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# Behavioral response bias and event-related brain potentials implicate elevated incentive salience attribution to alcohol cues in emerging adults with lower sensitivity to alcohol

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## Abstract

**Aims:** This study used a behavioral approach-avoidance task including images of alcoholic beverages to test whether low sensitivity to alcohol (LS) is a phenotypical marker of a dispositional propensity to attribute bottom-up incentive value to naturally conditioned alcohol cues.

**Design, setting and participants:** Experimental study with a measured individual difference variable at a university psychology laboratory in Missouri, MO, USA. Participants were 178 emerging adults (aged 18–20 years) varying in self-reported sensitivity to alcohol's acute effects.

**Measurements:** Participants completed the alcohol approach-avoidance task while behavior (response time; RT) and the electroencephalogram (EEG) were recorded. Stimulus-locked event-related potentials (ERPs) provided indices of integrated (top-down and bottom-up) stimulus incentive value (P3 amplitude) and conflict between top-down task demands and bottom-up response propensities (N450 amplitude).

**Findings:** Linear mixed models showed faster RT for 'alcohol-approach' relative to 'alcohol-avoid' trials for lower-sensitivity (LS) [ $\text{mean}_D \pm \text{standard error}_D$  ( $M_D \pm SE_D$ ) =  $29.51 \pm 9.74$  ms,  $t_{(328)} = 3.03$ ,  $P = 0.003$ ] but not higher-sensitivity (HS) individuals ( $M_D \pm SE_D = 2.27 \pm 9.33$  ms,  $t_{(328)} = 0.243$ ,  $P = 0.808$ ). There was enhanced N450 amplitude (response conflict) for alcohol-avoid relative to alcohol-approach trials for LS participants ( $M_D \pm SE_D = 0.811 \pm 0.198$   $\mu\text{V}$ ,  $Z = 4.108$ ,  $P < 0.001$ ) and enhanced N450 amplitude for alcohol-approach relative to alcohol-avoid for HS participants ( $M_D \pm SE_D = 0.419 \pm 0.188$   $\mu\text{V}$ ,  $Z = 2.235$ ,  $P = 0.025$ ). There was also enhanced P3 amplitude for alcohol-approach relative to alcohol-avoid for LS ( $M_D \pm SE_D = 0.825 \pm 0.204$   $\mu\text{V}$ ,  $Z = 4.045$ ,  $P < 0.001$ ) but not HS ( $M_D \pm SE_D = 0.013 \pm 0.194$   $\mu\text{V}$ ,  $Z = 0.068$ ,  $P = 0.946$ ).

**Conclusions:** Findings from a human laboratory study appear to support the notion that low sensitivity to alcohol indexes a propensity to attribute bottom-up incentive value to naturally conditioned alcohol cues.

## KEYWORDS

Alcohol sensitivity, approach-bias, conflict-monitoring, cue-reactivity, event-related potentials, incentive salience, sign-tracking.

## INTRODUCTION

Applied to alcohol, the incentive sensitization theory of addiction (ISTA) [1, 2] posits that, with repeated alcohol use, susceptible individuals become progressively hyperreactive (namely, 'sensitized') to the incentive (i.e. motivational) properties of alcohol and its predictive cues. Resulting behavioral manifestations include cue-elicited approach, attentional biases and subjective craving [3, 4]. Pre-clinical work suggests that the propensity to attribute incentive value to reward cues, indexed by a cue-directed, cue-elicited approach [i.e. sign-tracking (ST)], is associated with addiction-like phenotypes [5]. Translating the ISTA into human models of addiction risk requires identifying ST-like phenotypes in humans [6].

Low sensitivity (LS) to alcohol is a heritable, trait-like variation in behavioral, cognitive, physiological and subjective responses to alcohol [7, 8]. LS confers risk for alcohol use disorder (AUD) [9–12] and can be observed in humans and rodents [13]. One mechanism by which LS may confer AUD risk is through over-attribution of incentive value to alcohol cues [3]. Consistent with this idea, alcohol cues (i) more effectively capture attention [14, 15]; (ii) elicit more approach [16]; (iii) elicit greater levels of subjective craving [17, 18]; and (iv) are more potent conditioned reinforcers [17] among individuals with LS relative to high-sensitivity (HS) phenotypes.

### Alcohol approach bias and its neural mechanisms

Among incentive-based responses to cues, approach behavior is unique in that it can facilitate instrumental actions required to ingest alcohol. In human laboratory models, such behavior can be measured using tasks that pit approach and avoidance tendencies against one another [19, 20]. In the alcohol approach-avoidance task (alcohol-AAT) [20], individuals push or pull a joystick in response to an irrelevant feature (e.g. orientation) of alcohol-related and control visual cues. Alcohol approach bias is indicated by the extent to which 'pull' reaction time (RT) is faster than 'push' RT for alcohol cues. Validation has been provided in studies showing that heavy drinkers and AUD patients show stronger approach biases than lighter drinkers [20–27]. However, heterogeneity in this effect [28–31] suggests the existence of individual differences in the extent to which alcohol use is driven by cue-elicited approach responses, as predicted by the ISTA [5, 32]. Consistent with this idea, two previous alcohol-AAT studies found that, among heavy drinkers, alcohol approach bias was evident among individuals with the A118G single nucleotide polymorphism (SNP) in the  $\mu 1$  opioid receptor (OPRM1) gene [20] or the LS phenotype [16]. Given that LS has been linked to this OPRM1 SNP [33, 34], convergent evidence supports the idea that LS-based AUD risk might involve alcohol approach bias.

