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P300, Alcoholism Heritability, and Stimulus Modality

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POLICH, J. AND F. E. BLOOM. *P300, alcoholism heritability, and stimulus modality*. ALCOHOL **17**(2) 149–156, 1999.—The P300 event-related brain potential (ERP) was elicited with auditory and visual stimuli from members of 13 families who were at high risk (HR) for alcoholism (father diagnosed as alcoholic) and 13 families at low risk (LR) for alcoholism. Each family consisted of a father, mother, and at least two biological children. The intrafamily member correlations (father vs. child, mother vs. child, child vs. child) for P300 amplitude were obtained for 15 electrode sites. P300 amplitude from auditory stimuli was not correlated among HR family members, but was positively correlated among LR family members. P300 amplitude from visual stimuli was positively correlated among both HR and LR family members. When taken in conjunction with previous findings, the present results suggest that P300 amplitude from auditory stimuli may not be as reliable as ERPs from visual stimuli for the assessment of alcoholism heritability. © 1999 Elsevier Science Inc. All rights reserved.

P300 Event-related brain potentials ERP Alcoholism Stimulus modality Heritability

P300 AND ALCOHOLISM

A variety of evidence suggests that predisposition for developing alcoholism is biologically mediated and perhaps inherited (6,53,54). In particular, children of alcoholic parents raised by nonalcoholic foster parents are at higher risk for developing alcoholism than are the biological children of nonalcoholic parents (5,11,18). Some electrophysiological findings support this distinction, in that boys who are high risk (HR) for alcoholism were reported to have more high-frequency alpha activity in their electroencephalograms (EEG) compared to boys who are low risk (LR) for alcoholism (14,17), although this result has not been obtained consistently [cf. (7,8,39,40)]. Event-related potential (ERP) differences also have been reported between abstinent alcoholics and control subjects for sensory-evoked potentials and cognitive ERP components (28,29,42–44). Because the P300 ERP component has been found to be smaller in long-term abstinent alcoholics [for excellent reviews, see (2,41)], the application of ERP procedures to assess individuals at risk for the development of alcoholism by virtue of their biological familial background was a natural progression of previous work [e.g., (3,15,30)].

Use of electrophysiological measures to assess alcoholism heritability is based upon the assumption that such variables are genetically transmitted. Indeed, EEG spectral characteristics have been found to be highly similar for identical twins (20,56), with strong associations also obtained for biologically related family members (13,59,60). Similarly, the P300 component of the ERP has been found to be strikingly similar for pairs of monozygotic compared to dizygotic twins or unrelated controls (21,25,35,47,57,58). Moreover, evidence for P300 heritability has been obtained from biologically related family members who produced significant interfamily member correlations for P300 measures from both auditory and visual stimulus paradigms (12). Thus, if aberrant P300 ERPs are detected in individuals at biological risk for alcoholism, this ERP component may serve as a diagnostic marker that could reflect the likelihood of alcoholism's heritability and, therefore, shed light on its etiology.

P300 FAMILY HISTORY STUDIES

Polich and colleagues (37) employed meta-analysis procedures to review in a comprehensive and quantitative fashion studies that used P300 amplitudes to compare HR sons of alcoholics and LR control subjects. Despite the general impression that P300 components are different between these two subject categories, analysis of 30 separate studies indicated that only 12 or 40% of the studies actually report a statistically

