Psychology of Addictive Behaviors
2007, Vol. 21, No. 4, 555–563

0893-164X/07/$12.00 DOI: 10.1037/0893-164X.21.4.555

Effects of Alcohol Sensitivity on P3 Event-Related Potential Reactivity to Alcohol Cues

Bruce D. Bartholow, Erika A. Henry, and Sarah A. Lust
University of Missouri–Columbia

Although alcoholics and individuals at risk for alcoholism often show smaller amplitude of the P3 event-related brain potential (ERP), recent data (K. Namkoong, E. Lee, C. H. Lee, B. O. Lee, & S. K. An, 2004) indicate that alcohol-related cues elicit larger P3 amplitude in alcoholics than in controls. Little is known concerning the ERP profiles or alcohol cue reactivity of social drinkers at risk for alcoholism due to low sensitivity to alcohol's effects. Participants differing in alcohol sensitivity viewed images of alcoholic and nonalcoholic beverages while ERPs were recorded and provided information about their alcohol use patterns at baseline and 4 months later. Compared to high-sensitivity participants, those low in sensitivity showed larger P3s to alcohol cues, even when recent alcohol use was statistically controlled for. Moreover, the P3 elicited by alcohol cues predicted alcohol use at follow-up, a finding supporting the idea that P3 amplitude reflects the motivational significance of substance-related cues. These findings point to risk status, not consumption history, as an important predictor of cue reactivity effects.

Keywords: cue reactivity, alcohol sensitivity, P3, event-related potentials, appetitive motivation

Electrophysiological methods, particularly event-related brain potentials (ERPs), have been used extensively to study the correlates and consequences of alcohol use (see Porjesz et al., 2005). The P3 (or P300) component of the ERP has proven particularly significant in the study of alcoholism, with numerous studies showing that reduced P3 amplitude is associated with risk for alcoholism (e.g., Begleiter, Porjesz, Bihari, & Kissin, 1984; Polich, Pollock, & Bloom, 1994; Porjesz et al., 2005) and related disorders of disinhibition (e.g., Bauer & Hesselbrock, 1999; Iacono, Carlson, Malone, & McGue, 2002; Iacono, Malone, & McGue, 2003; Patrick et al., 2006). These findings have led some to conclude that small P3 is an endophenotype for alcoholism risk (Carlson, Iacono, & McGue, 2004; Hesselbrock, Begleiter, Porjesz, O'Connor, & Bauer, 2001; Porjesz et al., 1998).

Although small P3s elicited by simple visual shapes or auditory tones have been associated with increased risk for alcoholism, a few studies suggest that alcoholics show larger P3s than nonalcoholics in response to more complex alcohol-related stimuli (e.g., Genkina & Shostakovich, 1983; Hermann et al., 2000). In one recent study, Namkoong, Lee, Lee, Lee, & An (2004) presented alcoholics and nonalcoholic control participants (social drinkers) with alcoholic and nonalcoholic beverage pictures in a visual oddball task. These authors found that whereas the P3 elicited by the alcoholic and nonalcoholic beverage pictures was equivalent among control participants, the alcohol-dependent participants showed a larger P3 to the alcoholic beverage cues than to the nonalcoholic beverage cues. Moreover, P3 amplitude elicited by alcoholic beverage cues was significantly correlated with subjective ratings of alcohol craving measured following cue exposure.

Such findings are consistent with the idea that P3 amplitude increases as a function of the motivational relevance or emotional salience of a stimulus (e.g., Ito, Larsen, Smith, & Cacioppo, 1998; Johnston, Miller, & Burleson, 1986; P. Lang, Bradley, & Cuthbert, 1997; Schupp et al., 2000). Specifically, some theorists (e.g., P. Lang et al., 1997; see also Cacioppo, Gardner, & Berntson, 1999) have argued that images that arouse emotional responses elicit larger P3 (and other physiological reactions) because they activate basic motivational systems (e.g., to approach or avoid). A dominant theoretical perspective on cue reactivity holds that exposure to substance-related cues elicits an appetitive/approach motivational state in substance users (see Carter & Tiffany, 1999; Stewart, DeWitt, & Eikelboom, 1984; see also A. Lang, Yegiyan, & Bradley, 2006). Thus, it is likely that P3 amplitude elicited by drug cues reflects the degree of activation of the appetitive motivational system.

A number of questions remain concerning the functional significance of P3 responses to substance-related cues, however. In particular, it is as yet unknown whether substance users who are at elevated risk for the development of abuse or dependence, but who have yet to develop a substance use disorder, would also show heightened P3 responses to relevant substance cues. This issue is critically important for understanding whether the enhanced P3 elicited by alcohol cues is a precursor to or a consequence of alcohol abuse. For example, it could be that alcohol-related stimuli take on particular motivational relevance only after the presence of clinically meaningful levels of alcohol abuse or the development of dependence (e.g., see Drummond, 2000; Kaplan, Meyer, & Stroebel, 1983). In other words, a drug-related stimulus could take on heightened motivational rele-

Bruce D. Bartholow, Erika A. Henry, and Sarah A. Lust, Department of Psychological Sciences, University of Missouri–Columbia.

Portions of this research were presented at the 2006 annual meeting of the Research Society on Alcoholism, Baltimore, MD. This research was supported by a Richard Wallace Research Incentive Grant from the University of Missouri Office of the Provost and by Grant T32 AA13526 from the National Institute on Alcohol Abuse and Alcoholism. We wish to thank Denis M. McCarthy for his helpful comments on a previous version of this article.

Correspondence concerning this article should be addressed to Bruce D. Bartholow, University of Missouri–Columbia, Department of Psychological Sciences, 210 McAlester Hall, Columbia, MO 65211. E-mail: BartholowB@missouri.edu

vance as the result of a classically conditioned response associating the drug with its positive effects (e.g., Monti et al., 1987). If so, alcohol-related cues should only be expected to elicit heightened P3 responses among individuals in a heightened state of drug motivation (e.g., abstinent alcoholics; see Namkoong et al., 2004). In contrast, neural responses to alcohol-related cues may serve as a marker of alcoholism risk such that some nondependent drinkers will react particularly strongly to them, perhaps due to genetic predisposition or other factors linking P3 with alcoholism risk. If so, social drinkers at elevated risk for alcoholism might show a pattern similar to that seen among alcoholics, which would suggest that heightened neural reactivity to alcohol cues predates dependence on the drug.

In fact, some forms of cue reactivity, such as changes in self-reported affect, motivation and urges to drink, and changes in autonomic responses have been observed in social drinkers (e.g., Collins & Brandon, 2002; Curtin, Barnett, Colby, Rohsenow, & Monti, 2005; Kambouropoulos & Staiger, 2004; Walitzer & Sher, 1990), indicating that the general phenomenon is not restricted to clinical alcoholics. The P3 has been used as a measure of cue reactivity in social drinkers in only one previous study. Hermann, Weijers, Wiesbeck, Böning, and Fallgater (2001) reported that the P3 elicited by alcohol versus neutral beverage cues was larger in heavier social drinkers compared to lighter social drinkers. However, this effect was only apparent at the midline frontal (Fz) electrode location and did not emerge at the midline parietal electrode (Pz), where P3 commonly is largest (see Fabiani, Gratton, & Federmeier, 2007). Thus, it is unclear how this finding should be interpreted in the context of other P3 cue reactivity studies (e.g., Hermann et al., 2000; Namkoong et al., 2004). Moreover, the extent to which the P3 elicited by alcohol cues predicts future drinking has never been determined.