In theory, approach bias measured by the alcohol-AAT depends upon the degree of behavioral approach elicited by alcohol cues, reflecting an acquired ability to activate the appetitive-motivation

system [35, 36],<sup>1</sup> and the extent to which the task-required behavioral response facilitates or conflicts with cue-elicited behavior. Specifically, congruence between the bottom-up goal activated by the cue and a top-down, task-dependent goal should increase activation of neural circuits encoding integrated (i.e. bottom-up + top-down) stimulus incentive value [39–41]. In contrast, when bottom-up and top-down goals are incongruent, activity should instead increase in neural circuits encoding stimulus–response conflict and the concomitant need for top-down inhibitory control over behavior [42, 43].

Findings from the few previous studies that have examined the neural underpinnings of alcohol approach bias have shown mixed support for such ideas. Using the alcohol-AAT, researchers have found increased activation of the medial prefrontal cortex (mPFC), nucleus accumbens and orbitofrontal cortex on alcohol-approach compared to alcohol-avoid trials among alcohol-dependent patients relative to controls [24–26]. These findings are consistent with alcohol cues' increased salience among alcohol-dependent individuals [44–47]. However, enhanced mPFC activation on alcohol-approach versus -avoid trials is ambiguous because such activation can reflect salience arising either from bottom-up (i.e. incentive-motivational responses) or top-down (i.e. response conflict) stimulus features [48]. Measuring cortical activity with higher temporal resolution via electroencephalography (EEG) during the alcohol-AAT can help to resolve this ambiguity.

### Current study

We examined the neural mechanisms underlying alcohol approach-congruent versus -incongruent behavior by measuring event-related potentials (ERPs) while emerging-adult drinkers varying in alcohol sensitivity completed the alcohol-AAT. We studied this population because our focus was on AUD risk propensity rather than consequences of sustained heavy drinking.

Considerable research supports the validity of two families of ERP measures reflecting stimulus incentive value and stimulus–response conflict, respectively. Specifically, the amplitude of the P3 component (and/or late positive potential; LPP) is known to index the incentive value of eliciting events and is sensitive to both top-down (e.g. task demands) and bottom-up (e.g. affective content) motivational factors [49]. In contrast, the extent to which stimuli elicit stimulus–response conflict is reflected in the amplitude of any of several mid-frontal negativities in the ERP, such as the N2 or N450 components<sup>2</sup> [50, 51], whose amplitude reflects activity in the mPFC

<sup>1</sup>It is an open, empirical question of whether or under what circumstances behavioral approach response tendencies are directly triggered by automatic (i.e. involuntary or implicit) stimulus evaluations and consequent activation of the subcortical appetitive motivational system in humans. Increasing evidence supports the idea that expression of behavioral approach response tendencies also can be mediated by automatic stimulus evaluation-related activation of cognitive representations of stimulus-congruent responses and outcomes (i.e. goals) (for review and discussion of the latter, see: [37, 38]).

<sup>2</sup>Whether N2 or N450 is observed in a given task appears to depend upon task parameters which, in turn, could reflect engagement of different facets of conflict-related cognitive processes (e.g. interference control versus pre-potent response inhibition). Although both are considered conflict monitoring signals, more research is needed to more clearly understand potential differences in the functional significance of the N2 and N450 [50, 51].

associated with top-down conflict monitoring and resolution processes [52, 53]. Here, P3 amplitude served as an index of alcohol cues' integrated incentive value, whereas N450 amplitude served as an index of the extent to which a top-down, task-required response conflicted with the behavioral response activated in a bottom-up manner by alcohol cues' incentive salience.

Based on the idea that alcohol cues may act as 'motivational magnets' [54] for LS drinkers and on previous findings [16], we advanced the following hypotheses.<sup>3</sup>

**Hypothesis 1.** For alcohol but not for other cue types (categorical predictor 1), the simple effect of response type [push (avoid) versus pull (approach)]; categorical predictor 2) on RT (outcome 1) would be enhanced as alcohol sensitivity (moderator) decreased, reflecting a greater degree of alcohol cue-specific approach bias.

**Hypothesis 2.** For alcohol cues, the simple effect of response type on N450 amplitude (outcome 2) would be enhanced as alcohol sensitivity decreased, reflecting greater stimulus-response conflict when top-down and bottom-up motivation are incongruent.

**Hypothesis 3.** For alcohol cues, the simple effect of response type on P3 amplitude (outcome 3) would be enhanced as alcohol sensitivity decreased, reflecting amplified incentive value when top-down and bottom-up motivation are congruent.

## METHOD

### Participants

Data in this report are from a large, prospective study examining individual differences in alcohol cue-reactivity in laboratory and real-world contexts among underage drinkers. Community-recruited study candidates completed an on-line eligibility screening survey. Individuals were invited to the laboratory if they were aged 18–20 years, reported at least monthly alcohol use in the past year and one binge-drinking episode (4+/5+ drinks in 2 hours for females/males, respectively) in the past 6 months, and reported no history of neurological disease, head injury or unsuccessful attempts to reduce alcohol use. See Supporting information for recruitment strategies and detailed inclusion–exclusion criteria. Of 769 individuals who completed the screener, 567 were eligible (although not all were invited to enroll). Eligible individuals were invited strategically to stratify the sample for biological sex and alcohol sensitivity levels. The present sample of 178 individuals (participant characteristics in Table 1) completed the

first laboratory session prior to suspension of data collection due to the SARS-CoV-2 pandemic.