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reliable difference between HR and LR subjects for P300 amplitude. More important, however, was that analysis of "moderator variables" across studies found that the largest effect sizes for P300 amplitude differences between HR and LR subject groups originated from tasks that employed visual stimuli. In addition, the complexity of the tasks was categorized as easy or difficult, based on a review of the methods descriptions in each study. The typical oddball paradigm was designated as "easy," whereas task situations requiring considerably more attention to produce adequate performance [e.g., the heads task used in (3)] were designated as "difficult." The studies that used difficult visual paradigms had the largest overall mean effect size in this set, and its 95% confidence interval excluded zero, such that HR had significantly smaller P300 amplitudes than LR males when difficult visual stimulus tasks were employed. Although the mean effect sizes for the easy auditory and visual conditions and for the difficult auditory conditions were positive, their confidence intervals included zero and, therefore, indicated that these studies did not yield statistically effect size differences between the subject groups [cf. (19,34,36,46)]. Indeed, almost all of the auditory stimulus studies demonstrated no reliable effect sizes when compared across reports [Fig. 2 in (37)], and no published study to date has employed auditory and visual tasks that vary in difficulty to compare the same samples of HR and LR subjects. In sum, the strongest HR vs. LR group differences for P300 amplitude across ERP studies stems from paradigms that employed visual stimuli and relatively difficult task situations.

P300, MODALITY, AND HERITABILITY

Given this outcome, it is important to establish whether any differences exist between HR and LR individuals for the heritability of modality-specific ERPs. As noted above, it is known that P300 measures from both auditory and visual stimuli are heritable among family members free of alcoholism (12). However, whether this is also the case for HR individuals needs to be determined so that any possible P300 ERP effects between individuals in each family history group can be attributed to fundamental population differences rather than a breakdown in genetic transmission. Toward this end, the present study was conducted to assess whether stimulus modality contributes to the differential heritability of P300 for HR compared to LR individuals. Families whose background indicated no alcoholism was prevalent (LR) were compared with families in whom alcoholism was prevalent, as defined by the father's diagnosis of alcoholism (HR). Each family group consisted of the biological father, mother, and several offspring. P300 ERPs were elicited with both auditory and visual stimuli using comparable procedures.

METHOD

Subjects

This study was part of the Collaborative Study on the Genetics of Alcoholism (COGA), a large ongoing evaluation of alcohol-dependent men and women, their first-degree and extended-family relatives and comparison subjects, and their families. Although six participating centers contribute to the COGA enterprise, only subjects from the San Diego site were employed in the present study. As described in detail previously (55), all initial probands were selected from among consecutive inpatients, outpatients, and persons receiving aftercare who were admitted to substance-use disorder programs. All probands met the criteria for both alcohol dependence as defined by DSM-III-R and definite alcoholism (16). Potential subjects were not excluded because of any additional Axis I or Axis II DSM-III-R disorder. However, they were excluded if they did not speak English, had a history of recent and repeated intravenous drug use, and if their nuclear family contained too few relatives available for evaluation. Subjects were also excluded if they were physically unable to perform the tasks, were taking psychotropic medication, or cognitively impaired (e.g., previous head trauma, neurologic disorders, etc.).

Comparison families were selected by a variety of methods, including individuals entering care for disorders other than alcoholism, driver's license records, and advertising. The probands and comparison subjects gave written informed consent for a structured face-to-face interview and agreed to potential interviews with all appropriate family members. The evaluation began with the Semi-Structured Assessment for the Genetics of Alcoholism, which was administered by trained personnel. This procedure permits the systematic evaluation across multiple diagnostic systems, including 17 axis I disorders, antisocial personality disorder, and psychotic symptoms relevant to DSM-III-R, and has a high level of interrater and intercenter reliability, as described in detail elsewhere (4).

A total of 13 HR and 13 LR families were obtained, each of which met the following additional criteria: 1) the father and mother were the biological progenitors of at least two offspring 12 years of age or older; 2) all subjects in each family were free from neurologic, psychiatric, or medical disorders other than alcoholism for the HR father; 3) each family member produced acceptable ERPs in all conditions. Table 1 summarizes the age characteristics of the two family groups.