The majority of extant research linking P3 amplitude with risk for alcohol-related problems has focused on individuals at risk due to their family history of alcoholism (e.g., see Porjesz et al., 2005). An additional known risk factor for the development of alcoholism is low sensitivity (i.e., a low level of response) to the acute effects of alcohol. Research has shown, for example, that individuals who show less motor impairment and report feeling less intoxicated after an alcohol challenge are more likely to develop an alcohol use disorder 10 or 20 years later (Schuckit, 1994; Schuckit, Smith, Anderson, & Brown, 2004); that individuals who report needing larger amounts of alcohol to experience its effects as young people are more likely to develop problematic levels of drinking later in life (e.g., Heath et al., 1999; Rodriguez, Wilson, & Nagoshi, 1993; Schuckit & Smith, 2000); and that retrospective self-reports of the intensity of alcohol's effects correlate significantly with subjective feelings of intoxication following alcohol consumption (e.g., Schuckit, Tipp, Smith, Wiesbeck, & Kalmijn, 1997).

No studies to date have tested whether cue reactivity effects differ as a function of alcohol sensitivity levels. Examining this issue can serve at least two complementary purposes for this literature. First, linking differential sensitivity with cue-reactivity effects could provide an additional form of construct validation for low sensitivity as a risk factor for alcohol abuse in a way that differs from the primarily descriptive work linking a low level of response with an increased probability of alcoholism later in life (e.g., Schuckit, 1994; Schuckit et al., 2004). Second, linking P3 measures of cue reactivity with differential sensitivity provides a way to characterize this risk factor in terms of cognitive and motivational processes whose neurochemical bases and links to decision making and other behaviors have been studied extensively (e.g., see Nieuwenhuis, Aston-Jones, & Cohen, 2005).

To date, very little research has tested how differences in alcohol sensitivity correspond to patterns of ERP response, and the extant evidence is inconsistent. In one study, Schuckit, Smith, Kalmijn, and Raimo (2000) found no evidence of a correlation between low level of response to alcohol and P3 amplitude. In a more recent study, however, Bartholow et al. (2003) found that individuals who self-reported relatively low sensitivity to alcohol's effects showed markedly smaller P3 amplitude during a cognitive control task compared to individuals who reported higher sensitivity. Given the very different conclusions reached in these two studies, it is clear that more research is needed to understand potential links between low alcohol sensitivity and P3 responses.

More generally, it is important to understand whether individual risk factors for drug abuse, such as sensitivity levels or family history, offer unique prediction of substance cue reactivity beyond what can be attributed to specific substance involvement. As recently noted by Stritzke, Breiner, Curtin, and Lang (2004), it is often assumed that differential responses to drug-related cues result from differences in idiosyncratic consumption histories (see Carter & Tiffany, 1999). This assumption is based on the notion that cue reactivity reflects conditioned associations between a drug and its consequences (e.g., Stewart et al., 1984). It follows, then, that individual differences in cue reactivity should largely attenuate when aspects of consumption history are statistically controlled. However, recent evidence suggests that, at least under some conditions, controlling for recent consumption does not eliminate cue exposure effects. For example, Palfai (2001) reported that temptation to drink in response to the presence of visual and olfactory alcohol cues predicted stronger urges to drink and increased alcohol consumption even when recent alcohol use was controlled for. Given that alcohol sensitivity and consumption generally are moderately correlated (see Bartholow et al., 2003; Schuckit et al., 2005), in the present study we controlled for recent consumption when testing whether individual differences in alcohol sensitivity would predict differential ERP responses to alcohol cues.

The present research had three main purposes: (1) to test whether social drinkers who are at risk for the development of alcohol problems due to low alcohol sensitivity show heightened P3 responses to alcohol cues; (2) to test whether this effect is robust to controlling for recent alcohol use; and (3) to test whether the P3 elicited by alcohol cues predicts future drinking. A secondary purpose of this study was to test whether self-reported alcohol sensitivity predicts unique variance in future drinking when we controlled for baseline alcohol use.

Method

Participants

Forty-six undergraduates (22 women, 24 men) at a large public university reporting no history of head injury, neurological disease, or other major medical or psychiatric disorders participated in exchange for credit toward a course requirement. Participants were recruited on the basis of self-reported subjective sensitivity to the effects of alcohol, measured as part of a large Web-based survey completed several weeks prior to the experiment (details on this measure are given in the next section). Specifically, 22 participants whose sensitivity scores fell within the upper 25% of all responses were selected for the high-sensitivity (HS) group (11 women, 11 men), and 24 participants whose responses fell within

the lower 25% of responses were selected for the low-sensitivity (LS) group (11 women, 13 men). Roughly equivalent numbers of participants in both groups reported some history of alcohol-related problems in first- or second-degree relatives (54% vs. 50% in LS and HS groups, respectively), $\chi^2(45) = 0.08$, $p = .77$ (see next section for details). Table 1 shows drinking-related data as a function of sensitivity group.

Self-Report Measures

Alcohol sensitivity. Sensitivity to the effects of alcohol was measured with a 16-item self-report questionnaire developed by O'Neill, Sher, and Bartholow (2002). The first 10 items relate to experiences typically associated with the ascending limb of the blood alcohol curve, such as feeling "buzzed," becoming more talkative, becoming more flirtatious, and so forth (i.e., positive, stimulating effects). For each item, respondents indicate whether they have ever experienced the given effect of drinking alcohol (e.g., "Do you ever become more talkative after drinking alcohol?"), and if they have, they then estimate the minimum number of standard drinks they could consume before feeling that effect. The remaining 6 items are related to experiences typically associated with the descending limb of the blood alcohol curve, such as feeling nauseated, vomiting, or passing out (i.e., negative, sedating effects). These items are structured like the first 10, except that participants estimate the maximum number of standard drinks they could consume without experiencing the effect. An overall sensitivity score is calculated by averaging the number of drinks a participant reports for all effects. However, for each participant, a given item is included in the score only if he or she reports having experienced that effect from drinking alcohol. O'Neill et al. (2002) reported excellent internal consistency for this scale ($\alpha = .97$). In the current sample, $\alpha = .95$. (For details concerning the factor structure of the measure and its relationship to similar constructs, see Bartholow et al., 2003.)

Although conceptually similar to the self-rating of the effects of alcohol (SRE) measure (e.g., Schuckit et al., 1997), the alcohol sensitivity measure used here is distinct in a number of respects. First, whereas the SRE measures a respondent's alcohol-related experiences in each of four conditions, the measure we used assesses 16 different effects. Second, the alcohol sensitivity scale assesses both ascending and descending limits on sensitivity. Finally, whereas the SRE requires respondents to report experiences within three time frames (first five drinking occasions, most recent 3 months of drinking, period of heaviest drinking), the current measure does not require respondents to differentiate their sensitivity according to particular periods of time that they might have limited ability to remember and compare.