## Materials

### Alcohol-AAT

On each trial, a color photograph of an alcoholic beverage (e.g. beer can; 'alcohol'), a non-alcoholic beverage (e.g. soft-drink can; 'NADrinks') or a non-comestible liquid (e.g. gasoline can; 'objects') was presented centrally on the monitor, tilted 3° left or right. Participants were instructed to push or pull a joystick to move images toward or away from themselves as quickly as possible based on image orientation (response mapping was counter-balanced across participants). Each image type appeared equally often in both orientations. Further details and example images are shown in the Supporting information.

### Alcohol sensitivity

Participants completed the 15-item Alcohol Sensitivity Questionnaire (ASQ) [56, 57], which queries the number of drinks a respondent must consume to experience various alcohol effects. More positive scores indicate lower alcohol sensitivity and predict higher subjective stimulation, lower subjective sedation and lower subjective intoxication during laboratory alcohol challenge [57]. Scores were standardized to reduce bias [58] and stratified by sex to avoid confounding with sex differences in pharmacokinetics [59]. Full details are given in the Supporting information. Raw scores are presented in Table 1. Associations between sensitivity scores and alcohol use are given in Table 2.

### Alcohol use

Participants completed questionnaire measures of past-year typical frequency (drinking days per week), typical quantity (drinks per drinking day) and maximum quantity of alcohol consumed within 24 hours, and of binge-drinking episodes per week in the past 6 months [60] (see Table 1). Participants also indicated age at first intoxication and age at onset of regular drinking. AUD symptoms were assessed using the Mini International Neuropsychiatric Interview (MINI) AUD module [61]. Full details and scaling are given in the Supporting information.

### Electrophysiological recording and ERP component scoring

EEG was recorded at 512 Hz from 32 Ag/AgCl electrodes (mastoid reference) arranged in the expanded 10–20 system [62].

<sup>3</sup>The hypotheses and analysis plans were not formally pre-registered, so results should be considered exploratory.

**TABLE 1** Participant characteristics (*n* = 178)

	<i>n</i> (%)		Equal representation? $\chi^2$ , d.f., <i>P</i>
Female	108 (61)		8.11, 1, 0.004
Ethnicity			
Hispanic	10 (6)		138.27, 1, < 0.001
Race			435.48, 3, < 0.001
American Indian/Alaskan Native	1 (< 0.1)		
Native Hawaiian/Pacific Islander	0 (0)		
Asian	5 (3)		
Black	7 (4)		
White	165 (93)		
Multiple selected	0 (0)		
None selected	0 (0)		
Handedness			
Right-handed	146 (82)		73.01, 1, < 0.001
Undergraduate student	170 (95)		147.44, 1, < 0.001
	Female	Male	
	Mean (SD); median (IQR)	Mean (SD); median (IQR)	Equal between sexes? <i>U</i> , <i>P</i>
Age at screening, years	19.25 (0.75); 19.06 (1.34)	19.10 (0.65); 19.04 (0.61)	4087, 0.361
Age at laboratory session, years	19.53 (0.77); 19.43 (1.40)	19.29 (0.66); 19.022 (0.67)	4332, 0.100
Age at first alcoholic intoxication, years	16.56 (1.40); 16 (2)	16.37 (1.63); 16 (3)	3761, 0.544
Age at regular alcohol use, ears	17.36 (1.19); 18 (1)	17.13 (1.26); 17 (1.25)	3949, 0.321
Years since first alcoholic intoxication relative to age at laboratory session	3.00 (1.48); 2.91 (2.15)	2.91 (1.69); 2.81 (2.70)	3756, 0.563
Years since regular alcohol use relative to age at laboratory session	2.18 (1.19); 1.93 (1.61)	2.15 (1.26); 1.90 (1.58)	3688, 0.878
Past year alcohol use			
Drinking days per week	1.62 (1.17); 2 (1.37)	1.74 (1.32); 2 (1.37)	3638, 0.741
Drinks per drinking day	4.49 (3.40); 3.5 (2)	6.27 (2.87); 5.5 (3.5)	2041, < 0.001
Maximum drinks in 24 hours	8.73 (4.12); 9.5 (3.5)	15.32 (7.28); 14.5 (11)	1609, < 0.001
Binges per week	0.74 (0.83); 0.62 (0.94)	1.14 (1.00); 0.81 (1.71)	2736, 0.002
ASQ score	3.56 (1.43); 3.18 (1.37)	5.53 (2.04); 5.45 (2.70)	1600, < 0.001
AUD symptom count	1.92 (1.85); 1.5 (3)	2.23 (2.30); 2 (4)	3628, 0.646
	<i>n</i> (%)	<i>n</i> (%)	Equal between sexes? $\chi^2$ , d.f., <i>P</i>
AUD category			1.45, 3, 0.694
No AUD (0–1 symptoms)	54 (50)	34 (49)	
Mild AUD (2–3 symptoms)	31 (29)	17 (24)	
Moderate AUD (4–5 symptoms)	19 (17)	14 (20)	
Severe AUD (6 + symptoms)	4 (4)	5 (7)	

Of the 10 participants who reported Hispanic ethnicity, nine self-identified as white and one self-identified as Asian. Right-handedness was defined as an Edinburgh Handedness Inventory short-form score of 61 or above [55]. Undergraduate student was defined as being enrolled in a 4-year college program (BA/BS-granting institution). Of the eight participants who were not undergraduate students, five were enrolled in a 2-year college program (AA/AS-granting institution), two were attending high school or working towards a high school equivalency credential (e.g. general educational development (GED) and one was not enrolled in any form of schooling.

Abbreviations: AUD = alcohol use disorder; SD = standard deviation; IQR = interquartile range; d.f. = degrees of freedom.