TABLE 1

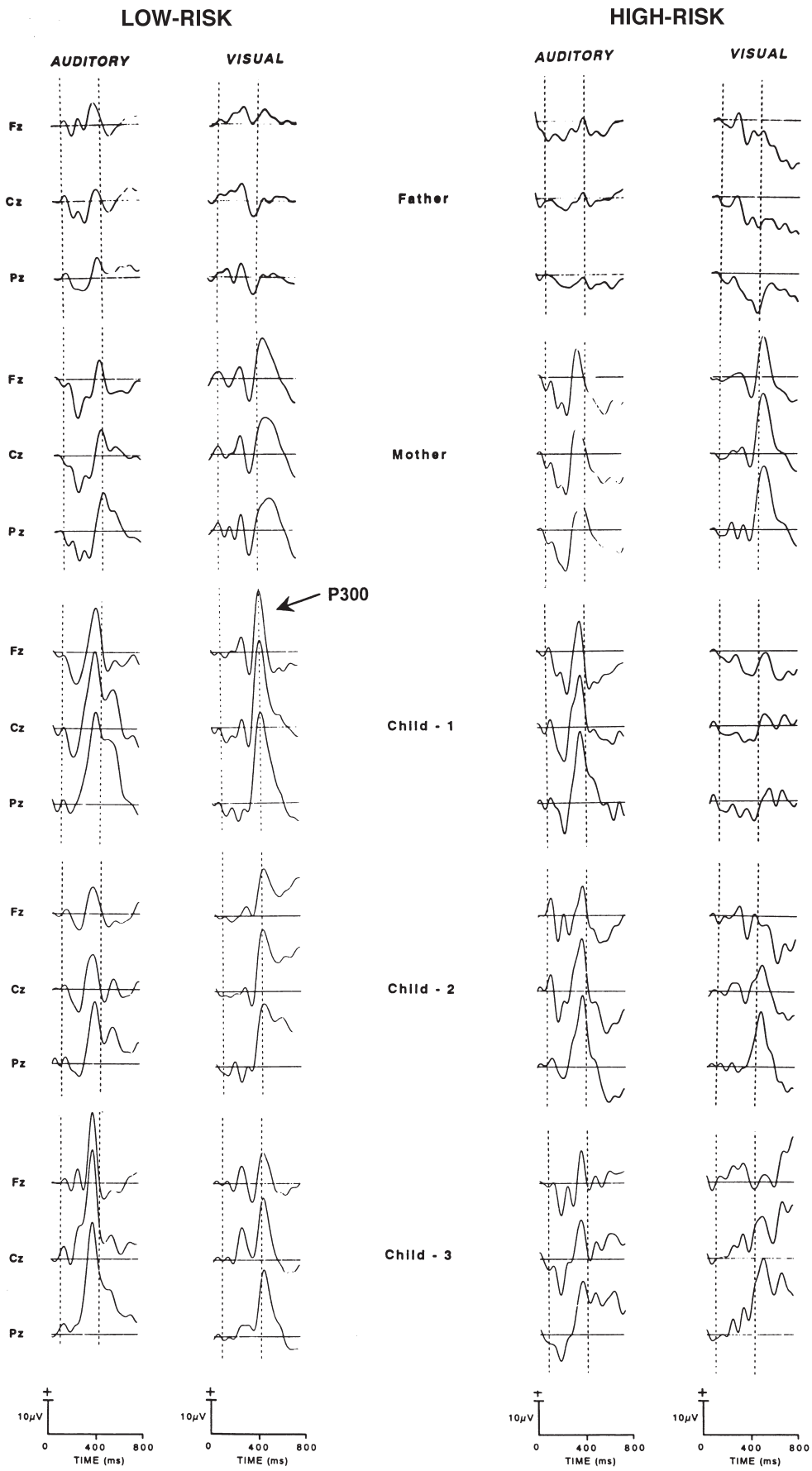
MEAN, STANDARD DEVIATION (SD), AND RANGE OF AGES (YEARS) FOR SUBJECTS IN EACH FAMILY RISK GROUP

	Low-Risk Families (n = 13)			High-Risk Families (n = 13)		
	Mean	SD	Range	Mean	SD	Range
Father	51.3	7.1	37–60	50.8	12.6	32–63
Mother	49.3	8.5	37–68	49.9	10.7	36–65
Child-1	26.0	7.5	18–39	29.6	7.7	17–41
Child-2	25.5	7.5	16–37	27.2	7.9	12–37
Child-3	20.8	7.2	14–34	21.5	8.5	12–33