Table 1
Means of Alcohol Use Variables as a Function of Sensitivity Group

Variable	Sensitivity group	
	LS	HS
Alc quantity (baseline)	9.96 (4.28)	3.44 (2.06)
Alc frequency (baseline)	2.51 (1.48)	0.81 (0.60)
Times drunk (follow-up)	1.54 (1.24)	0.32 (0.47)
Binge episodes (follow-up)	2.43 (1.63)	0.47 (0.85)

Note. All between-groups mean differences are significant ($p < .01$). Standard deviations are given in parentheses. LS = low alcohol sensitivity group; HS = high alcohol sensitivity group; Alc quantity = typical number of drinks consumed on a given drinking occasion in the past 3 months (scored as per week); Alc frequency = number of drinking occasions in the past 3 months (scored as per week); Times drunk = typical number of times drunk in past month (scored as per week); Binge episodes = number of times consumed five or more drinks on one occasion (scored as per week). Times drunk and binge episodes were not assessed at baseline, and thus, follow-up data are presented here for those variables.

Alcohol problems. Participants completed a number of self-report items meant to assess indicators of alcohol abuse or dependence. These items were embedded in a larger set of items inquiring about various negative consequences of drinking. The dependence-related items were "Have you ever felt that you had a problem with alcohol?" "Have you ever felt physically or psychologically dependent on alcohol?" "Have you ever had 'the shakes' after stopping or cutting down on drinking?" and "Have you ever been told by a doctor or other health professional that you have a drinking problem?" Response options included *never*, *yes, but not in the past year*, *in the past year but not the past 3 months*, and *yes, in the past 3 months*, scored as 0, 0.3, 0.5, and 1, respectively. In the current sample, only 7 individuals ($n = 5$ LS, $n = 2$ HS) responded with anything other than *never* to any of these items.

Family history of alcoholism. We assessed familial risk for alcoholism using Mann, Sobell, Sobell, and Pavin's (1985) family tree questionnaire. This measure instructs respondents to list each of their first- and second-degree relatives and to indicate for each one whether he or she is (or was) a nondrinker, a nonproblem drinker, or experienced problems from drinking. For current purposes, participants were considered to be at increased familial risk if any first- or second-degree relatives were identified as having an alcohol problem ($n = 24$) and at low familial risk if no relatives were identified as such ($n = 22$).

Typical alcohol use at baseline. Participants were asked to report their alcohol use within the past 3 months and past year by estimating the number of drinks they typically consume on a given drinking occasion and the number of drinking occasions they typically experience per week. We created a composite alcohol quantity/frequency variable (baseline ALC) by multiplying the number of typical weekly drinking occasions by the estimated number of drinks typically consumed per occasion.

Alcohol use at follow-up. Approximately 4 months following their laboratory session, all participants were asked to complete a brief follow-up questionnaire assessing their alcohol involvement since the experiment. Participants reported the number of times in the past 3 months (scored on a per week basis) that they had some kind of beverage containing alcohol using a 9-point scale (response options ranged from 1 = *I did not drink in the past 3 months* to 9 = *twice a day or more*), and they reported the number of drinks they usually had on any one occasion using an 11-point scale (response options ranged from 1 = *I did not drink in the past 3 months* to 11 = *16 or more drinks*). We determined a Time 2 quantity/frequency score (Time 2 ALC) by multiplying responses on these two items. We determined recent heavy drinking (Time 2 HEAVY) by averaging responses to items inquiring about the number of times an individual was high or light-headed from alcohol, the number of times an individual was drunk, and the number of times 5 or more drinks were consumed at a single sitting (i.e., binge drinking episodes), all within the past month.

Picture Viewing Task

A visual oddball task was used to present alcohol and nonalcohol beverage cues amid neutral context pictures. The neutral context images were taken from the International Affective Picture System (P. J. Lang, Bradley, & Cuthbert, 2001) and included such things as a chess board, an electrical outlet, and a towel lying on a table.[1] These images together had a mean valence rating of 5.02 and a mean arousal rating of 2.83 (both on 1–9 scales) according to the normative data reported by P. J. Lang et al. (2001). The nonalcohol beverage images included a water fountain, several types of juice in bottles (apple, mango, orange), a bottle of sports drink, a bottle of Snapple, a glass of milk, a glass of lemonade, a six-pack of juice in cans, and a bottle of water. The alcohol beverage images included a keg, two different beer bottles, a shot glass, a tequila bottle, a gin bottle, a rum bottle, a glass of wine, a beer bottle cap, and a pitcher of beer. None of the beverage images contained people in order to avoid contamination of reactivity to beverage cues with reactions to the emotional responses of people paired with those beverages (Stritzke et al., 2004). All images were presented in the center of a computer monitor. At a viewing distance of 90 cm, the images subtended a visual angle of 13.7 degrees.

Participants saw a total of 450 images, of which 30 were alcohol beverages and 30 were nonalcohol beverages (i.e., each of the 10 alcohol and 10 nonalcohol targets was repeated three times). Trials were structured so that presentation of successive beverage pictures was separated by at least 3 neutral images. Each trial consisted of a 100 ms baseline, an image presented for 900 ms, and an interstimulus interval that varied randomly between 900 ms and 1,500 ms. Participants were instructed to categorize beverage pictures as either alcoholic or nonalcoholic by pressing one of two buttons with their right or left index fingers (counterbalanced across participants) as quickly as possible and to do nothing whenever any other kind of image was presented. Participants were given a brief break after the first half of the trials before completing the remaining trials.

Electrophysiological Recording

The electroencephalogram (EEG) was recorded from 28 tin electrodes fixed in a stretch-lycra cap and placed according to an expanded version of the standard 10–20 system (American Encephalographic Society, 1991). All electrodes were referenced online to the right mastoid; an average mastoid reference was calculated offline. Vertical and horizontal electrooculographic activity was recorded with additional electrodes placed above and below the left eye and approximately 2 cm outside the outer canthus of each eye, respectively. A ground electrode was seated along the frontal midline (FPz). All signals were amplified with a Neuroscan Synamps amplifier (Compumedics, El Paso, TX) and filtered online at .05 to 30 Hz at a sampling rate of 1000 Hz. Impedance was kept below 5KΩ. Ocular artifacts (i.e., blinks) were corrected from the EEG signal offline with a regression-based procedure (Semlitsch, Anderer, Schuster, & Presslich, 1986). Trials containing voltage deflections of +/− 75 microvolts (μV) were discarded before the averaging of waveforms. After artifact elimination, EEG data were averaged offline according to participant, electrode, and stimulus conditions and low-pass filtered at 12 Hz. Only correct response trials were used in average waveforms. The smallest number of trials from which an average ERP was derived was 24. We quantified the P3 by examining each participant's average waveforms for each stimulus type and averaging over the 300 ms following stimulus onset when the component was largest (generally 400–700 ms). Thus, the measurement window was tailored for each participant.

