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Temporal Recovery of Auditory Evoked Potentials in Individuals at Risk for Alcoholism

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COHEN, H. L., B. PORJESZ AND H. BEGLEITER. *Temporal recovery of auditory evoked potentials in individuals at risk for alcoholism.* ALCOHOL **13**(4) 333–339, 1996.—The present investigation examined auditory evoked potential (AEP) recovery functions in both high-risk (HR, $N = 23$, mean = 22.3) and low-risk (LR, N = 27, mean = 23.0) males. A series of binaural auditory stimuli, with randomly interposed interstimulus intervals (ISIs) of 0.5, 1.0, and 10.0 s, were used to elicit the N1 and P2 components of the AEP. Scalp potentials were recorded from the 19 electrodes comprising the 10/20 International System. For purposes of statistical analysis, five electrode groups were created: frontal (F), central (C), parietal (P), occipital (O), and temporal (T). The results of within-group MANOVA demonstrated that in both LR and HR individuals, increases in the ISI produced significant N1 and P2 amplitude increases without significant latency differences. These amplitude increases occurred primarily in the F and C regions. However, the results of between-group MANOVA indicated that there were no differences in the recovery functions of the two risk groups. Our results indicate that in both LR and HR individuals, recovery functions are responsive to changes in increasing ISI. However, they did not effectively discriminate between risk groups. It is speculated that risk group differences may be apparent with the use of an ethanol challenge.

Low risk High risk Alcoholism Recovery function Auditory evoked potential

INVESTIGATIONS into the electrophysiological differences between individuals at high risk for the development of alcoholism (high risk = HR) and matched, low-risk controls (low risk = LR) have frequently proceeded by comparing either baseline EEG activity (9,14–16,18,26,35,48), the latency, morphology, and topography of event related potentials (ERPs) elicited by a variety of information processing paradigms [for reviews see (34,39)], or changes in each of these responses following an ethanol challenge (10,14–16,26,27,35,38,39,48).

The majority of ERP studies have evaluated the P300 component, and generally agree that P300 amplitude is reduced in HR individuals compared to LR individuals without an alcohol challenge [for reviews see (34,39)]. Evidence from several recent studies (11,32,34) suggests that family history and the influence of genetic factors may contribute to the P300 amplitude reduction. Moreover, it has been hypothesized that this deficit antecedes the development of alcoholism and is a highly heritable trait that may be considered as a biologic phenotypic marker for its development (4,32).

In contrast to the numerous investigations comparing risk group differences in P300, only a limited number of studies have examined differences in ERP components such as N100 (N1). For example, one study (1) used an auditory selective attention paradigm and found that HR individuals had significantly larger N1 amplitudes in the attention condition. Whereas one interpretation of this result was that HR individuals were more attentive than were LR individuals, a more likely interpretation was that the responses were those of an atypical HR population that had not yet manifested any alcohol-related problems, and was possibly beyond the age of risk to develop alcoholism. In another study (31), the authors employed a bimodal paradigm (auditory and visual stimuli) in both abstinent alcoholics and controls, and the first-degree, family history-positive (FHP) relatives of each. Although the amplitude of the visual N1 component was reduced in the alcoholics, the amplitude of the auditory N1 component was reduced in the FHP individuals. Lastly, a study (47) that recorded auditory ERPs in both alcoholics and their family

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members documented that N1 amplitude was decreased in both the affected and unaffected relatives in the alcoholic families.

To establish whether there are risk group differences in ERPs, a wide variety of information processing paradigms have been utilized. Interestingly, there is one classical experimental design that has almost never been applied to the study of alcohol-related phenomena, that is, the generation of the recovery function (cycle) (28) or excitability cycle (6,13,20). The recovery function is a measure of CNS excitability obtained by assessing changes in ERP morphology as a function of the interstimulus interval (ISI) between paired adequate or electrical stimuli. The morphological changes evidenced reflect both the absolute and relative refractory states of the neurons comprising the activated population (5,8,13,20).