Recording Conditions

EEG activity was recorded monopolarly using an electrode-cap at 19 electrode sites [Fp1/2, F3/4, C3/4, P3/4, F7/8,

FIG. 1. Event-related potentials (ERPs) from auditory and visual tasks from a single low-risk (LR) and high-risk (HR) family. The P300 component is the large, positive-going waveform that is indicated by the label and arrow. Note that ERPs from both modalities for the LR children are a blend of the father and mother, whereas ERPs from the auditory modality for the HR children are quite different from the father and mother.


LOW-RISK
HIGH-RISK
AUDITORY
VISUAL
AUDITORY
VISUAL
Fz
Cz
Pz
Father
Mother
Child - 1
Child - 2
Child - 3
P300
10μV
0
400
800
TIME (ms)

T7/8, P7/8, O1/2, Fz, Cz, Pz; see (52)] referred to the nose, with a forehead ground and impedances maintained at 5 kOhms or less. Electro-ocular (EOG) activity was assessed with two channels referred to the nose. One electrode was placed at the outer canthus of the left eye to measure vertical eye movement, and the second electrode was located on the forehead to monitor horizontal eye movement. The filter bandpass was 0.02–50 Hz (3 dB down, 6 dB octave/slope). The EEG was digitized at 3.9 ms/point for 1500 ms, with a 187-ms prestimulus baseline. ERP data were averaged on line with the same computer as used to control the stimulus presentation and artifact rejection. Trials on which the EEG or EOG exceeded ± 73.3 μV were rejected automatically.

Procedure and Stimuli

Auditory ERPs were elicted with 400 auditory binaurally presented stimuli consisting of 600 Hz (standard) and 1600 Hz (target) tones presented at 60 dB SPL (10 ms r/f, 60 ms plateau). Auditory stimuli were generated by the computer and presented via ear plugs, with intensity levels calibrated using an external reference. The interstimulus interval was 1.5 s, and the target tone occurred randomly with a probability of 0.25. Subjects were instructed to press a key pad with their forefinger whenever a target tone was detected, and to refrain from responding to the standard. Visual ERPs were elicted with 280 stimuli presented on a computer monitor for a duration of 60 ms, with an interstimulus interval of 1.6 s. The target stimulus was a white "X" (4×4 cm, $2.9° \times 2.9°$), novel stimuli (5×5 cm, $3.6° \times 3.6°$) consisted of nonrepeating colored geometric shapes (e.g., blue hexagons, red pentagons, green triangles, etc.) arranged in variegated patterns, and the standard stimulus was a white square (4×4 cm, $2.9° \times 2.9°$). Novel stimuli were purposefully designed so that each occurrence was a unique perceptual event in order to elicit a robust nontarget P300 component. All stimuli were viewed from a distance of 110 cm, with low-level diffuse ambient lighting provided by a ceiling fixture. The target and novel stimuli each occurred with a probability of 0.125; the standard stimuli occurred with a probability of 0.75. Subjects were instructed to focus on a dot located in the center of the monitor, to press a key pad with their forefinger whenever a target stimulus was detected, and to refrain from responding when the novel or standard stimuli occurred. Response hand was counterbalanced across subjects. Stimulus presentation was concluded when 25 target and 75 standard artifact-free stimuli were acquired for the auditory stimuli, and when 25 target, 25 novel, and 150 standard artifact-free trials were acquired for the visual stimuli. This procedure permitted the acquisition of more than a sufficient number of artifact-free trials for the ERP average, even though all of the stimuli in a given paradigm may not have been presented [cf. (10,32)]. Both paradigms have demonstrated interlaboratory consistency (1,9), and the small differences in target probability between the tasks (31), or the presence of the infrequent nontarget stimuli in the visual paradigm, do not affect P300 amplitude from the target stimulus (22,23). Each modality was presented in a separate task condition, with the auditory paradigm presented first as required of the COGA ERP protocol.