Procedure

Approximately 6 weeks prior to the experiment, participants completed a subset of the alcohol sensitivity items noted previously as part of a Web-based mass testing session. Participants whose scores fell within the upper and lower quartiles for this subset were contacted by the experimenters and asked to take part in a lab experiment on picture viewing and brain activity. Participants were not informed of the basis for their selection (i.e., their alcohol sensitivity scores). Upon arrival at the lab, participants signed a consent form and then completed the questionnaire measures described previously. Next, participants were moved to the electrophysiological recording room where an experimenter attached the recording electrodes. Once electrodes were placed and tested, the experimenter explained the picture viewing task and then left the room while participants completed it. After the task, participants were shown to a private restroom to clean up and were then debriefed about this phase of the study. As part of the debriefing procedure, participants were asked whether they would be willing to complete a brief follow-up questionnaire in a few months. Participants were then thanked and dismissed.

Approximately 4 months following their initial lab appointment, participants were contacted via e-mail and asked to complete the follow-up questionnaire described previously by logging on to a secure Web site. Thirty-four participants (74% of the initial sample) completed the follow-up questionnaire and were paid $10 each for doing so.

Results

Behavioral data (reaction times and accuracy for classifying beverage cues) are presented in Table 2. ERP waveforms measured at multiple electrodes for alcohol and nonalcohol cues as a function of sensitivity group are shown in Figure 1. Our primary prediction was that alcohol beverage cues would elicit larger P3 amplitude among LS participants compared to HS participants but that nonalcohol beverage cues would elicit similar P3 amplitudes among all participants (i.e., a Group $\times$ Cue interaction). We also tested for this interaction in the behavioral data. Finally, we conducted a regression analysis to test whether the effect of sensitivity group on the P3 elicited by alcohol cues would remain after we controlled for baseline ALC.

Data from the 4-month follow-up were analyzed with a series of regression equations in which drinking at Time 2 was predicted from measures taken at baseline. We had two primary interests regarding the follow-up data. First, we tested whether the P3 elicited by alcohol cues would predict later drinking when we controlled for P3 elicited by nonalcohol cues to test the specificity of alcohol cue reactivity (as distinct from P3 reactivity more

[1] The neutral images used in this study, as identified in the International Affective Picture System manual (Lang et al., 2001), were as follows: 2840, 2890, 6150, 7002, 7004, 7090, 7020, 7034, 7050, 2880, 7160, 7161, 7179, 7185, 7187, 7233, 7235, 7950, 2850, and 9070.

Table 2
Mean Reaction Times and Accuracy Rates for Classifying Beverage Cues as a Function of Sensitivity Group and Sex

	HS group		LS group	
Variable	Men	Women	Men	Women
Reaction time				
Alcohol cue	747 (141)	714 (122)	703 (81)	715 (79)
Nonalcohol cue	782 (132)	723 (69)	725 (56)	755 (85)
Accuracy				
Alcohol cue	.91 (.07)	.94 (.04)	.94 (.04)	.95 (.04)
Nonalcohol cue	.94 (.07)	.98 (.03)	.92 (.06)	.98 (.03)

Note. Reaction times are reported in milliseconds; accuracy is reported as proportion correct. Numbers in parentheses are standard deviations. HS = high alcohol sensitivity; LS = low alcohol sensitivity.

generally). Second, we tested whether alcohol sensitivity scores would predict later drinking when we controlled for baseline ALC as an additional way to determine whether sensitivity scores represent something beyond mere consumption history.

P3 Amplitude

Initial analyses of P3 amplitude across electrode locations indicated that P3 amplitude was largest at the Pz electrode site. Thus, we focused our initial analysis on data from the Pz electrode site using a 2 (group: HS, LS) × 2 (sex: women, men) × 2 (cue: alcohol, nonalcohol) mixed factorial analysis of variance (ANOVA) with repeated measures on the last factor. This analysis produced a significant main effect of cue, $F(1, 42) = 5.60$, $p < .05$, qualified by the predicted Group × Cue interaction, $F(1, 42) = 10.73$, $p < .01$. Planned comparisons showed that among those in the LS group, the P3 elicited by alcohol beverages ($M = 10.13$ μV, $SD = 6.08$ μV) was significantly larger than the P3 elicited by nonalcohol beverages ($M = 6.59$ μV, $SD = 5.20$ μV), $t(23) = 4.81$, $p < .001$, $d = 1.18$. Among those in the HS group, however, the P3s elicited by the alcohol ($M = 6.10$ μV, $SD = 3.78$ μV) and nonalcohol ($M = 6.67$ μV, $SD = 4.22$ μV) beverage cues did not differ significantly, $t(21) = -0.56$, $d = -.19$. Additional comparisons showed that the P3 elicited by alcohol cues was significantly larger among LS participants compared to HS participants, $F(1, 44) = 6.97$, $p < .01$, $d = .78$, but the P3 elicited by nonalcohol cues did not differ between the two groups, $F(1, 44) = 0.02$, $p = .65$, $d = .04$. The main effects of both group and sex were nonsignificant in this analysis, $Fs(1, 42) < 2.3$, $ps > .10$. Additional models showed that neither familial alcoholism risk nor indicators of alcohol dependence were significant covariates of these effects.

To test for potential differences in the distribution of these effects across the scalp, we conducted a second analysis of P3 amplitudes with data from every electrode shown in Figure 1 using a 2 (group) × 2 (sex) × 2 (cue) × 5 (coronal location: frontal, fronto-central, central, centro-parietal, parietal) × 3 (lateral location: left, midline right) mixed factorial ANOVA. This analysis produced a main effect of coronal location, $F(4, 168) = 133.5$, $p < .001$, indicating that the P3 became larger from more anterior to more posterior locations, and a Coronal × Lateral interaction, $F(8, 336) = 2.08$, $p < .05$, indicating that the P3 was larger at midline and right-hemisphere electrodes at more posterior locations but was generally no different across lateral electrodes at more frontal locations. A significant Group × Cue interaction, $F(1, 42) = 4.00$, $p = .05$, indicated that the pattern observed at Pz, described previously, also was apparent at the other electrodes. Finally, the analysis showed a significant Group × Cue × Lateral location interaction, $F(2, 84) = 3.72$, $p < .05$ (Greenhouse-Geisser adjusted), indicating that the Group × Cue interaction effect was somewhat larger at midline electrodes ($\eta^2 = .12$) than at left and right hemisphere electrodes ($\eta^2 = .07$ and $\eta^2 = .04$, respectively).

A step-wise regression model tested whether controlling for baseline ALC would eliminate the significant effect of sensitivity level on the P3 elicited by alcohol cues. Step 1 showed a significant positive association between baseline ALC and alcohol-cue P3 amplitude ($\beta = .33$, $p < .05$), supporting models linking cue reactivity with consumption history (see Carter & Tiffany, 1999). Adding sensitivity level to this model in Step 2 reduced the effect of baseline ALC to nonsignificance ($\beta = .08$, $p > .10$) and produced a significant effect of sensitivity ($\beta = .39$, $p < .05$, $R^2_{change} = .07$, $p < .05$).