Because of their utility in evaluating CNS excitability, recovery functions have been used to assess: 1) normal reflexes [e.g., corneal, blink (12), and Hoffman (21)] and their age-related changes (21); 2) the sequelae of pathologic conditions known to alter CNS excitability, such as Parkinson's disease (25), Huntington's chorea (7), and multiple sclerosis (17,29); and 3) the CNS effects of various pharmacological agents (46) [e.g., cardiazol (5), a CNS stimulant that shortens the recovery function of visual evoked potentials, and lithium carbonate (19) and haloperidol (30), which both decrease the recovery function of somatosensory evoked potentials (SSEP)].

Previous investigations that utilized recovery functions have generally demonstrated that the amplitudes of the N1 and P2 components of auditory, visual, and somatosensory ERPs increase as a function of increasing ISI up to about 10 s (8,13,20,22,40). Although it had once been posited that the N1 and P2 components comprised a single response, one study (40) demonstrated that the N1 and P2 components of auditory evoked potentials (AEPs) should be considered separately. The study incorporated three randomly presented ISIs, multiple stimulus intensities, and both an attention and inattention condition. It documented that P2 amplitude, compared to N1 amplitude, was more sensitive to both increasing ISI and stimulus intensity. Further, whereas P2 was largest at Cz, N1 was largest at Fz and Cz. However, in contrast to their differences, both N1 and P2 were similarly affected by attentional mechanisms; directing attention to the stimuli significantly increased N1 and P2 latencies without altering component amplitudes. The latter findings contrast with those obtained from Nd (negative difference) studies (23,24,33) wherein Nd amplitude, which is related to the allocation of attentional resources, increases as a function of increasing attention.

As indicated earlier, few studies have examined recovery functions in either normal individuals or alcoholics, following alcohol ingestion, or have compared differences in recovery functions between LR and HR individuals. In one study (2), somatosensory evoked potential (SSEP) recovery functions were used to evaluate the hypothesis that in humans, withdrawal from alcohol is characterized by CNS hyperexcitability. The subjects were males with a 10-year history of alcoholism. Initially, they were required to remain abstinent for the 3 weeks prior to testing. Then, SSEP recovery functions were obtained over both a 3-week control period and a 3-week period of experimental alcoholization and withdrawal. The order of the control and experimental sessions was randomized across subjects. The results demonstrated that during alcoholization, SSEP recovery functions increased following increasing alcohol ingestion, although peak excitability occurred on the first day following withdrawal. There was additional evidence that withdrawal following as little as 1 day of drinking was characterized by increased excitability in SS cortex. The study concluded that as evidenced by recovery functions, periods of partial and total withdrawal following heavy alcoholization are characterized by cortical hyperexcitability. In another study (36), abstinent alcoholics were found to manifest lower recovery functions and reduced N1 and P2 amplitudes, perhaps reflecting hypoexcitability during prolonged abstinence. Lastly, auditory recovery functions were compared in boys at high risk for alcoholism (mean = 13.1 years) and matched, low-risk (mean = 12.9 years) controls (3). In both groups, N1 and P2 amplitudes, but not latencies, increased as a function of increasing interstimulus interval (0.5, 1.0, and 5.0 s). In contrast, none of the risk group comparisons produced any statistically significant differences, although in the LR group, the larger P2 amplitude at Cz approached significance ($P < 0.06$).

The present investigation examined differences in auditory evoked potential (AEP) recovery functions between carefully defined populations of adult HR and LR males, in contrast to the previous investigation from this laboratory (3) that examined adolescent males.

Measures of the N1 and P2 components of the AEP were determined in response to a series of binaurally presented auditory stimuli with three randomly interposed interstimulus intervals. To determine topographic differences in the responses, recordings were made from 19 electrodes arranged in five regional groupings.