There was no sex difference in standardized Alcohol Sensitivity Questionnaire (ASQ) scores, *U* = 3485, *P* = 0.380.

Impedance was kept below 10 k $\Omega$ . Off-line, the EEG was re-referenced to the average of the two mastoids, re-sampled at 256 Hz and bandpass-filtered (second-order Butterworth with half-amplitude cut-offs: 0.1–30 Hz) using eeglab [63] and erlab [64].

Independent components analysis (ICA) was conducted, and an eeglab routine was used to identify and remove components corresponding to blinks as well as eye movements and other artifacts [65]. The EEG was then segmented into stimulus-locked

**TABLE 2** Associations among alcohol use variables controlling for sex

	1.	2.	3.	4.	5.	6.	7.
1. ASQ	-						
2. Drinking days per week	0.403***	-					
3. Drinks per drinking day	0.287***	0.143	-				
4. Max drinks in 24 hours	0.592***	0.433***	0.331***	-			
5. Binges per week	0.493***	0.667***	0.360***	0.426***	-		
6. Years since first intoxication	0.113	0.264***	0.040	0.263***	0.133	-	
7. Years since regular use	0.166*	0.243**	0.010	0.268***	0.131	0.650***	-
8. AUD symptom count	0.230**	0.329***	0.243**	0.415***	0.311***	0.432***	0.211**

Entries in column 1 represent semipartial Pearson's correlation coefficients between standardized ASQ scores and alcohol use measures controlling for any potential effect of biological sex in the alcohol use measure. Entries in columns 2, 3, 4, 5, 6 and 7 represent partial Pearson's correlation coefficients between the two alcohol use measures controlling for any potential effect of biological sex in both measures.

Abbreviations: AUD = alcohol use disorder; ASQ = Alcohol Sensitivity Questionnaire.

\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

epochs and underwent additional artifact detection and rejection routines. Artifact-free segments were then averaged together to obtain the ERP. N450 mean amplitudes were quantified over nine frontal/central electrodes. P3 mean amplitudes were quantified over nine parietal/occipital electrodes. Time-windows used for quantification are indicated on the grand average ERP waveforms shown in Figure 1a,b. Scalp topography is shown in Supporting information, Figure S1. For each component, there were 54 observations per person (six trial types  $\times$  nine electrodes). Additional details on EEG recording, preprocessing and ERP component scoring are shown in the Supporting information.

## Procedure

Upon arrival, participants provided informed consent and sobriety was verified by breathalyzer (0.000 g%). Participants were prepared for EEG recording and then completed the AAT. See Supporting information for additional laboratory procedure details.

## Analytical approach

Data were analyzed using linear mixed models (LMMs) fitted according to best practices for determining random-effects structures [66]. Because sex and handedness can affect task performance and ERPs [67–69], both were entered as effect-coded binary covariates.<sup>4</sup> Plots of the sample means and unconditional LMM-estimated

covariate-adjusted means can be found in the Supporting information. Hypotheses were tested by estimating the image content  $\times$  response type  $\times$  (continuous) ASQ score effect in each model and then comparing the LMM-estimated, covariate-adjusted means representing 'high sensitivity' (HS; ASQ  $Z = -1$ ) and 'low sensitivity' (LS; ASQ  $Z = +1$ ).<sup>5</sup> Exploratory Johnson–Neyman style [70] analyses identifying the ASQ score ranges over which significant congruency effects were observed are provided in the Supporting information.

## Behavioral data

In keeping with previous studies [20, 24, 71], we discarded error trials [mean  $\pm$  standard deviation (SD) =  $5.37 \pm 3.58\%$  trials per participant] and correct trials with RTs  $< 100$  ms (mean  $\pm$  SD =  $1.05 \pm 0.70\%$  trials per participant) or  $\geq 3$  SD from each person's mean RT (mean  $\pm$  SD =  $1.91 \pm 0.63\%$  trials per participant) and then computed six person-level median RTs<sup>6</sup> corresponding to three image content categories (alcohol, NADrinks, objects) by two response types (pull, push).<sup>7</sup>

## EEG/ERP data

EEG data from error trials were discarded. EEG data from one participant could not be segmented (event markers were not recorded) and

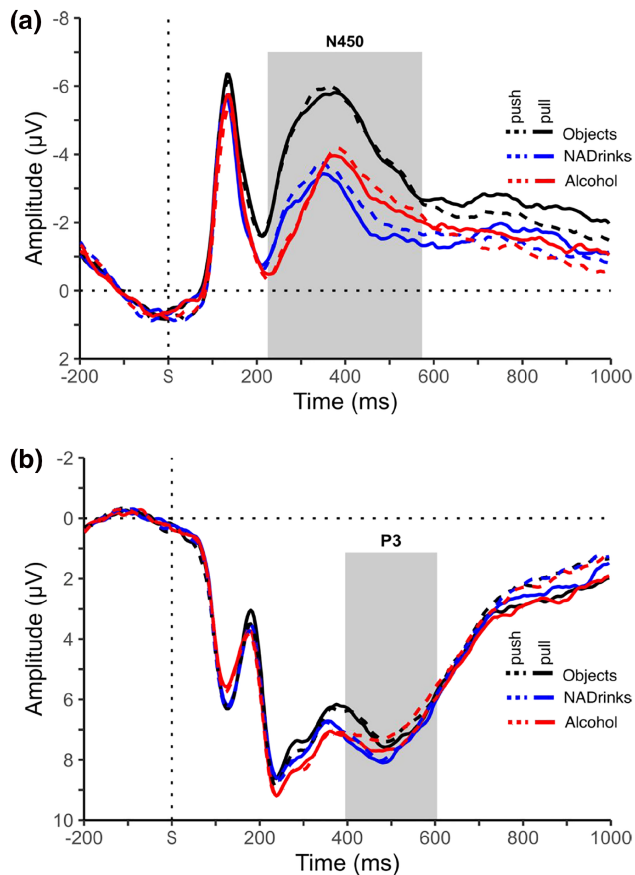
<sup>4</sup>Task version also was entered as an effect-coded covariate. Due to an experimenter error, 100 of 178 participants received only 240 experimental trials. The task was inadvertently shortened when the E-prime software (Psychology Software Tools, Inc., Sharpsburg, PA, USA) was upgraded partway through data collection, which unfortunately we did not notice until data were being processed for this report. Ancillary analyses indicated that this factor did not interact with image content  $\times$  response type effects on RT or on ERP component mean amplitudes. There was a marginally significant main effect of total trial count on RT only, such that individuals who completed 240 trials tended to be slower on average than their counterparts who completed 360 trials,  $t_{(176)} = 1.90$ ,  $P = 0.059$ ,  $d = 0.287$ .