Accuracy and Reaction Time

The behavioral data were analyzed with separate 2 (group) × 2 (sex) × 2 (cue) mixed factorial ANOVAs. The ANOVA on response times showed a main effect of cue, $F(1, 42) = 7.53$, $p < .01$, $d = .56$. Participants were faster in categorizing alcohol cues ($M = 719$ ms, $SD = 105$ ms) than nonalcohol cues ($M = 745$ ms, $SD = 89$ ms). The Group × Cue interaction was not significant, $F(1, 42) = 0.24$, $p = .48$; however, the difference in reaction times to alcohol versus nonalcohol cues was larger among LS participants ($M = 31$ ms), $d = .66$, $t(23) = 3.24$, $p < .01$, than among HS participants ($M = 22$ ms), $d = .27$, $t(21) = 1.27$, $p > .10$. The main effect of group was not significant ($F < 1$).

We examined accuracy data by first computing the arcsine of the square root of error rates for each participant and condition (to create a more normal distribution suitable for the ANOVA). The ANOVA on these data showed only two main effects: for sex, $F(1, 42) = 6.67$, $p < .05$, $d = .20$, indicating that women made fewer errors overall ($M = .04\%$, $SD = .03\%$) than did men ($M = .07\%$, $SD = .04\%$), and for cue type, $F(1, 42) = 8.49$, $p < .01$, $d = .24$, indicating that participants misclassified alcohol cues as nonalcohol beverages more often ($M = .07\%$, $SD = .05\%$) than they misclassified nonalcohol cues as alcohol beverages ($M = .04\%$, $SD = .06\%$). No other effects were significant in this analysis.[2]

Predicting Time 2 Drinking From Baseline Cue Reactivity

To test whether the P3 elicited by alcohol cues significantly predicted future alcohol use, we regressed Time 2 quantity/

[2] Although accuracy rates did not differ significantly as a joint function of cue type and sensitivity group, it remains possible that discrimination of alcohol from nonalcohol beverage cues differed between the groups. In signal detection theory, d' is considered a bias-free measure of the sensitivity of a system to differentiate a target from nontarget or noise stimuli (e.g., Wickens, 2001). Here, we computed d' for each participant as the standardized proportion of correctly identified alcohol cues (i.e., hits) minus the standardized proportion of misidentified nonalcohol cues (i.e., false alarms), or d' = z(hits) – z(false alarms). These d' values were analyzed with a 2 (sensitivity group) × 2 (sex) factorial ANOVA. Neither the main effect of sex ($F < 1$), nor the main effect of group, $F(1, 42) = 1.86$, $p = .18$, was significant, nor was their interaction ($F < 1$). Thus, it appears that alcohol sensitivity did not affect discrimination of alcohol from nonalcohol cues.

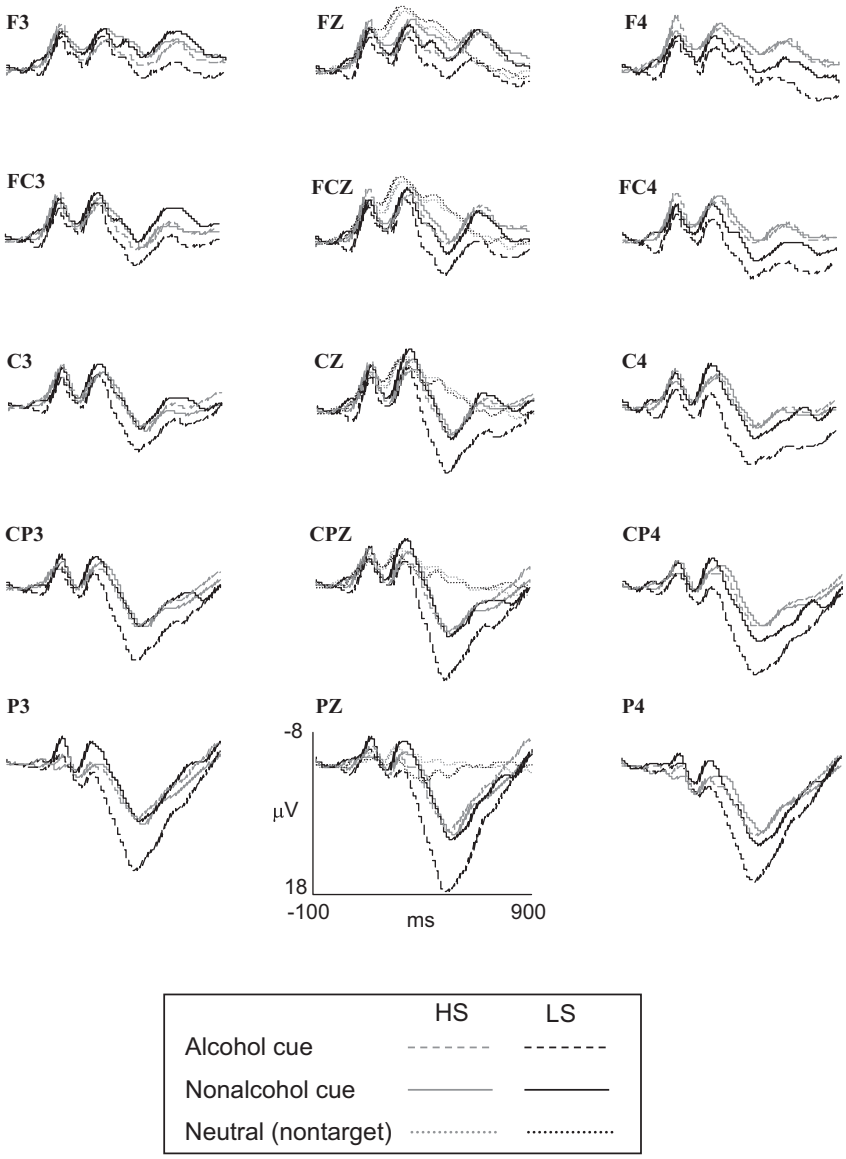

Figure 1. Event-related brain potential waveforms elicited by alcoholic and nonalcoholic beverage cues as a function of sensitivity group. Waveforms elicited by frequent neutral (nontarget) images are presented for midline locations to illustrate the oddball effect in these data. HS = high alcohol sensitivity group; LS = low alcohol sensitivity group. Stimulus onset occurred at 0 ms. Electrodes are arrayed from most anterior (top) to most posterior (bottom) and from left to right as they were positioned on the scalp.

frequency and heavy drinking data on the mean P3 amplitude elicited by alcohol cues while also controlling for sex and for the P3 elicited by nonalcohol cues using a step-wise regression procedure. Step 1 included the two control variables; the P3 to alcohol cues was added in Step 2. We structured the models this way in order to test whether inclusion of the P3 to alcohol cues in the second step contributed significant incremental variance to the model. Table 3 shows the results of this analysis. In both the quantity/frequency and heavy drinking models, inclusion of the alcohol-cue P3 in Step 2 significantly increased the variance accounted for by the predictors; indeed, alcohol-cue P3 was the only significant predictor in Step 2.

A secondary interest concerning the follow-up drinking data was whether sensitivity scores would account for unique variance in future alcohol use beyond that accounted for by baseline alcohol use. Step-wise regression models tested the unique effects of sensitivity and baseline ALC (with sex also controlled for) in predicting Time 2 ALC and Time 2 HEAVY. The results of these models are given in Table 4. Not surprisingly, baseline drinking was a strong predictor of future drinking. However, including sensitivity scores produced a significant increase in explained variance and a significant main effect in both models.