METHOD

Subjects

The subjects were 50 males ranging from 18 to 30 years of age. The LR ($N = 27$, mean = 23.0, SD = 2.99) subjects were recruited either through newspaper ads or via notices posted in the Health Science Center. In contrast, the HR ($N = 23$, mean = 22.3, SD = 3.21) individuals had a father undergoing treatment for alcohol dependency (DSM III-R criteria). The initial screening procedure required each prospective subject to fill out a questionnaire detailing alcohol and drug use and the medical and psychiatric histories for both himself and his first- and second-degree relatives. Participation in the study depended upon the responses to the questionnaire. The requirement for an individual's inclusion in the HR group was that his father be classified as alcohol dependent (DSM III-R) and a high incidence of alcoholism in the first- and second-degree relatives of these individuals. Inclusion in the LR group required that none of the candidate's first- or second-degree relatives be diagnosed as alcoholic. Exclusion criteria for either group included an alcoholic mother, major medical problems, a current requirement for medication that affected the CNS, or a history of psychiatric problems and/or drug abuse in himself and his first- and second-degree relatives. Upon meeting the aforementioned criteria, each subject was invited to the laboratory wherein he underwent a detailed psychiatric interview (HB and BP) that focused on questions of drug and alcohol use, and the medical and psychiatric history for himself and his first- and second-degree relatives. Table 1 summarizes the subject characteristics for each group. The two groups were the same age and had similar educational backgrounds but differed significantly in two measures of drinking history: the number of drinking days per month (LR = 4.01, HR = 8.13; $P < 0.04$) and the Drink Index (the product of the number of drinking days per month by the number of drinks per occasion) (LR = 11.6, HR = 45.0; $P < 0.02$).

TABLE 1
SUBJECT CHARACTERISTICS FOR THE LOW RISK AND HIGH RISK GROUPS

	Low Risk ($N = 27$)	High Risk ($N = 23$)
Age (years)	Mean 23.0, SD 2.99 Range 19–30	Mean 23.3, SD 3.21 Range 18–29
Education (years)	Mean 16.2, SD 2.79 Range 12–20	Mean 13.8, SD 1.65 Range 12–17
Days per month*	Mean 4.01, SD 3.35 Range 0–14	Mean 8.13, SD 8.8 Range 0–30
Drinks per occasion	Mean 2.61, SD 1.58 Range 0–7	Mean 3.74, SD 3.15 Range 0–10
Drink index†	Mean 11.6, SD 12.2 Range 0–42	Mean 45.0, SD 63.2 Range 0–260
Number of alcoholic relatives	Individuals in this group could not have any first- or second-degree alcoholic relatives	Mean 2.74, SD 1.89 Range 1–8

*$p < 0.04$.
†$p < 0.02$.

Experimental Design

The subject was seated comfortably in a dimly lighted, temperature-regulated, sound-attenuated chamber (Industrial Acoustics Corp.). Each subject wore a fitted electrode cap (Electro-Cap International, Inc.) using the entire 10/20 International System. The nasion served as reference and the forehead as ground. Both horizontal and vertical eye movements were monitored.

While the subject focused on a fixation target presented on a computer monitor, he received a series of brief auditory clicks [70 dB, 1500 Hz, 40 ms duration (5 ms rise and fall time, 30 ms plateau)], generated by a Grass click–tone control module and presented binaurally through TDH headphones.

ERP activity was amplified 20 k with a Grass Neuro Data Acquisition System. Prestimulus activity (80 ms) and poststimulus activity (400 ms) were sampled continuously at a sampling rate of 250 data points per second (bandpass 0.1–100 Hz). The data were then digitally filtered with a 30-Hz low pass filter. Artifact rejection (EMG, EOG, and saturation artifact) was performed online.

The series of binaural auditory stimuli was presented with randomly interposed interstimulus intervals (ISIs) of 0.5, 1.0, and 10.0 s. Data acquisition terminated when 30 artifact-free responses were acquired for each ISI.