<sup>5</sup>This procedure takes all the data into account, even though the estimated means are compared at two representative points in the range of the continuous predictor variable. The LMM is used to generate two estimates of the predicted value of the outcome variable for each of the six levels of the image content  $\times$  response type interaction: one assuming ASQ  $Z = -1$  and another assuming ASQ  $Z = +1$ .

<sup>6</sup>Median RTs were used to ensure comparability of the results with previous studies of the AAT [20, 24, 71], which have used median RTs in computing the response bias effect. Nonetheless, similar results were obtained when we used mean RTs. In keeping with the sensitivity of the mean to extreme values, however, the mean RTs were 40–50 ms larger (slower) than the median RTs.

<sup>7</sup>Before data cleaning and reduction, there were 55 134 observations across 178 participants; afterwards there were 1068 observations among 178 participants available for the RT model.





**FIGURE 1** Stimulus-locked event-related potential (ERP) waveform as a function of image content and response type. Objects = non-comestible control liquid images; NADrinks = non-alcoholic beverage images; alcohol = alcoholic beverage images. Data represent 147 individuals. The y-axis is inverted (negative-going up) following conventions in the ERP literature; 'S' on the x-axis indicates the time of image onset. (a) Average ERP waveform across persons and electrodes used in analyses (F3, F4, Fz, FC3, FC4, FCz, C3, C4, Cz). N450 component and quantification window (225–575 ms) indicated by a gray rectangle. (b) Average ERP waveform across persons and electrodes used in analyses (O1, O2, PO7, PO8, P7, P8, P3, P4, Pz). P3 component and quantification window (400–600 ms) indicated by a gray rectangle. (a,b) For topographic maps of the ERP as a function of image content and response type, see Supporting information, Figure S1

were excluded. EEG data from 30 additional participants were excluded because they contained fewer than 20 artifact-free epochs<sup>8</sup> per condition. Thus, ERP analyses were based on data from 147 participants.<sup>9</sup>

<sup>8</sup>In ancillary analyses, we applied a less-stringent minimum trial cut-off (12 artifact-free trials per condition) so as to retain more participants' data. Results of models based on this more inclusive sample, reported in the Supporting information, were very similar to those reported in the main text.

<sup>9</sup>The mean  $\pm$  SD number of artifact-free trials per condition was  $36 \pm 9$ . Among 147 participants and nine electrodes, there were 7936 total observations available for the N450 and P3 LMMs, respectively.

All procedures were approved by the University of Missouri Institutional Review Board.

## RESULTS

Effects of the predictor variables on each dependent measure in the base and moderator models are shown in Table 3; parameter estimates from the best-fitting LMMs are given in the Supporting information. In each model, results were unchanged when controlling for alcohol use-related measures.

## RT

As shown in Table 3, in the base RT model the image content  $\times$  response type interaction was significant, but in the moderation model the omnibus image content  $\times$  response type  $\times$  ASQ interaction was not significant. Nonetheless, we proceeded with a priori hypothesis testing, as described previously. Alcohol pull responses were significantly faster than push responses at LS but not HS (Figure 2), supporting hypothesis 1.<sup>10,11</sup>

## ERPs

### N450 amplitude

As shown in Table 3, in the base N450 amplitude model the image content  $\times$  response type interaction effect was significant, and in the moderation model the omnibus image content  $\times$  response type  $\times$  ASQ

interaction was significant. N450 was significantly larger (more negative) for alcohol push than pull at LS, supporting hypothesis 2, and the reverse was true at HS (Figure 3).

<sup>10</sup>Readers concerned about the non-significant omnibus test of the interaction effect on RTs should note that the Johnson–Neyman plots indicated the simple effect of response type (push–pull contrast) within alcohol images was significant at ASQ  $Z > -0.31$  (see Supporting information, Figure S5). Supporting information, Figure S5 also shows that the magnitude of the contrast increases with increasing ASQ score. If instead of treating ASQ as a continuous predictor we had chosen to use it, as in some previous studies, to group participants (LS = individuals with scores in the upper quartile of ASQ scores; HS = lower quartile of ASQ scores; group intermediates = all other ASQ scores), then the omnibus test of the interaction effect in the median RT model would have been significant,  $F_{(4,533)} = 3.78$ ,  $P < 0.005$ ,  $\eta^2 = 0.224$ . As expected, based on Supporting information, Figure S5, the push–pull contrast within alcohol images was only significant for LS,  $t_{(327)} = 2.61$ ,  $P < 0.01$ ,  $d = 0.289$  and intermediates,  $t_{(327)} = 2.45$ ,  $P < 0.05$ ,  $d = 0.271$ . This also held when modeling mean RTs.

