Event-Related Potentials in Alcoholics and Their First-Degree Relatives

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STEHNAUER, S. R., S. Y. HILL AND J. ZUBIN. Event-related potentials in alcoholics and their first-degree relatives. ALCOHOL 4(4) 307-314, 1987.—Preliminary results are presented for auditory ERPs recorded from members of alcoholic families during performance of a counting task and a choice reaction task. Alcoholic families included three adult male siblings (alcoholic proband, a second affected sib, and an unaffected sib) and parents. Control families included two adult male sibs and parents. In all experimental conditions, the N100 component was decreased in amplitude for all sibs (affected and unaffected) of the alcoholic families. The latency of the P300 component was increased for both affected and unaffected sibs compared to controls in the counting task, indicating a familial difference irrespective of drinking status. In the choice reaction task, longer P300 latencies were observed among the probands and their affected sibs as compared to their unaffected sibs, suggesting that in this more demanding task, increased latency was associated with a significant drinking history. ERP findings for children of the alcoholic probands are also discussed. The effects of differences in task complexity, drinking variables, and criteria for family selection are considered.

Alcoholism Event-related potential (ERP) Family studies P300 Siblings

THERE are now several lines of evidence which indicate that vulnerability to alcoholism is, at least in part, genetically mediated. Alcoholism runs in families [8], and exhibits greater concordance among genetically similar individuals [12,13]. Adoption studies indicate a four-fold increase for risk among biological sons of alcoholics adopted away since birth [5].

While it has been assumed that specific cognitive changes (neuropsychological and neurophysiological) observed in alcoholics are a debilitating consequence of alcohol usage, it may well be that some of these measures are, in fact, antecedent to alcoholism. Thus, it is of considerable importance to study measures of cognitive functioning which, though deviant in alcoholics, may represent antecedent conditions. To identify etiological factors in alcoholism, it is necessary to begin with measures which distinguish alcoholics from normals. Ideally, one would begin with a marker having known heritability, but few neurobehavioral indices appear to meet this test.

Over a decade’s worth of research has established the occurrence of event-related potential (ERP) deviations among alcoholics [15,16]. Not only are there modifications in the early temporal components, related more closely to sensory processing, but the long-latency components, especially the P300 wave, have also been reported deviant. As P300 and related components are distinctly reflective of information processing activities, ERP assessment fulfills the first of our criteria.

Of compelling interest, though, is that the ERP generated during information processing tasks shows greater similarity among identical twins than for dizygotic twins or siblings, who are still more similar than unrelated subjects [2]; Surwillo has replicated these findings for identical twins compared to unrelated subjects [21]. In both studies, correspondence among related pairs was greater for the long-latency measures than for earlier time segments. In Fig. 1, ERP data from our laboratory are presented for a rare auditory stimulus, in which waveforms have been superimposed for pairs of subjects who are (a) unrelated, (b) non-twin siblings, (c) dizygotic twins, or (d) monozygotic twins. Especially notable is the resemblance even among non-twin siblings.

Our research team has been actively involved in exploring how different etiological factors may be related, in combination with particular environmental stresses, in eliciting episodes of psychopathology. The vulnerability model first proposed dealt with the development of schizophrenia [23], and indicated that an interaction among biologically based models (e.g., genetic, neurophysiological, biochemical) and environmental models (developmental, learning, ecological) might be sought to provide an understanding of the factors contributing to an individual's vulnerability. In providing a framework for distinguishing specific variables as either long-term vulnerability markers, not related to the current presence of disorder, or as specific episode markers, the importance of examining first degree relatives of probands,

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especially their siblings, was emphasized [24]. The notion of
a "psychological vulnerability" to alcoholism had been
suggested by Jellinek as early as 1960 [11]. However, Jel-
l inek did not attempt to deal with the specific conditions
which might increase psychological vulnerability. The notion
of vulnerability to psychopathology as outlined by Zubin and
colleagues [23–25] has been adapted and extended by Hill
[7, 10] to deal with vulnerability to alcoholism.

As an outgrowth of the development of these models, it
became clear that a multifactorial approach was necessary to
examine the relationships among a variety of factors which
might increase our understanding of vulnerability to alco-
holism. Especially critical in this respect was the aim of ex-
amining not only an individual identified as alcoholic, but
also additional family members, including siblings and par-
ents. We present some of the preliminary event-related po-
tential findings collected as one component of a program
designed to assess multiple biological and psychological
measures in families of alcoholics.