Discussion

The main finding from this study confirmed the hypothesis that LS individuals would show significantly larger P3 to alcohol cues than HS individuals, even after we controlled for the influence of

Table 3
Step-Wise Regression Predicting Time 2 Alcohol Use From P3 Elicited by Alcohol Cues, With Sex and P3 Elicited by Nonalcohol Cues Controlled for

	Time 2 ALC		Time 2 HEAVY	
Variable	Adj Δ R^2	β	Adj Δ R^2	β
Step 1	.09†		.02	
Sex		.40*		.30
Nonalc P3		.06		.04
Step 2	.09*		.10*	
Sex		.29		.20
Nonalc P3		−.04		−.06
Alc P3		.36*		.36*

Note. Nonalc P3 = P3 amplitude elicited by nonalcoholic beverage cues; Alc P3 = P3 amplitude elicited by alcoholic beverage cues; Time 2 ALC = quantity/frequency of alcohol use at follow-up; Time 2 HEAVY = heavy drinking composite score at follow-up; Adj Δ R^2 = change in adjusted R^2 by adding the second step.
† $p < .10$. * $p < .05$.

recent alcohol use, family history, and indicators of alcohol dependence. This finding has a number of implications. First, it shows that individuals at risk for alcoholism but who currently are not dependent show a pattern of P3 cue reactivity similar to that seen among alcoholics (e.g., Hermann et al., 2000; Namkoong et al., 2004). It has been unclear from these previous studies whether increased P3 to alcohol cues is a precursor to or a consequence of alcoholism. The data from the current study support the idea that P3 cue reactivity may precede the onset of alcohol-related problems. This finding is conceptually similar to research showing that the reduced P3 commonly reported among alcoholics in basic oddball tasks is more appropriately viewed as a marker for alcoholism risk rather than as an outcome of heavy alcohol abuse (e.g., see Begleiter et al., 1984; Polich et al., 1994; Porjesz et al., 2005).

Moreover, cue reactivity was enhanced in the current data not as a function of previous alcohol use but rather as a function of risk status, defined here in terms of self-reported alcohol sensitivity. This finding is inconsistent with the widely held idea that reactivity to substance cues is largely or entirely dependent upon an individual's degree of previous substance use (e.g., see Carter & Tiffany, 1999; Stritzke et al., 2004). As Carter and Tiffany (1999) have pointed out, such a conditioning interpretation assumes a more-or-less direct (i.e., one-to-one) relationship between the psychological processes underlying conditioning and the magnitude of physiological responses to drug cues. In other words, as drug use increases, so should the strength of the conditioned response and associated physiological reactivity. Such direct relationships are almost never observed in psychophysiological research (see Cacioppo & Tassinary, 1990). If cue reactivity effects in the current study depended upon use-related conditioning processes, then controlling for recent use should have eliminated or significantly reduced those effects. Thus, the current findings, along with other recent work showing that controlling for recent consumption does not eliminate behavioral cue reactivity effects (Palfai, 2001), suggest that some alternative mechanism(s), such as genetic or other factors that increase risk for substance abuse, should be considered in explaining cue reactivity effects.

The P3 data reported here also are consistent with other reports in which the effects of recent alcohol use on P3 amplitude have been examined among individuals with varying risk status (e.g., Polich & Bloom, 1987; Polich, Haier, Buchsbaum, & Bloom, 1988). For example, Pfefferbaum, Ford, White, and Mathalon (1991) found that P3 amplitude was reduced among alcoholic men with a positive family history of alcoholism, but that this effect was independent of participants' own lifetime consumption patterns. Similar findings were reported by Hill, Steinhauer, Zubin, and Baughman (1988), who examined ERP characteristics among alcoholic and nonalcoholic siblings and parents. These authors concluded that "the within-family differences observed reflect relative risk for developing alcoholism rather than experience with alcohol" (p. 545). Our findings extend this previous work by showing that P3 differences associated with a different marker of risk (low alcohol sensitivity) also are not driven by differences in recent alcohol consumption. However, it should be noted that the task used in the present study differed in one very important respect from those used in most other studies assessing effects of risk status on P3 amplitude in that the complex images used here likely engaged semantic processing mechanisms. Thus, direct comparisons with the results of previous oddball studies of alcoholism risk (e.g., see Porjesz et al., 2005) should be made with some caution.

We have conceptualized the P3 response to alcohol cues in terms of the activation of the appetitive motivational system. In this context, our findings are consistent in some respects with the conditioned appetitive-motivational model of Stewart et al. (1984), who posited that drug-related cues can become conditioned stimuli that elicit central nervous system responses associated with the positive reinforcing effects of the drug. However, our findings suggest an extension of this model to include the possibility that cue-induced activation of this motivational process is not necessarily conditioned on previous use, but that it also can occur because of (possibly genetic) risk factors that make substances of abuse particularly appealing to some users. A recent compelling theory of the P3 (Nieuwenhuis et al., 2005) posits that this component reflects activation of the locus-coeruleus norepinephrine system. Specifically, Nieuwenhuis et al. argue that this neuromodulatory system serves an important information-processing function, which is to "potentiate the response to motivationally

Table 4
Step-Wise Regression Predicting Time 2 Alcohol Use From Alcohol Sensitivity, With Sex and Baseline Alcohol Use Controlled for

	Time 2 ALC		Time 2 HEAVY	
Variable	Adj Δ R^2	β	Adj Δ R^2	β
Step 1	.47**		.61**	
Sex		.15		.02
Time 1 ALC		.64**		.79**
Step 2	.12**		.06*	
Sex		.03		−.07
Time 1 ALC		.41**		.62**
Sensitivity		.46**		.34*

Note. Time 1 ALC = quantity/frequency of alcohol use at baseline; Time 2 ALC = quantity/frequency of alcohol use at follow-up; Time 2 HEAVY = heavy drinking composite score at follow-up; Adj Δ R^2 = change in adjusted R^2 by adding the second step.
* $p < .05$. ** $p < .01$.

significant events" (p. 510), and that the P3 represents an outcome of stimulus evaluation and decision making by this system. Viewed from this perspective, the current findings suggest that the P3 response to alcohol cues represents a neural marker for a motivational process that ultimately will increase the likelihood of a decision to seek and consume alcohol. Thus, the current findings extend the literature linking alcohol sensitivity to risk for alcoholism by advancing a characterization of sensitivity based on cognitive-motivational processes important for decision making.

This study suffered from a number of limitations that should be considered. First, although we assessed both family history of alcoholism and indicators of alcohol dependence in our participants and tested these as potential covariates of our predicted effects, this study was not designed specifically to address potential interactions between these factors and alcohol sensitivity. In future work, researchers should consider sampling individuals on the basis of these additional factors to better test their influence on P3 cue reactivity. Also, the measure of alcohol sensitivity used here has not been studied extensively, particularly compared to the SRE developed by Schuckit et al. (1997). The extent to which these two measures tap the same underlying construct currently is unknown. In future studies researchers should include both measures in order to determine the extent of overlap in their prediction of cue reactivity in general and P3 responses more specifically.