RESULTS

Task performance across all subjects was virtually perfect, with very few errors made for either the auditory or visual paradigms (<0.5% misperceived target stimuli). Mean response times for the target stimuli were shorter for the auditory (385 ms) compared to visual (440 ms) stimulus task $p < 0.05$), but did not differ between risk groups ($p < 0.35$). These outcomes stemmed from the relatively simple nature of the paradigms requirements, and indicate that all subjects performed the tasks with high accuracy and alacrity.

P300 Measurement and Analyses

Because the primary purpose of the present study was to ascertain the heritability for the P300 component, only waveforms for the target stimuli were assessed. For both the auditory and visual modalities, component measurement was done visually and individually for each subject to identify amplitudes and latencies of the P300 components at each electrode site by locating the most positive component after the P100–N100–P200–N200 complex within the latency window of 350–600 ms. Amplitude was measured relative to the mean of the prestimulus baseline, with latency defined as the time point of maximum positive or negative amplitude within the latency window.

The amplitudes of the P300 component from each electrode site were then obtained from each family member and the product-moment correlation coefficient (Pearson's r) computed between the each pair of biologically related individuals (e.g., father vs. child-1, mother vs. child-1, child-1 vs. child-2 etc.) across the $n = 13$ families within each family risk group. Although the mothers in both families were not alcoholic, the correlations between them and their offspring were included to control for the mother's contribution to the child's ERP measures across both family types. This approach was deemed the most conservative way to account for the mother's genetic influence, because it would serve to strengthen the HR compared to LR intrafamilial associations and because the mother would not pass on any heritable risk ERP deficits in both types of families. The mean correlations for each family group and stimulus modality condition were computed and then transformed by employing the Fisher-z procedure (r') to normalize the distribution's members, and was used as the dependent variable for all statistical analyses. Component latency measures and overall group effects will not be presented, because latency is unrelated to the issue of alcoholism, and the present study was not designed to obtain strong group effects [cf. (37)].

Correlational Analyses

Representative waveforms of the members from a single LR and HR family for each stimulus modality are presented in Fig. 1. The LR data illustrate how the P300 component for the children is a blend of those for the biological father and mother [cf. Fig. 1 in (12)]. However, the auditory ERPs from the HR subjects demonstrate little resemblance to both parents, although the visual stimulus ERPs appear to be a mixture of the father and mother. Thus, LR families produced similar P300s for both auditory and visual stimuli, whereas HR families produced similar P300s only for visual stimuli.

Figure 2 presents the mean correlation coefficients for P300 amplitude taken across families for the auditory and visual stimulus conditions for electrode position (LL = left lateral, LM = left medial, M = central–midline, RM = right medial, RL = right lateral) at each coronal location (frontal = F7–F3–Fz–F4–F8; central = T7–C3–Cz–C4–T8; parietal = P7–P3–Pz–P4–P8). These figures illustrate the primary 15 electrode positions that were used in all statistical analyses

(Fp1/2 and O1/2 were omitted to maintain electrode anterior-to-posterior and lateral symmetry in the analyses). A four-factor (2 family risk groups × 2 stimulus modalities × 3 frontal-to-posterior location × 5 lateral electrode site) analyses of variance was performed on the mean familial correlation coefficients from the amplitude data obtained from each of the $n = 13$ families. Greenhouse-Geisser corrections were applied to the *df* for all repeated measures factors with more than two levels to defray the effects of sphericity assumption violations. Only the corrected probability values are reported here. The results described below are based on the patterns in Fig. 2.