Studies aimed at finding markers for alcoholism using
ERP techniques have contrasted individuals with and with-
out a family history of alcoholism (family history positive
[FH+] and family history negative [FH−]). As we have
previously detailed [10], among any group of FH+ individu-
als there will be some with depression within their extended
family; for some, there will be multiple cases of alcoholism,
but for others, few cases; either the father or mother alone
may be alcoholic, or for some cases, both parents may be
affected.

Even though risk markers for alcoholism may be iden-
tified using the FH+/FH− strategy, the specificity of such
markers is open to question unless some care is taken to
determine the presence or absence of other psychopathol-
ogy within the family. We chose to overcome this potential
pitfall in the FH+/FH− strategy by studying only well charac-
terized families. Furthermore, assessing families in which
there are only single cases of alcoholism is not as likely to
maximize detection as is the study of families with multiple
cases, where the genetic loading is presumed to be greater.
A single occurrence of alcoholism within a family may simply
represent a sporadic case.

Families were ascertained through an alcoholic proband
who was identified while in treatment. We selected for study
families in which two adult male alcoholic siblings, one male
non-alcoholic sib, and one or both parents were available for
assessment. A typical constellation of those tested in an af-
fected family is depicted in Fig. 2. The proband and siblings
are the primary focus in the current discussion.

Our strategy for studying multiplex families—that is,
families which included multiple cases of the disorder—was
selected so that it would be possible to examine reported
differences in alcoholics (e.g., components of the ERP), and
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compare these measures in siblings who were at high risk but had never met criteria for alcoholism. Furthermore, by including families with two affected siblings, we could compare the concordant pairs of affected siblings with the discordant pairs (affected vs. unaffected) siblings. Thus, the contribution of alcohol abuse could be contrasted with familial similarity (while familial similarity primarily implies the role of genetic factors, we recognize the fact that similarities among siblings may reflect either genetic determination or shared family environment).

METHOD

Subject Selection

In our ongoing study, a total of 30 affected and 30 control families are being evaluated; the data reported here are drawn from an initial subset analyzed to date. Every effort is made to select families in which all males sibs were over the age of 30, to minimize the likelihood that a non-affected sib would later become alcoholic.

"Affected" families were selected as follows: male adult alcoholic probands [n=17, aged 33.9±7.2 years (mean, standard deviation)] were identified through visits to treatment centers in the Pittsburgh area. Testing of probands was carried out after at least one month of abstinence. Each proband had an affected male sib (n=17, aged 33.6±6.8 years) who met Feighner criteria for alcoholism. In addition, an unaffected male sib (n=13, aged 33.2±7.6 years) was chosen by the absence of a lifetime diagnosis of alcohol abuse or alcoholism; none of the unaffected sibs were heavy drinkers.

Index control male subjects and their brothers (n=20, aged 34.7±5.4 years) were recruited from families in which no first-degree relatives met criteria for alcohol abuse or alcoholism. Like the unaffected sibs, our index controls and their sibs were screened for absence of heavy drinking as were the parents of controls who were also recruited for study.

All subjects received a series of diagnostic evaluations, including a structured psychiatric interview (a combination of the Renard Diagnostic Interview [6] and the Diagnostic Interview Schedule [17]). Careful assessment of drinking history was obtained for the 30-day period preceding testing; subjects were requested to abstain from using alcohol or drugs (non-prescribed) during the 48 hours preceding testing. Verifying of self-report data was provided by blood samples taken on the day of testing for analysis of the liver enzymes SGOT, SGPT and GGPT.

Procedure

A modified version of the oddball paradigm has been implemented in our laboratory. Two tasks—counting of high-pitched tones, and a differential finger press to high vs. low tones, were employed. Subjects were presented with high-pitched tones (1500 Hz) or low-pitched tones (800 Hz), at 65 dB, 40 msec in duration, through a speaker placed in front of the subject. One tone was presented every 3 seconds for a total of 80 tones (trials) per block.

Subjects were first asked to identify sample tones as "high" or "low" in pitch. The subject was then instructed to silently count the number of "high" tones, reporting the number of "highs" (targets), but not the number of low tones (non-targets), at the end of each block. Subjects were told (1) that there would be fewer high than low tones, and (2) that there would never be two high tones in succession (prior to recording, subjects were asked what would occur next if a high tone was heard; all subjects could correctly answer that a low tone would occur next).

The sequence of tones was generated randomly by computer to produce high tones at an overall probability of 0.25, restricted only by the requirement that high tones not occur in succession. The generated sequences resulted in 17 to 23 high-pitched tones per block.