Data Analysis

For each subject in the LR and HR groups, an automatic peak detection program determined both the latency and amplitude of the N1 and P2 components of the AEP at each electrode. The peaks were then manually edited. N1 was defined as the largest negativity between 60 and 160 ms, whereas P2 was defined as the maximum positivity between 160 and 290 ms. Measurements of both N1 and P2 amplitudes and latencies were made for the 0.5-, 1.0-, and 10.0-s ISIs. To evaluate topographic response characteristics, the 19 electrodes of the 10/20 International System were divided into five regional groups: frontal (F), FP1, FP2, F7, F8, F3, F4, Fz; central (C), C3, C4, Cz; parietal (P), P3, P4, Pz; occipital (O), O1, O2; and temporal (T), T7, T8, P7, P8 (see Fig. 1).

For both the LR and HR groups, within-group multivariate analyses of variance (MANOVA, SAS v 6.09) were used to determine the effects of the 0.5-, 1.0-, and 10.0-s ISIs on N1 and P2 amplitudes and latencies. Separate analyses were performed for the F, C, P, O, and T regions. Next, between-group MANOVAs were used to compare response differences between the LR and HR groups. Again, separate comparisons were made for each of the five regional electrode groups.

RESULTS

The results demonstrated that in both the LR and HR groups, N1 and P2 amplitudes increased as the ISI increased from 0.5 to 10.0 s and from 1.0 to 10.0 s; no increases were observed with the ISI increase from 0.5 to 1.0 s. In contrast to the amplitude increases, no changes in either N1 or P2 latency were observed with increasing ISI. Moreover, in each group, the amplitude increases were generally localized to the frontal (electrodes FP1, FP2, F7, F8, F3, F4, Fz) and central (electrodes C3, C4 and Cz) regions (see Fig. 1). Within the frontal

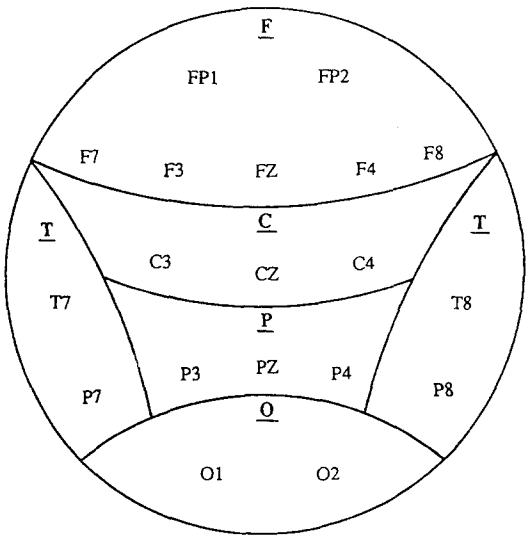

FIG. 1. The recording electrode ($N = 19$) montage and the regional groupings (F = frontal, C = central, P = parietal, O = occipital, and T = temporal) used in the statistical analyses.

