads.

(2) The trait must be present in unaffected biological relatives. To address this criterion, first-degree relatives of COGA probands were compared to individuals from families selected as community controls [36]. In this analysis, the unaffected family members of the alcoholic proband did have P_{300} amplitudes that were significantly lower than those of relatives of control probands ($p < 0.01$; table 1). Further, the unaffected stage II family members were almost 7 times more likely than control group family members to have a P_{300} amplitude 2 standard deviations lower than the entire sample mean.

(3) The trait must be present in individuals known to be at high risk for developing the disorder. This criterion was directly tested using information from the COGA by comparing 16- to 25-year-old unaffected offspring of an alcohol-dependent father with offspring of male probands from the control group (table 1). As predicted, the offspring 'at risk' for alcohol dependence of an alcoholic father had significantly lower P_{300} amplitude voltages to a visual stimulus than their age- and sex-matched controls [36].

(4) The trait must be predictive of an increased likelihood for developing the disorder. At this time, this criterion has not been tested in the COGA data set, as only cross-sectional baseline data are available. However, a 5-year follow-up study of the COGA sample is currently under way. The follow-up data on alcohol use and problems will allow us to determine the usefulness of P_{300} amplitude for predicting the occurrence of alcohol-related problems, including alcohol dependence, among the offspring of alcohol-dependent probands as well as control probands.

(5) The trait must be heritable. Using a sib pair analysis, the heritabilities of P_{300} amplitude voltages at the 19 leads assessed were determined from the first 103 families in the COGA data set. Using n = 758 pairs of siblings, the heritabilities (h^2) were found to range between 0.280 and 0.505, with most in the range of 0.35–0.45 [6].

Importantly, a quantitative trait analysis (QTL) has also been conducted on these data using the same sib pairs. The QTL analysis found a significant linkage for the P_{300} amplitude at the O2 electrode on chromosome 2

(LOD = 3.28; $p < 0.0299$)) and on chromosome 6 (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 2, 5 and 13 [6]. A replication sample of an additional 157 COGA families containing 1,295 individuals is currently undergoing analyses. The preliminary findings suggest that the significant P_{300} QTL analyses reported by Begleiter et al. [6] will be replicated in the second portion of the COGA sample.

(6) The trait should have biological manifestations that can be directly linked to gene expression. Evidence supporting this criterion is found in a bivariate genetic analysis of the COGA data set that examined the correlation of P_{300} amplitude and a diagnosis of alcohol dependence to determine the extent of shared genetic influences [40]. The correlation of P_{300} amplitude and a formal diagnosis (DSM-III-R, DSM-IV, ICD-10) of alcoholism was negative at all leads. The central and temporal leads produced the highest genetic correlations, ranging from –0.61 to –0.71, $p < 0.01$. Trivial, nonsignificant genetic correlations were found at the occipital leads. When examined using a bivariate linkage analysis of P_{300} at Cz and a DSM-IV diagnosis of alcohol dependence, evidence for linkage was found for a region on chromosome 4 near the alcohol dehydrogenase gene cluster (LOD = 5.79) and for a region on the long arm of chromosome 6 (LOD = 3.49).

Discussion

This paper used data from the COGA to evaluate the potential utility of P_{300} amplitude as an endophenotype of alcohol dependence. Six separate criteria for an endophenotype, as specified by Gottesman and Shields [21], were examined. In each case, the COGA data supported the individual criterion, suggesting that P_{300} amplitude would be a useful endophenotype. It was found that alcoholics from stage II families with a high risk for alcoholism had lower P_{300} voltages compared to alcoholics from control families (criterion 1), and that the unaffected relatives of stage II probands had lower P_{300} voltages than relatives of control probands (criterion 2). Criterion 3 was also met as the unaffected offspring of alcoholics were found to have lower P_{300} amplitudes than offspring of controls. Together these data indicate that the P_{300} endophenotype is identifiable in persons with the trait (alcohol dependence), among the biological relatives of probands and among individuals at increased risk for developing the disorder. Criterion 4, regarding the value of P_{300} amplitude for predicting the later development of alcohol dependence, could not be tested in the current cross-sectional COGA data set. Criterion 5 and criterion 6 require that an endophenotype be heritable and directly tied to gene expression. In the COGA sample, P_{300} amplitude was found to be highly heritable among family members. Additional genetic analyses have also shown evidence of genetic linkage between P_{300} amplitude and certain regions of chromosomes 2 and 6. Importantly, bivariate linkage analyses using P_{300} amplitude and a diagnosis of alcohol dependence identified regions on chromosomes 4 and 6 that may contain susceptibility genes. For each of the criteria considered, the results described above based upon the COGA sample provide strong evidence in support of the use of P_{300} amplitude voltage as an endophenotype for alcohol dependence.

However, two other issues regarding P_{300} amplitude as an endophenotype deserve comment. First, a low P_{300} amplitude is not unique to persons with alcohol dependence or at risk for developing alcohol dependence. Reduced P_{300} amplitudes have been found in several other psychiatrically ill populations and among persons susceptible to these conditions. Low P_{300} voltages have been reported among samples with schizophrenia [39] and Alzheimer's disease [35]. Similarly, persons at risk for poor adult outcome, such as individuals with conduct disorder or antisocial personality disorder [2–4, 33] or other psychiatric disorders such as schizophrenia or bipolar illness [19] also display P_{300} amplitudes lower than control subjects.

Secondly, the relationship of a reduced P_{300} amplitude to behavior is not well understood. While Begleiter and Porjesz [5] identify a reduced P_{300} amplitude as an indicator of neuronal disinhibition, the relationship of P_{300} amplitude to behavioral manifestations is less clear. Although it is tempting to suggest that neuronal disinhibition is directly associated with behavioral disinhibition, direct evidence is lacking. As indicated above, Polich [34] has reported that several aspects of cognitive functioning, including attention and the maintenance of working memory, are positively correlated with P_{300} amplitude. Our laboratory [30] has reported similar results, including findings from a sample that contained individuals with antisocial personality disorder [29]. Using the sample from the latter study, the association of P_3 amplitude was also examined in relation to several different personality traits. No significant association was found between P_{300} amplitude and the Reward Dependence subscale of the Tri-dimensional Personality Questionnaire [10] with correlation coefficients ranging from 0.03 to –0.12 across the F8, Fz and Pz leads where P_{300} was recorded. Similarly,

the association between P_{300} and a childhood behavior rating scale indicating impulsivity [27] produced nonsignificant correlation coefficients which ranged from 0.06 to 0.17 [unpubl. data]. These preliminary findings suggest that P_{300} amplitude may be related to some cognitive skills, but not to more global indices of personality. Clearly further studies are required to examine the association between neural disinhibition and behavioral disinhibition to better understand the etiological importance of a reduced P_{300} amplitude for developing alcohol dependence. However, such a demonstrated association would not be mandatory for P_{300} amplitude to have value as an endophenotype for alcohol dependence in the search for susceptibility genes.

Acknowledgement

The 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. Support for this work was also obtained from M01-RR6192 and P50-AA03510.

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