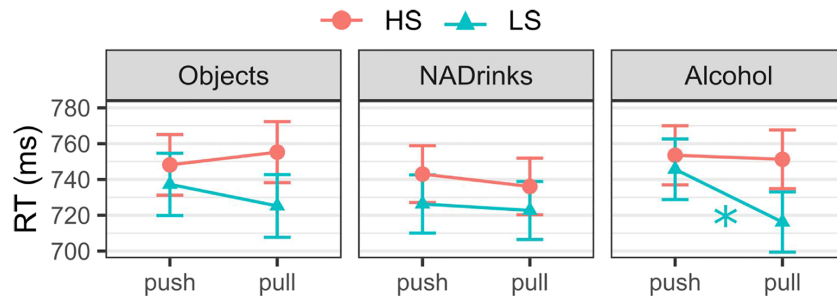
<sup>11</sup>Readers may be concerned that accounting for task version (240 versus 360 total trials) as a between-subject factor does not adequately control for within-task learning effects and that these confounding effects may explain our findings (e.g. perhaps LS individuals benefited more from additional trials). If within-task learning effects accounted for the ASQ moderation effect, then we would expect analyses of RTs based on only the first 240 trials would dampen or eliminate the observed moderation effect on RT. However, when we analyzed median RTs based on only the first 240 trials, the omnibus ASQ  $\times$  image content  $\times$  response type interaction effect was significant,  $F_{(2,531)} = 3.49$ ,  $P = 0.031$ ,  $\eta^2 = 0.114$ , and the push–pull contrast within alcohol images was again only significant for LS,  $t_{(348)} = 3.63$ ,  $P < 0.001$ ,  $d = 0.389$ . This also held when modeling mean RTs.

**TABLE 3** Tests of effects in linear mixed models of RT, N450 amplitude and P3 amplitude

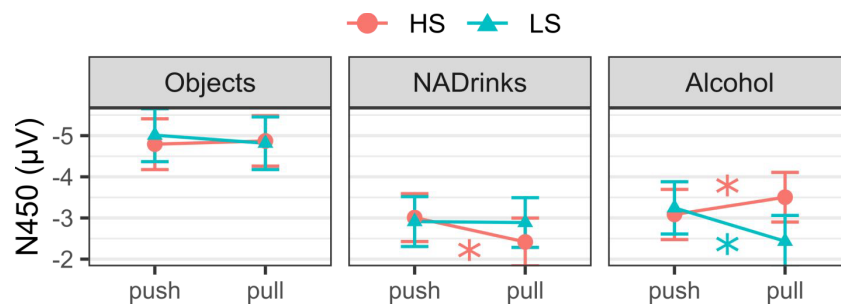
Predictors	RT models				N450 models				P3 models			
	F	d.f.	P	$\eta^2$	F	d.f.	P	$\eta^2$	F	d.f.	P	$\eta^2$
Base model												
Total trials	3.68	1179	0.055	0.088	0.75	1147	0.389	0.002	0.05	1147	0.823	0.001
Sex	0.46	1179	0.499	0.012	0.03	1147	0.851	< 0.001	0.23	1147	0.633	0.005
Handedness	6.40	1179	0.012	0.144	2.64	1147	0.106	0.007	0.46	1147	0.500	0.010
Image content	8.70	2281	0.001	0.314	163.31	2147	< 0.001	0.483	10.82	2147	< 0.001	0.330
Response type	2.70	1178	0.102	0.066	2.99	1147	0.086	0.008	4.42	1147	0.037	0.091
Image × response type	3.66	2533	0.026	0.162	8.10	26 173	< 0.001	0.044	8.60	26 172	< 0.001	0.281
Moderation model												
Total trials	3.51	1178	0.063	0.071	0.75	1147	0.389	0.002	0.08	1147	0.783	< 0.001
Sex	0.45	1178	0.504	0.010	0.03	1147	0.853	< 0.001	0.26	1147	0.609	0.002
Handedness	6.44	1178	0.012	0.123	2.63	1147	0.106	0.006	0.44	1147	0.506	0.004
ASQ score	0.70	1178	0.404	0.015	0.05	1147	0.943	< 0.001	2.83	1147	0.095	0.027
Image content	8.60	2276	< 0.001	0.273	163.53	2147	< 0.001	0.423	10.57	2147	< 0.001	0.170
Response type	2.88	1178	0.091	0.059	3.20	1147	0.075	0.007	4.48	1147	0.036	0.042
ASQ × image	0.43	2258	0.649	0.019	1.92	2147	0.150	0.008	2.93	2147	0.057	0.054
ASQ × response type	1.21	1178	0.272	0.026	1.12	1147	0.291	0.002	0.07	1147	0.788	< 0.001
Image × response type	3.84	2533	0.022	0.143	7.23	26 173	< 0.001	0.031	10.25	26 172	< 0.001	0.166
ASQ × image × response type	2.44	2533	0.088	0.096	46.81	26 173	< 0.001	0.173	23.63	26 172	< 0.001	0.315

Total trials is a between-subject factor (two levels: 240 trials, 360 trials). Sex is a between-subject factor (two levels: female, male). Handedness is a between-subject factor (two levels: right-hand dominant, not right-hand dominant). Image content is a within-subject factor (three levels: alcoholic beverages, non-alcoholic beverages, non-comestible liquids). Response type is a within-subject factor (two levels: push, pull). Alcohol sensitivity questionnaire (ASQ) score is a between-subject covariate representing the standardized ASQ score. Degrees of freedom (d.f.) were estimated using Satterthwaite's method (1941) [72]. RT = response time.