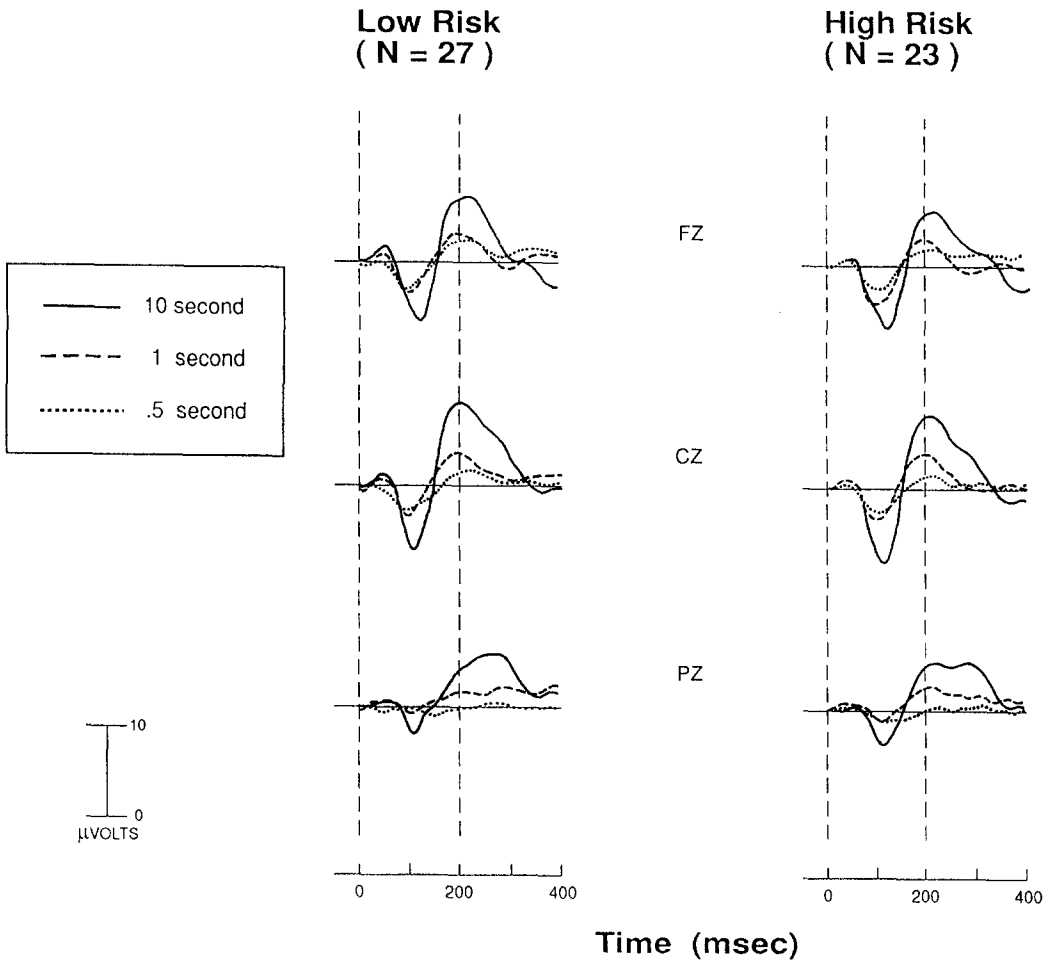

FIG. 2. Grand mean waveforms for N1 and P2 responses at electrodes Fz, Cz, and Pz, for both low risk (LR) and high risk (HR) individuals at 0.5 (dotted line), 1.0 (broken), and 10.0 second (solid line) interstimulus intervals.

region, increased N1 and P2 amplitudes were most evident at electrodes F3, F4, and Fz. Little change was manifested in the more anterior (FP1 and FP2) and lateral (F7 and F8) electrodes.

Before comparing recovery functions between the two risk groups, it was necessary to consider that the HR group consumed significantly more alcohol than did the LR group (see Table 1). As such, the finding of a significant risk group difference might simply reflect the difference in drinking histories. To test this hypothesis, individuals in the HR group were assigned to either a "light drinker" or "heavy drinker" group based upon their Drink Index scores. The "light drinkers" ($N = 14$) had a mean index of 5.07, SD = 4.65, whereas the "heavy drinkers" ($N = 9$) had a mean index of 107.2, SD = 61.8. A between-groups MANOVA was then used to compare the responses of the light and heavy drinkers. The results demonstrated no statistically significant differences between the responses of the two groups. Subsequently, a between-groups MANOVA was used to compare the recovery functions of the LR and HR individuals. The results demonstrated that there were no significant risk group differences in either N1 or P2 amplitudes or latencies in any region.

Figure 2 displays grand mean waveforms for both the LR and HR groups, at 0.5-, 1.0-, and 10.0-s ISIs at the Fz, Cz, and Pz electrodes, and indicates the similarities in the responses of the two groups. Table 2 presents mean amplitudes and latencies, as well as SD, for both the N1 and P2 components.