During four blocks of trials [COUNTING], subjects silently counted the number of high tones, reporting the number of targets at the end of each block. For two additional blocks of trials [CHOICE REACTION], subjects were instructed not to count any tones, but instead, to press a button with the left thumb when one tone was presented, or with the right thumb when the other tone was heard (counterbalanced by block). Only blocks of trials in which no more than three errors occurred were included for analysis; however, all subjects have performed well with few errors.

Psychophysiological Recording

The electroencephalogram was recorded with Ag/AgCl electrodes from midline frontal, vertex, parietal, and occipital locations (Fz, Cz, Pz, Oz), and modified left and right parietal (P3 and P4) locations, referred to linked ears, using a bandpass of 0.01 to 30 Hz, with digitized samples obtained every 8 msec for a 1200 msec epoch beginning 200 msec prior to stimulus onset. An additional channel monitored eye movement artifacts. All recording, storage and data analysis was performed by digital computer.

Average ERPs were computed from artifact-free trials.
FIG. 3. Grand mean ERPs at the Pz electrode during the counting task for alcoholic probands and their two sib groups (affected and unaffected), and for index controls and their sibs. The prominent upward-going deflection in all waveforms is the N100 component. The P300 component is seen as a large downward deflection in the \( p = 0.33 \) condition (Target) which decreases in positivity as the relative probability of events increases in the \( p = 0.67 \) condition and \( p = 1.00 \) Non-Target conditions.

FIG. 4. Grand mean ERPs at the Pz electrode during the choice reaction task, for the same groups presented in Fig. 3.

FIG. 5. Grand mean ERPs in the Target (0.33) condition of the counting task for unaffected sibs of alcoholic probands (solid line) and both control sibs (dashed line) at Cz. The increased negativity of the N100 component among control subjects was seen in all experimental conditions and across tasks (the amplitude difference for P300 was not significant).

While oddball tasks are most typically analyzed according to rare and frequent events, there are clear effects based on sequences of stimuli [19,22]. It has been useful for us to segregate stimuli according to their second order sequence—that is, the conditional probability of each event established by the event on the prior trial. High tones are labelled as Targets (T), and low tones as Non-Targets (NT). When a Non-Target was preceded by a Target, then its occurrence was predictable, that is, the conditional probability was equal to 1.00 (this condition is therefore labelled NT/T). However, once a Non-Target has occurred, then the next trial will be a Target one-third of the time—that is, the conditional probability of T is equal to 0.33—and the occurrence of a Non-Target will occur two-thirds of the time (conditional probability for NT/NT = 0.67). Thus, three types of events, varying in conditional probability from 0.33 to 0.67 to 1.00, could be computed for each subject for each task. In comparison to the usual analysis of ‘oddball’ paradigms, the Target (high) tone is analogous to the rare event, while the average of both types of Non-Target (low) tones would represent the frequent event.

RESULTS

Grand mean ERPs are shown for all of the sib groups from the affected and control families at the midline parietal electrode (at which the P300 component tends to be largest in these paradigms) for both the counting task (Fig. 3) and the choice reaction task (Fig. 4), with lowest conditional probability (0.33 for T) shown to the left (in all waveforms presented, positivity is downward). Increasing P300 amplitude is associated with decreasing conditional probability across both tasks. Overall, this association with conditional probability, which we have reported previously [20], was seen among each of the subject groups—siblings, mothers and fathers of both the affected as well as the control families.

Individual component peaks from P50 to P300 were identified using an interactive computer algorithm. Consistent
FIG. 6. Mean latencies of P300 by condition in the counting task for all sibs within affected families (proband, affected and unaffected sibs, n=47, solid line) and both sibs within control families (n=20, dashed line). Increased P300 latency for sibs within affected families was most pronounced in the 0.67 and 1.00 probability conditions.

FIG. 7. Latencies of P300 by condition in the counting task for only the unaffected sibs from affected families (n=13, solid line) and both sibs of control families (n=20, dashed line, same data as in Fig. 6).

with other data in the literature, P300 was maximum at Pz, while earlier components showed a Cz maximum. Increased latency and lower amplitudes were observed for mothers and fathers from both affected and control families as compared to their sons, beginning with the P200/N250 complex. These findings are to be expected due to increased age of the parents. Mothers in both groups tended to show larger amplitudes than the fathers.

Of primary relevance to the present discussion are the comparisons among the adult male sibling groups for the N100 and P300 components. Both latency and amplitude of these components were evaluated.

N100 Component

One of our most consistent findings was that the amplitude of the N100 component (a large negative peak at approximately 100 msec, maximum in amplitude at Cz) was significantly reduced (less negative) in both the counting (p=0.044) and choice reaction tasks (p=0.02) for sibs from the affected families—both affected and unaffected—as compared to control family siblings. The decreased N100 amplitude for unaffected sibs, compared to controls, can be seen as the large negative-going wave for the midline vertex electrode (Fig. 5). N100 latency did not differ among groups.