The primary result of interest is best illustrated in the parietal portion of Fig. 2. For the LR subjects, the mean P300 amplitude intrafamily correlations from the auditory ($r = 0.260$) and visual ($r = 0.291$) stimulus conditions were relatively strong and highly similar across modalities. However, for the HR subjects, the mean P300 amplitude intrafamily correlations were essentially zero for the auditory ($r = -0.094$), and

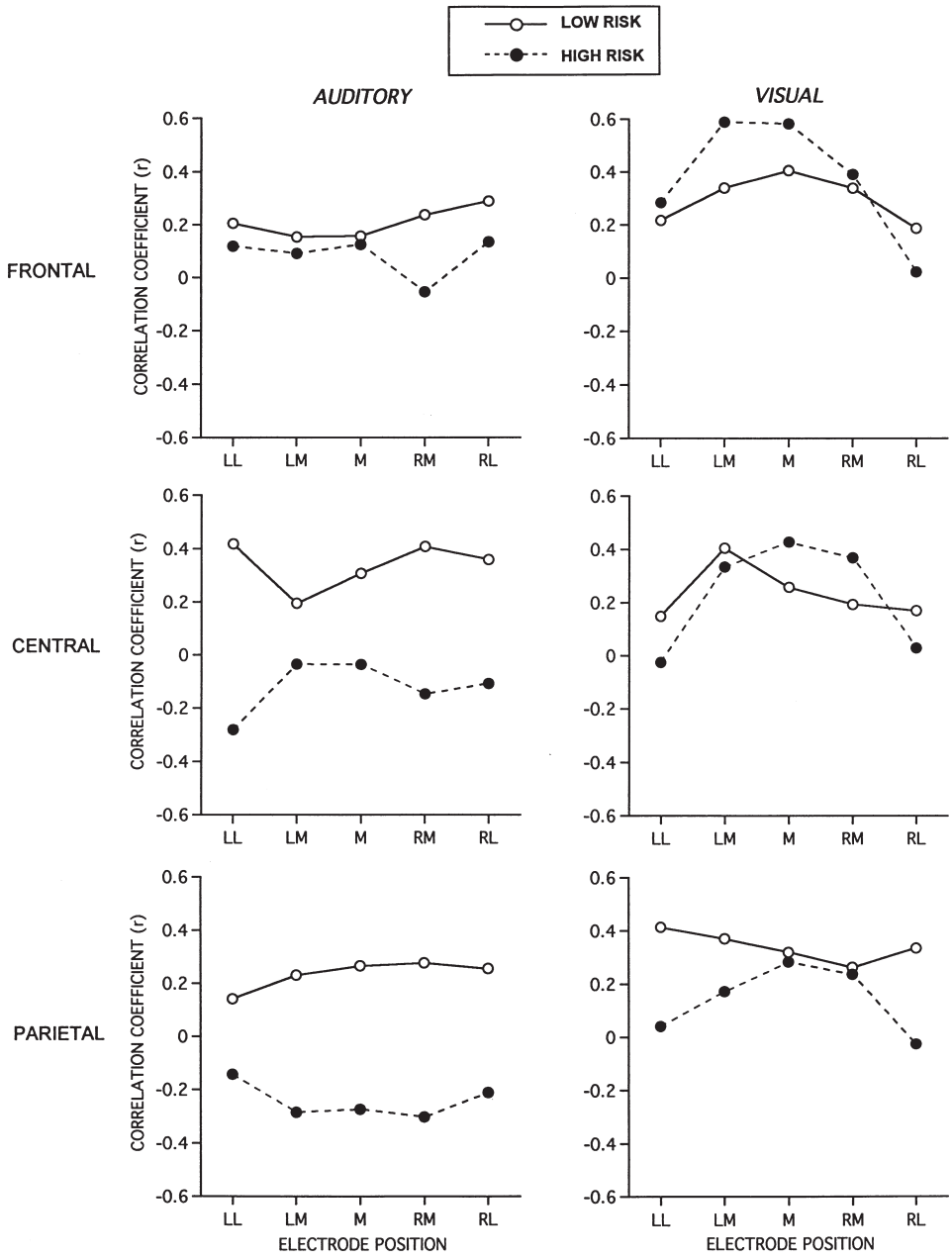


FIG. 2. Mean P300 amplitude intrafamily correlation coefficients computed across the low-risk (LR) and high-risk (HR) families from the frontal, central, and parietal coronal electrode arrays for the auditory and visual modalities (LL = left lateral, LM = left medial, M = medial, RM = right medial, RL = right lateral). Note that the LR and HR families differ in the degree of intrafamily correlation for P300 components from the auditory stimulus condition, whereas both families demonstrate very similar correlational patterns for the visual stimulus condition.