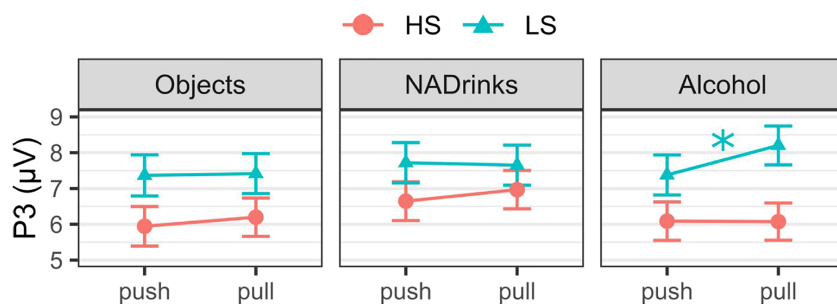




**FIGURE 2** Correct response time (RT) as a function of image content and response type: moderation by self-reported alcohol sensitivity. Objects = non-comestible control liquid images; NADrinks = non-alcoholic beverage images; alcohol = alcoholic beverage images. Data represent 178 individuals. Moderation hypothesis testing model-estimated marginal mean  $\pm$  standard error (SE) for the person-level median correct RTs adjusting for the following covariates: biological sex (female or male), handedness (right-hand dominant or not), and task version (240 or 360 total trials). HS = high sensitivity questionnaire [Alcohol Sensitivity Questionnaire (ASQ)  $Z = -1$ ]; LS = low sensitivity (ASQ  $Z = +1$ ). In the alcohol panel, the asterisk indicates  $P < 0.005$  for push–pull contrast at LS. ASQ score ranges over which this motivational congruency effect holds are shown in Supporting information, Figure S5



**FIGURE 3** N450 mean amplitude ( $\mu\text{V}$ ) as a function of image content and response type: moderation by self-reported alcohol sensitivity. Objects = non-comestible control liquid images; NADrinks = non-alcoholic beverage images; alcohol = alcoholic beverage images. Data represent 147 individuals. The y-axis is reversed with negative voltages going up because the N450 is a negative-going event-related potential (ERP) component (more negative values indicate larger amplitude). Moderation hypothesis testing model-estimated marginal mean  $\pm$  standard error (SE) for the person-level N450 mean amplitudes adjusting for the following covariates: biological sex (female or male), handedness (right-hand dominant or not) and task version (240 or 360 total trials). HS = high sensitivity questionnaire [Alcohol Sensitivity Questionnaire (ASQ)  $Z = -1$ ]; LS = low sensitivity (ASQ  $Z = +1$ ). In the NADrinks panel, the asterisk indicates  $P < 0.005$  for the push–pull contrast at HS. In the alcohol panel, the asterisks indicate  $P < 0.05$  for the push–pull contrast at HS, and  $P < 0.001$  for the push–pull contrast at LS. ASQ score ranges over which these motivational congruency effects hold are shown in Supporting information, Figure S6



**FIGURE 4** P3 mean amplitude ( $\mu\text{V}$ ) as a function of image content and response type, and moderation by self-reported alcohol sensitivity. Objects = non-comestible control liquid images; NADrinks = non-alcoholic beverage images; alcohol = alcoholic beverage images. Data represent 147 individuals. Moderation hypothesis testing model-estimated marginal mean  $\pm$  standard error (SE) for the person-level P3 mean amplitudes adjusting for the following covariates: biological sex (female or male), handedness (right-hand dominant or not) and task version (240 or 360 total trials). HS = high sensitivity [ASQ  $Z = -1$  standard deviation (SD)]; LS = low sensitivity (ASQ  $Z = +1$  SD). In the alcohol panel, the asterisk indicates  $P < 0.001$  for the push–pull contrast at LS. ASQ score ranges over which these motivational congruency effects hold are shown in Supporting information, Figure S7

Additionally, at HS, N450 was significantly larger for NADrinks push than pull.

### P3 amplitude

As shown in Table 3, in the base P3 amplitude model the image content  $\times$  response type interaction was significant, and in the moderation model the omnibus image content  $\times$  response type  $\times$  ASQ score interaction was significant. P3 to alcohol was significantly larger (more positive) for pull than push at LS (Figure 4), supporting hypothesis 3.

## DISCUSSION

Consistent with hypothesis 1, alcohol approach bias increased as a function of decreasing alcohol sensitivity (see Figure 2, Supporting information, Figure S5). Wiers and colleagues reported that alcohol approach bias was moderated by a SNP in the OPRM1 gene [20]. OPRM1 SNPs have been linked to LS [33, 34, 73–75], alcohol cue-induced craving [76, 77] and alcohol cue-induced neural reactivity [78–80]. Thus, the current pattern is consistent with Wiers *et al.* and the broader notion that alcohol sensitivity might reflect a heritable susceptibility to over-attribute incentive salience to alcohol cues.

Consistent with hypothesis 2, as a function of decreasing alcohol sensitivity, alcohol cues requiring avoidance-like responses elicited more conflict (N450) than those requiring approach-like responses; the opposite pattern was observed as a function of increasing alcohol sensitivity (see Figure 3, Supporting information, Figure S6). This dissociation suggests that alcohol cues may activate the appetitive-motivation system in LS drinkers and the defensive-motivation system in HS drinkers.<sup>12</sup> These findings provide in-principle replication of studies showing greater stimulus–response conflict during inhibition of alcohol cue-elicited prepotent responses among high-risk drinkers [15, 16, 81].