P300 Component

P300 latency was significantly increased (main effect, p<0.02) among siblings of affected families (both affected and unaffected) compared to controls in the counting task (Fig. 6). This effect was largely the result of increased latencies in the 0.67 and 1.00 probability conditions. Similar results are seen when only the unaffected sibs of the alcoholic probands are compared to controls (Fig. 7). The alcoholic probands and their affected sibs did not differ in latency from their unaffected sibs.

For the choice reaction task, the ANOVAs between sibs of the affected families vs. controls, or affected sibs only vs. controls, were not significant. However, there were significantly longer P300 latencies for probands and their affected sibs as compared to their unaffected sibs (p<0.05), most
prominently in the 0.33 and the 0.67 conditions (Fig. 8). In neither the counting nor choice reaction tasks were significant differences in P300 amplitude obtained among groups.

DISCUSSION

Our major findings for long-latency components among adult siblings of alcoholic families involve decreased amplitudes for N100 and increased latencies for the P300 component relative to controls. These findings were observed even among unaffected sibs who were social drinkers, averaging only 1.5 drinks/day, which is similar to the consumption of our control subjects. In the choice reaction task, P300 latency was significantly increased among the alcoholic probands and their affected sibs, as compared to their unaffected sibs, indicating, perhaps, that an initial latency prolongation due to membership in a high risk family is further prolonged by alcohol abuse.

A number of previous studies have noted decreased amplitudes for N100 in alcoholics during a cognitive task (see [9,10]). Our data indicate that even the unaffected siblings of alcoholics exhibit reduced N100 negativity. In fact, the amplitude difference for N100 between sibs of affected and control families (approximately 2 microvolts at vertex) was considerably greater than amplitude differences between groups for later components. This strongly suggests a difference in initial attentional activity among the high risk siblings.

Were we to have observed ERP differences only for probands and their affected sibs our conclusions would be that, indeed, the neurophysiological differences from controls reflected chronic alcohol use. However, the fact that our unaffected, social drinking sibs from the same families also show deviations in N100 and P300 suggest that a familial characteristic (high risk status) is also important in explaining the results obtained.

With regard to the findings for P300, it is latency, rather than amplitude, which differentiates alcoholic and non-alcoholic siblings, and further, differentiates siblings (irrespective of drinking status) who are members of affected families from siblings ascertained from control families. The fact that no significant differences were found in amplitude across groups suggests that the quality of the information employed in evaluating the nature of each stimulus was adequate; had there been difficulty in discriminating the differences between stimuli (equivocation), we would have expected P300 amplitude to be decreased, which was generally not observed. Rather, the completion of the evaluation, as represented by P300 latency, was of longer duration. It will be especially interesting to examine the covariation of individual alcohol use and P300 latency among all groups when our larger study is complete. Polich [14] has reported prolongation of latency associated with both family membership and quantity of alcohol consumed per occasion, though Polich (this volume) has indicated that the results may not be robust when the typical FH+/FH− strategy is employed to contrast subject groups.

Several questions arise from the preceding discussion: (1) what can ultimately account for our observations that both high risk family status and alcohol abuse in adults are independently associated with increases in P300 latency in this study and other studies (e.g., [3]); (2) what can account for the fact that in some studies, latency differences have not been obtained, but decreased amplitudes have been reported for adult alcoholics; and (3) what questions might be resolved by examining individuals who have minimal lifetime exposure to alcohol?

One way in which minimal alcohol exposure can be studied is through use of children and adolescents who have not begun to use alcohol. Having already successfully recruited two generations (adult male siblings and their parents), it seemed logical to take advantage of the fact that a third generation was available—children and adolescents who are the offspring of the adult siblings previously described. Here, exposure to alcohol was minimal and marker data was available for the previous two generations. During our ongoing study, the report of Begleiter and colleagues [1] appeared in which amplitude reduction of the late positive complex was clearly described for children with and without alcoholic fathers. We have collected pilot data on two dozen third generation members of our affected and control families. In general, children whose fathers were alcoholic tended to show similar amplitudes in the infrequent (0.33) probability condition, but decreased amplitudes in the 0.67 and 1.00 probability conditions as compared to children of controls.

In the counting task, there was a significant interaction ($p<0.01$) between Family History and the Probability Condition for the latency of P300. In parallel with the adult data, P300 latency was longer in the 0.67 and 1.00 conditions for the children of alcoholics than for the children of controls.