We have argued that the current results are inconsistent with the notion that consumption history entirely explains cue reactivity effects. However, our data do not reveal specifically what other mechanism(s) might produce differential cue reactivity. On the basis of other research (e.g., Li, 2000; Schuckit et al., 2001), we have speculated that the alcohol sensitivity variable likely represents differential genetic susceptibility to alcohol-related problems, which we presume to be independent of personal consumption. The models showing that sensitivity level uniquely predicted follow-up drinking when baseline drinking was controlled for are consistent with the notion that, although correlated, sensitivity level and typical alcohol use are not redundant constructs. However, it would be premature to conclude that the unique variance associated with sensitivity level reflects genetic predisposition; this idea remains to be systematically tested in future research.

It also remains to be determined whether low sensitivity to alcohol is specifically associated with heightened P3 responses to alcohol cues, or rather, if low sensitivity is more broadly associated with reactivity to a range of appetitive stimuli. Although the nonalcohol beverage cues used here were all consumable and therefore appetitive to some degree (an important characteristic of control stimuli in cue reactivity studies; see Stritzke et al., 2004), it is likely that alcohol-related stimuli are more arousing, at least to at-risk individuals, than nonalcoholic stimuli. Given that the P3 is thought to be sensitive to the arousal properties of stimuli (e.g., Delplanque, Silvert, Hot, Rigoulot, & Sequeira, 2006), the current findings could be interpreted in terms of arousal rather than alcohol-specific reactivity. We are testing this idea with ongoing research in our laboratory by including other appetitive arousal cues in the picture viewing task used here.

In conclusion, the present data show that a low level of sensitivity to alcohol's effects is associated with heightened neural reactivity to alcohol cues in social drinkers. In addition, this study is the first to demonstrate that P3 amplitude elicited by alcohol cues can predict drinking prospectively. These findings suggest that alcohol cues have particular motivational relevance for individuals with low sensitivity to alcohol's effects, which could help to explain why such individuals are at increased risk for alcohol use disorders. The current findings also indicate that in addition to small P3 serving as a marker for alcoholism risk (Polich et al., 1994; Porjesz et al., 1998, 2005), increased P3 to motivationally-relevant substance-related cues may also mark an increased likelihood of heavy drinking or risk for alcohol-related problems.

References

American Encephalographic Society. (1991). Guidelines for standard electrode position nomenclature. *Journal of Clinical Neurophysiology, 8,* 200–222.

Bartholow, B. D., Pearson, M. A., Sher, K. J., Wieman, L. C., Fabiani, M., & Gratton, G. (2003). Effects of alcohol consumption and alcohol susceptibility on cognition: A psychophysiological examination. *Biological Psychology, 64,* 167–190.

Bauer, L. O., & Hesselbrock, V. M. (1999). P300 decrements in teenagers with conduct problems: Implications for substance abuse risk and brain development. *Biological Psychiatry, 46,* 263–272.

Begleiter, H., Porjesz, B., Bihari, B., & Kissin, B. (1984, September 28). Event-related potentials in boys at risk for alcoholism. *Science, 225,* 1493–1496.

Cacioppo, J. T., Gardner, W. G., & Berntson, G. G. (1999). The affect system has parallel and integrative processing components: Form follows function. *Journal of Personality and Social Psychology, 76,* 839–855.

Cacioppo, J. T., & Tassinary, L. G. (1990). Inferring psychological significance from physiological signals. *American Psychologist, 45,* 16–28.

Carlson, S. R., Iacono, W. G., & McGue, M. (2004). P300 amplitude in non-alcoholic adolescent twin pairs who become discordant for alcoholism as adults. *Psychophysiology, 41,* 841–844.

Carter, B. L., & Tiffany, S. T. (1999). Meta-analysis of cue-reactivity in addiction research. *Addiction, 94,* 327–340.

Collins, B. N., & Brandon, T. H. (2002). Effects of extinction context and retrieval cues on alcohol cue reactivity among nonalcoholic drinkers. *Journal of Consulting and Clinical Psychology, 70,* 390–397.

Curtin, J. J., Barnett, N. P., Colby, S. M., Rohsenow, D. J., & Monti, P. M. (2005). Cue reactivity in adolescents: Measurement of separate approach and avoidance reactions. *Journal of Studies on Alcohol, 66,* 332–343.

Delplanque, S., Silvert, L., Hot, P., Rigoulot, S., & Sequeira, H. (2006). Arousal and valence effects on event-related P3a and P3b during emotional categorization. *International Journal of Psychophysiology, 60,* 315–322.

Drummond, D. C. (2000). What does cue-reactivity have to offer clinical research? *Addiction, 95*(Suppl. 2), S129–S144.

Fabiani, M., Gratton, G., & Federmeier, K. D. (2007). Event-related brain potentials: Methods, theory, and applications. In J. T. Cacioppo, L. Tassinary, & G. G. Berntson (Eds.), *Handbook of psychophysiology* (3rd ed., pp. 85–119). Cambridge, UK: Cambridge University Press.

Genkina, O. A., & Shostakovich, G. S. (1983). Elaboration of a conditioned reflex in alcoholics using an unrecognizable motivationally significant word. *Zhurnal Vysshei Nervnoi Deyatelnosti Imeni IP Pavlova, 33,* 1010–1018.

Heath, A. C., Madden, P. A., Bucholz, K. K., Dinwiddie, S. H., Slutzke, W. S., Bierut, L. J., et al. (1999). Genetic differences in alcohol sensitivity and the inheritance of alcoholism risk. *Psychological Medicine, 29,* 1069–1081.

Hermann, M. J., Weijers, H. G., Wiesbeck, G. A., Aranda, D., Böning, J., & Fallgater, A. J. (2000). Event-related potentials and cue-reactivity in alcoholism. *Alcoholism: Clinical and Experimental Research, 24,* 1724–1729.

Hermann, M. J., Weijers, H. G., Wiesbeck, G. A., Böning, J., & Fallgater, A. J. (2001). Alcohol cue-reactivity in heavy and light social drinkers as revealed by event-related potentials. *Alcohol & Alcoholism, 36,* 588–593.

Hesselbrock, V., Begleiter, H., Porjesz, B., O'Connor, S., & Bauer, L. (2001). P300 event-related potential amplitude as an endophenotype of

alcoholism: Evidence from the Collaborative Study on the Genetics of Alcoholism. *Journal of Biomedical Science, 8,* 77–82.

Hill, S. Y., Steinhauer, S. R., Zubin, J., & Baughman, B. A. (1988). Event-related potentials as markers for alcoholism risk in high density families. *Alcoholism: Clinical and Experimental Research, 12,* 545–554.

Iacono, W. G., Carlson, S. R., Malone, S. M., & McGue, M. (2002). P3 event-related potential amplitude and the risk for disinhibitory disorders in adolescent boys. *Archives of General Psychiatry, 59,* 750–757.

Iacono, W. G., Malone, S. M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *International Journal of Psychophysiology, 48,* 147–178.

Ito, T. A., Larsen, J. T., Smith, K., & Cacioppo, J. T. (1998). Negative information weighs more heavily on the brain: The negativity bias in evaluative categorization. *Journal of Personality and Social Psychology, 75,* 887–900.

Johnston, V. S., Miller, D. R., & Burleson, M. H. (1986). Multiple P3s to emotional stimuli and their theoretical significance. *Psychophysiology, 23,* 684–694.