strong only for the visual modality ($r = 0.247$). These differences were substantiated by a significant family risk group × modality interaction, $F(1, 24) = 5.3$, $p < 0.03$, which contributed to the weaker correlations obtained for auditory ($r = 0.083$) compared to visual ($r = 0.269$) stimulus conditions, $F(1, 24) = 7.8$, $p < 0.02$.

Intrafamily correlations were strongest overall at the frontal compared to central and parietal electrode sites, $F(2, 48) = 3.8$, $p < 0.05$. However, as suggested by the family risk group differences illustrated in Fig. 2, the frontal-to-parietal change in correlational strength was evident only for the HR subjects to produce a significant family risk group × frontal-to-posterior interaction, $F(2, 48) = 6.3$, $p < 0.01$. Finally, correlational size varied systematically between modalities for the overall lateral electrode placements to yield a significant interaction, $F(4, 96) = 5.2$, $p < 0.01$. Taken together, these results indicate that P300 amplitude is strongly correlated for both auditory and visual modalities with LR families but correlated only for visual stimulus ERPs within the HR families.

DISCUSSION

Comparison of HR and LR families using both stimulus modalities to elicit the P300 ERP found that the intrafamily correlations for auditory stimuli were much lower among HR family members for auditory compared to visual stimuli, whereas the same correlational analysis of LR family members found relatively high associations for both stimulus modalities as previously reported for EEG and ERPs from normal families (12,13). Hence, the present results indicate that P300 amplitude from auditory stimuli may not be inherited in the same fashion as that from visual stimuli in families with children at high risk for inheriting alcoholism. The outcome agrees with the findings from a meta-analysis of ERP LR/HR risk studies, because the strongest and most reliable differences for P300 amplitude data male offspring of alcoholic fathers were obtained using visual stimuli and relatively difficult information processing task situations (37). Thus, the P300 component from visual processing tasks may be useful for assessing alcoholism heritability, but auditory tasks do not produce as reliable results.

Stimulus Modality and Heritability

The reasons underlying this modality/heritability HR/LR family difference are not clear. However, the rationale for assessing modality effects stems from the theoretical implication that more difficult tasks require increase in attentional resources relative to easier tasks to produce P300 peak amplitudes that are smaller than relatively easy tasks (24,33,61). Subject groups who vary in their information processing capabilities for specific stimulus configurations may, therefore, be affected by task difficulty variation, and demonstrate stronger differential group P300 effects as processing requirements are increased in conjunction with stimulus modality differences. In this context, it is noteworthy that the HR/LR intrafamilial correlation differences for P300 amplitude were observed to be greatest at the central-parietal electrode sites—locations where P300 is largest. Thus, if the attentional resource allocation capabilities are different for these two subject groups, it is likely that such effects would be observed most strongly at exactly these electrode sites [cf. (27,38,45)].

This interpretation implies that information processing tasks that engage and/or manipulate resource allocation requirements might be useful in maximizing ERP differences between HR and LR for alcoholism subject populations. Indeed, neuropsychological studies indicate that visuospatial deficits in male HR subjects originate from their comparative inability to attend to and discern the critical features of a visual display (26,48–51). These findings suggest that paradigms that require visuospatial processing operations yield the strongest HR vs. LR differences—an outcome consistent with the theoretical assumption that P300 reflects between-group attentional processing capability. Auditory stimulus ERP paradigms used in HR/LR comparisons to date have not engaged comparable spatial processing requirements. Moreover, when auditory task difficulty has been manipulated, reliable family risk differences are sometimes not obtained [cf. (19,34,36,46)]. Thus, it may be that processing task requirements are the critical dimension underlying the present study's observed modality differences for heritability of the P300 ERP.

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