Because this was a small, mixed sexed sample between the ages of 8 and 14, we were concerned that age and sex differences might have accounted for some of the effects. Therefore we covaried out age for these data, and also performed the analyses with males (of whom there were only a few) removed. In neither case were the findings changed.

With respect to P300 amplitude at the midline parietal electrode in the counting task, a significant interaction between Family History and Probability was also observed ($p<0.01$), with significantly larger amplitudes for the children of alcoholics in the 0.33 condition, but smaller amplitudes in the 1.0 condition as compared to children of controls. Again, age and sex did not account for the findings.

Significant findings did not emerge for the analysis of P300 at the P2 location in the choice reaction task. We are examining these data more carefully with respect to demographic differences. The data also showed greatest amplitude differences at the vertex, rather than parietal, locations.

We are intrigued by these pilot data, but are also cautious: children tested were between the ages of 8 and 14, and both male and female children were tested. Thus, we are concerned that age variation, sex, even pre- and post-pubertal classification must be considered. However, plans are underway to extend our study to all third generation offspring so that these factors may be clarified.

Accounting for differences across laboratories in which either P300 amplitude or P300 latency differences are reported is a major difficulty. The concern with differences in populations tested has been raised by many of the investigators who are contributors to this volume. Since there are fairly high correlations between socioeconomic status (SES) and performance on achievement and IQ tests, is it possible that differences in SES may predict differences in psychophysiological measures obtained during cognitive tasks?

Unravelling the effects of alcohol is undoubtedly a complicated task: as illustrated by the literature on neuropsychological test performance [9], it is imperative in both alcoholics and social drinkers to ultimately separate those effects that represent relatively permanent changes in brain
structure and functioning from reversible toxic effects. The permanence or transience of experimental findings must then be considered with respect to risk status within a particular family.

A number of drinking-related variables are also of interest: (1) severity of alcoholism (treated vs. untreated), (2) duration of abstinence before testing, particularly in alcoholics or other drug abusers, (3) number of years of heavy drinking, (4) typical quantity consumed per occasion, and (5) frequency of binge drinking or degree of physical dependence, to name only a few. Obviously, any experimental result must thus be evaluated by taking into account long-term consequences of alcohol (possible brain damage), short-term toxic effects, and the risk status of the individual.

One characteristic which has also been considered, and needs further exploration, is with regard to the nature of the tasks employed, and in this respect, we will offer merely a speculation. When auditory stimuli have been employed in relatively simple tasks, then increased latency of P300 seems to be the predominantly reported phenomenon. We observed the greatest differences between sibs from affected families, including those not affected by alcoholism, as compared to controls, during the counting task in the 0.67 and 1.00 probability conditions. These two conditions are distinctive in that they required no overt response. Given the attentional deficit suggested by lowered N100 amplitude, it may be that increased P300 latency reflects greater time to complete an undemanding evaluation among high risk individuals.

The implementation of the choice reaction task, requiring a response to every stimulus, makes greater demands on the subject to both identify stimuli, and select and initiate responses appropriate to the evaluation. Especially in this case, the unaffected sibs of the probands seem to benefit the most, performing more like controls, but those who are affected tend to have longer latencies. Thus, a slightly increased demand appears to normalize the responses of the unaffected sibs.

In more complex tasks, especially those involving visual discrimination, abstinent alcoholics have exhibited smaller amplitudes of P300. In parallel with our discussion, this might be attributed to difficulty in evaluation of stimuli. Consistent with these findings are the data of Begleiter et al. [1] and others reported in this volume that high risk children and adult offspring of alcoholics show reduced P300 amplitudes during relatively difficult visual discrimination tasks. Snyder et al. [18] have pointed out that visual stimuli tend to be less alerting than auditory stimuli, which thereby increases the "effortful processing" required in visual tasks involving P300 generation.

Summarizing the previous points, it may be that the demands of the task have an inverted U-shaped effect with relation to P300 generation, especially in the unaffected sibs of alcoholics: simple tasks show a deviation in P300 latency, more demanding tasks leading to sufficient arousal for the deviations to be compensated for, but even more difficult tasks leading to decreased amplitudes. If this speculation has any kernel of truth, then it would have to be tested by using a variety of tasks which differ according to both task difficulty and stimulus discriminability. At present, the data across laboratories and using different stimuli are not quite so consistent with this formulation as it may have been made to appear.

We are continuing to record from subject populations in order to reexamine the preliminary findings using a full sample, and have begun to look in greater depth at the relationships among groups, including across generations. The correspondence of the ERP measures to other psychophysiological and behavioral variables among subject groups is also under study.

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