Kambouropoulos, N., & Staiger, P. K. (2004). Reactivity to alcohol-related cues: Relationship among cue type, motivational processes, and personality. *Psychology of Addictive Behaviors, 18,* 275–283.

Kaplan, R. G., Meyer, R. E., & Stroebel, C. F. (1983). Alcohol dependence and responsivity to an ethanol stimulus as predictors of alcohol consumption. *British Journal of Addiction, 78,* 259–267.

Lang, A., Yegiyan, N. S., & Bradley, S. D. (2006). Reactivity to risky products: Is motivational activation appetitive or aversive? *Psychophysiology, 43*(Suppl. 1), S56–S57.

Lang, P., Bradley, M. M., & Cuthbert, B. N. (1997). Motivated attention: Affect, activation, and action. In P. Lang, R. F. Simons, & M. Balaban (Eds.), *Attention and orienting: Sensory and motivational processes* (pp. 97–136). Hillsdale, NJ: Erlbaum.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2001). *International affective picture system (IAPS): Instruction manual and affective ratings* (Tech. Rep. No. A-5). Gainesville, FL: University of Florida, Center for Research in Psychophysiology.

Li, T. K. (2000). Pharmacogenetics of response to alcohol and genes that influence alcohol drinking. *Journal of Studies on Alcohol, 61,* 5–12.

Mann, R. E., Sobell, L. C., Sobell, M. B., & Pavin, D. (1985). Reliability of a family tree questionnaire for assessing family history of alcohol problems. *Drug and Alcohol Dependence, 15,* 61–67.

Monti, P. M., Binkoff, J. A., Abrams, D. B., Zwick, W. R., Nirenberg, T. D., & Liepman, M. R. (1987). Reactivity of alcoholics and nonalcoholics to drinking cues. *Journal of Abnormal Psychology, 96,* 122–126.

Namkoong, K., Lee, E., Lee, C. H., Lee, B. O., & An, S. K. (2004). Increased P3 amplitudes induced by alcohol-related pictures in patients with alcohol dependence. *Alcoholism: Clinical and Experimental Research, 28,* 1317–1323.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision-making, the P3, and the locus coeruleus-norepinephrine system. *Psychological Bulletin, 131,* 510–532.

O'Neill, S. E., Sher, K. J., & Bartholow, B. D. (2002). Alcohol susceptibility and tolerance in young adults. *Alcoholism: Clinical and Experimental Research, 26,* 119A.

Palfai, T. P. (2001). Individual differences in temptation and responses to alcohol cues. *Journal of Studies on Alcohol, 62,* 657–666.

Patrick, C. J., Bernat, E., Malone, S. M., Iacono, W. G., Krueger, R. F., & McGue, M. K. (2006). P300 amplitude as an indicator of externalizing in adolescent males. *Psychophysiology, 43,* 84–92.

Pfefferbaum, A., Ford, J. M., White, P. M., & Mathalon, D. (1991). Event-related potentials in alcoholic men: P3 amplitude reflects family history but not alcohol consumption. *Alcoholism: Clinical and Experimental Research, 15,* 839–850.

Polich, J., & Bloom, F. E. (1987). P300 from normals and adult children of alcoholics. *Alcohol, 4,* 301–306.

Polich, J., Haier, R. J., Buchsbaum, M., & Bloom, F. E. (1988). Assessment of young men at risk for alcoholism with P300 from a visual discrimination task. *Journal of Studies on Alcohol, 49,* 186–190.

Polich, J., Pollock, V. E., & Bloom, F. E. (1994). Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychological Bulletin, 115,* 55–73.

Porjesz, B., Begleiter, H., Reich, T., Van Eerdewegh, P., Edenberg, H. J., Foroud, T., et al. (1998). Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: Preliminary results from the COGA project. *Alcoholism: Clinical and Experimental Research, 22,* 1317–1323.

Porjesz, B., Rangaswamy, M., Kamarajan, C., Jones, K. A., Padmanabhapillai, A., & Begleiter, H. (2005). The utility of neurophysiological markers in the study of alcoholism. *Clinical Neurophysiology, 116,* 993–1018.

Rodriguez, L. A., Wilson, J. R., & Nagoshi, C. T. (1993). Does psychomotor sensitivity to alcohol predict subsequent alcohol use? *Alcoholism: Clinical and Experimental Research, 17,* 155–161.

Schuckit, M. A. (1994). Low level of response to alcohol as a predictor of future alcoholism. *American Journal of Psychiatry, 151,* 184–189.

Schuckit, M. A., Edenberg, J., Kalmijn, J. A., Flury, T. L., Smith, T., Reich, L., et al. (2001). A genome-wide search for genes that relate to a low level of response to alcohol. *Alcoholism: Clinical and Experimental Research, 25,* 323–329.

Schuckit, M. A., & Smith, T. L. (2000). The relationships of a family history of alcohol dependence, a low level of response to alcohol and six domains of life functioning to the development of alcohol use disorders. *Journal of Studies on Alcohol, 61,* 827–835.

Schuckit, M. A., Smith, T. L., Anderson, K. G., & Brown, S. A. (2004). Testing the level of response to alcohol: Social information processing model of alcoholism risk: A 20-year prospective study. *Alcoholism: Clinical and Experimental Research, 28,* 1881–1889.

Schuckit, M. A., Smith, T. L., Beltran, I., Waylen, A., Horwood, J., & Davis, J. M. (2005). Performance of a self-report measure of the level of response to alcohol in 12- to 13-year-old adolescents. *Journal of Studies on Alcohol, 66,* 452–458.

Schuckit, M. A., Smith, T. L., Kalmijn, J. A., & Raimo, E. N. (2000). The relationship of a low response to alcohol to ERP and personality measures. *Alcoholism: Clinical and Experimental Research, 24,* 27A.

Schuckit, M. A., Tipp, J. E., Smith, T. L., Wiesbeck, G. A., & Kalmijn, J. A. (1997). The relationship between self-rating of the effects of alcohol and alcohol challenge results in ninety-eight young men. *Journal of Studies on Alcohol, 58,* 397–404.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T. A., & Lang, P. J. (2000). Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology, 37,* 257–261.

Semlitsch, H. V., Anderer, P., Schuster, P., & Presslich, O. (1986). A solution for reliable and valid reduction of ocular artifacts, applied to the P300 ERP. *Psychophysiology, 23,* 695–703.

Stewart, J., DeWitt, H., & Eikelboom, R. (1984). The role of conditioned and unconditioned drug effects in the self-administration of opiates and stimulants. *Psychological Review, 91,* 251–268.

Stritzke, W. G. K., Breiner, M. J., Curtin, J. J., & Lang, A. R. (2004). Assessment of substance cue reactivity: Advances in reliability, specificity, and validity. *Psychology of Addictive Behaviors, 18,* 148–159.

Walitzer, K. S., & Sher, K. J. (1990). Alcohol cue reactivity and ad lib drinking in young men at risk for alcoholism. *Addictive Behaviors, 15,* 29–46.

Wickens, T. D. (2001). *Elementary signal detection theory*. Oxford, UK: Oxford University Press.

Received December 14, 2006
Revision received February 26, 2007
Accepted March 10, 2007 ■