DISCUSSION

The present investigation demonstrates that in both LR and HR individuals, the auditory recovery function is responsive to increases in ISI. Consequently, as the ISI increased, there were significant increases in both N1 and P2 amplitudes. However, the increases in component amplitudes were not accompanied by latency changes. It was also observed that in both groups, the increases in N1 and P2 amplitudes occurred primarily in the frontal and central regions. Lastly, in contrast to the significant within-group differences in recovery functions was the lack of a significant between-groups effect, indicating that auditory recovery functions did not discriminate effectively between LR and HR individuals.

Our initial observation was that in both LR and HR individuals, N1 and P2 amplitudes increased as the ISI increased from 0.5 to 10.0 s, and from 1.0 to 10.0 s. These findings agree with those of most previous investigations demonstrating that the amplitude of the N1 and P2 components of auditory, visual, and somatosensory ERPs increase as a function of increasing ISI up to about 10 s (8,13,20,22,40). With increases in ISI, it becomes more probable that the second of the paired

TABLE 2

MEAN N1 AND P2 AMPLITUDES AND LATENCIES AT Fz, Cz, AND Pz FOR EACH INTERSTIMULUS INTERVAL (ISI), IN BOTH THE LOW-RISK AND HIGH-RISK GROUPS

	Low Risk				High Risk		
	ISI (s)	AMPL (μV)	LAT (ms)		ISI (s)	AMPL (μV)	LAT (ms)
			Fz				
N1	0.5	−2.87 (2.85)	103.5 (23.6)	N1	0.5	−2.59 (2.79)	105.6 (18.9)
	1.0	−3.42 (3.01)	100.4 (16.2)		1.0	−4.31 (2.69)	101.9 (15.6)
	10.0	−7.01 (4.74)	119.3 (16.6)		10.0	−7.73 (4.43)	118.9 (18.5)
P2	0.5	2.95 (2.46)	199.6 (27.7)	P2	0.5	2.23 (3.97)	201.5 (26.2)
	1.0	3.97 (3.08)	193.5 (28.2)		1.0	3.42 (5.28)	189.1 (18.9)
	10.0	7.49 (5.11)	204.8 (29.0)		10.0	6.71 (6.91)	205.0 (19.2)
			Cz				
N1	0.5	−2.57 (2.48)	112.4 (27.7)	N1	0.5	−2.65 (3.30)	105.4 (23.5)
	1.0	−2.89 (2.66)	99.6 (16.8)		1.0	−3.59 (2.79)	104.8 (14.5)
	10.0	−7.60 (4.95)	112.6 (15.5)		10.0	−8.66 (6.00)	116.3 (13.0)
P2	0.5	2.31 (2.87)	205.0 (27.9)	P2	0.5	1.76 (3.15)	200.4 (26.4)
	1.0	4.77 (3.40)	192.0 (29.2)		1.0	4.31 (4.98)	191.3 (21.2)
	10.0	10.13 (5.61)	199.6 (28.4)		10.0	9.00 (7.61)	200.0 (18.8)
			Pz				
N1	0.5	−0.36 (2.13)	125.2 (29.1)	N1	0.5	−1.57 (2.98)	110.6 (22.0)
	1.0	−0.74 (2.01)	114.7 (22.5)		1.0	−1.34 (2.91)	102.8 (19.6)
	10.0	−3.14 (3.73)	113.7 (20.4)		10.0	−4.33 (4.24)	116.9 (16.9)
P2	0.5	0.34 (2.51)	207.9 (30.2)	P2	0.5	0.32 (3.21)	198.7 (28.1)
	1.0	2.31 (2.91)	189.6 (34.1)		1.0	2.97 (3.84)	190.0 (25.2)
	10.0	5.73 (5.54)	202.0 (37.5)		10.0	5.82 (6.01)	203.3 (26.3)

stimuli, S2, will be presented when the neurons activated by S1 are no longer hyperpolarized, as when they are in either their absolute or relative refractory periods. Instead, membrane potentials have returned to resting levels. The lack of a significant amplitude increase in N1 or P2 as the ISI increased from 0.5 to 1.0 s reflects the fact that when S2 was presented, many of these neurons were still hyperpolarized as a consequence of their activation by S1.

Another observation of this study relates to the topographic distribution of N1 and P2 responses. Although most previous investigations have examined recovery functions at a limited number of recording sites (e.g., midline electrodes Fz, Cz, Pz, and Oz) (2,3,40), the present investigation utilized recordings from 19 electrodes in five regional groups. Our results demonstrated that the topographic distribution of responses in both the LR and HR groups was quite similar. That is, the N1 and P2 amplitude increases occurred primarily in the frontal and central regions. These findings generally agree with those of a study (40) that reported that P2 was largest at Cz, whereas N1 was largest at Fz and Cz. However, in contrast to the amplitude increases, no latency differences were observed in any region.

Lastly, we documented that the AEP recovery functions did not effectively discriminate between LR and HR individuals. In this context it is important to note that with the exception of P300 [for reviews see (34,39)] and the limited findings regarding N1 (1,31,47), there are few baseline electrophysiological responses that reliably discriminate between LR and HR individuals. For example, if one combines the results of most LR-HR EEG studies, thereby encompassing the slow alpha to fast beta frequency range, multiple scalp regions, and several EEG measures (9,14,15,26,35,48), the results document no risk group differences. However, in contrast, two studies (16,18) reported that at baseline, HR individuals have more fast activity (> 18 Hz) (18) and more fast alpha power (9–12 Hz) (16) than LR individuals.

Interestingly, several of the studies that reported no risk group differences at baseline observed significant differences following an ethanol challenge. Among the measures that yielded differences were: slow and fast alpha energy and mean alpha frequency (35), both slow and fast alpha energy (48), the coefficient of variation in both slow and fast alpha (14), beta activity (15), and both acute sensitization and acute tolerance in slow alpha (10).

Similarly, there are several ERP studies in which risk group differences were manifested only after an ethanol challenge. For example, one investigation (45) reported that whereas ethanol ingestion increased P300 latencies in both LR and HR individuals, the HR group demonstrated a faster return to normal values. The same observations were documented in a second study (38); whereas P300 latencies in the HR group returned to normal values at 90 min post ethanol ingestion, those in the LR group did not return to normal values within the 130-min duration of the experiment. Additionally, whereas both groups displayed an ethanol-induced decrease in N1 amplitude, the return to normal amplitudes again occurred more rapidly in the HR group (90 min vs. > 130 min).

Furthermore, the reports of risk group differences being manifested mainly after an ethanol challenge have not been restricted solely to EEG and ERP studies, but have been observed in measures of plasma hormones (43,44), muscle tension (41), and cognitive and psychomotor performance (42). These findings, along with the results of the aforementioned electrophysiological studies, suggest that whereas the underly-

ing physiology of both LR and HR individuals is generally quite similar, the two groups are differentially sensitive to the effects of ethanol.

Lastly, whereas the use of recovery functions did not yield significant risk group differences, our results should not negate the use of similar paradigms in additional studies. First, because of the aforementioned evidence that, at baseline, only studies of P300 have reliably demonstrated risk group differences, and second, the limited number of studies that have utilized recovery functions mean there is little evidence against which any results can be compared. For example, both the present investigation and the previous study from this laboratory (3) utilized auditory stimuli; recovery function studies in either the visual or somatosensory modalities have yet to be performed. Moreover, there appear to be no studies comparing risk group differences in recovery functions in any modality, following an ethanol challenge. Such a study is presently underway in this laboratory.

In summary, the present investigation demonstrates that in both LR and HR individuals, recovery functions are sensitive to increases in interstimulus interval; both N1 and P2 amplitude increases were obtained as a function of increasing ISI. Moreover, the amplitude increases were observed primarily in frontal and central scalp regions. However, in contrast to significant within-group differences in recovery functions, between-group differences were not obtained.

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