Consistent with hypothesis 3, as a function of decreasing alcohol sensitivity, alcohol cues requiring approach-like responses had greater integrated incentive value (P3) than those requiring avoidance-like responses (see Figure 4, Supporting information, Figure S7). In contrast, as a function of increasing alcohol sensitivity, non-alcohol cues (appetitive or not) requiring approach-like responses had greater integrated incentive value than those requiring avoidance-like responses (see Figure 4, Supporting information, Figure S7). Overall, these findings are consistent with previous research showing that P3/LPP is larger when top-down and

bottom-up motivational factors are congruent [39–41, 82–84]. Moreover, the current results clarify previous findings that alcohol images elicit larger P3 among LS than HS drinkers [85–87].<sup>13</sup> Previous studies have used versions of a visual oddball task in which alcohol images were relatively infrequent and required overt affective categorization. These task features tend to equate top-down attention and motivation with the affective content of images, thereby failing to isolate top-down and bottom-up contributions to the P3. Here, use of an overtly neutral classification task and manipulating congruence between top-down and bottom-up motivational features arguably permits the inference that it is the bottom-up component (incentive salience) that drives the differential P3 response to alcohol cues among LS and HS drinkers in other paradigms.

Although potentially surprising at first, the (null) finding that accounting for typical alcohol use and AUD symptomatology does not diminish the effect of individual differences in alcohol sensitivity on behavioral and EEG responses is in keeping with findings from our previous studies [14, 16, 17, 57, 85–87] and with the heterogeneity of mechanisms for alcohol use and AUD [88]. Statistically, this finding can be explained by the fact that, as in our previous studies, ASQ scores were only modestly correlated with heavy or hazardous alcohol use (see Table 2), indicating that substantial variance unique to alcohol sensitivity remains when statistically controlling for alcohol involvement measures. Conceptually, this finding reflects the idea that alcohol use (and AUD) is caused by multiple and heterogeneous biological, environmental and psychosocial factors. For example, alcohol use may be driven by different motives in different people and different motives at different times in the same individual [89–91]. A similar logic applies to differences in the extent to which alcohol use is driven by specific neurobiological mechanisms [92–94], including those described in the ISTA [5, 32]. For these reasons, only a small portion of variance in measures of alcohol involvement may be attributable to incentive salience-related processes. Given that the behavioral and EEG responses examined here are meant to reflect incentive salience-related processes, it is not surprising that accounting for measures of alcohol involvement fails to alter the findings.

### Clinical and theoretical implications

The current findings add to the evidence that LS drinkers attribute greater incentive value to alcohol cues [17, 85–87]. That these effects are evident in emerging adults relatively early in their drinking careers and when accounting for AUD symptoms suggests a potential role for incentive-sensitization in linking LS with AUD risk [3] rather than its consequences. Replicating the current findings in a longitudinal design is an important next step. Some theories suggest

<sup>12</sup>Conflict between top-down goals and bottom-up motivation also could be due to consciously held consumption control goals rather than the task-based goal. Alas, we did not assess whether participants were actively trying to control their consumption of either alcoholic beverages or non-alcoholic drinks (or both) for dietary or other reasons at the time of the baseline laboratory session. In fact, it is conceivable that any consciously held goals related to alcoholic beverage or non-alcoholic drink consumption could contribute to the observed neural conflict signals. Exploring the role of consciously held consumption control goals on approach bias and its neural correlates is an important future direction.

<sup>13</sup>In the current study, when we collapse response type, we also observe a significantly larger P3 response to alcohol but not non-alcohol or non-comestible object images for LS compared to HS (Supporting information, Figure S8),  $M_D \pm SE_D = 1.710 \pm 0.788 \mu V$ ,  $Z = 2.188$ ,  $P = 0.029$ .

that chronic drug use begets more 'stimulus-driven' drug-seeking [95]. To the extent that alcohol approach bias and its neural mechanisms strengthen over time, theories of LS-based risk for AUD can be refined to incorporate the role of incentive-sensitization. To the extent that emergent individual differences in alcohol approach bias endure and contribute to AUD progression, they may be suitable for targeted prevention and intervention efforts (e.g. [96, 97]). Finally, given that training to reverse attentional and approach biases (cognitive bias modification; CBM) can improve AUD treatment outcomes [98–102], additional research incorporating neurocognitive measures (e.g. [103–105]) may aid identification of treatment mechanisms to improve clinical outcomes.

## Limitations

Our findings are tempered by several caveats. First, the sample was relatively homogenous in socio-demographics, so findings may not generalize to emerging adults from ethnic/racial minority groups in the United States or to emerging adults in other countries. Additionally, potential sex differences in approach bias and its neural correlates remain to be examined in future studies. Secondly, the P3 was maximal over occipitoparietal regions, whereas the P3/LPP in traditional picture-viewing tasks tends to be maximal over centroparietal regions [49]. We attribute this discrepancy to partial temporal overlap with the prominent and frontocentrally maximal N450 elicited in this paradigm. Thirdly, the measure of LS used here differs from measures used in the studies that first characterized the LS phenotype [9–12]. Thus, current results might not generalize to LS as indexed by other measures (but note that different LS measures tend to correlate strongly; see [57]). Fourthly, modeling person-level RTs by stimulus and response category may have limited power to detect the hypothesized interaction effect using the omnibus *F*-test, which was not significant. Using the trial-by-trial data would allow stimulus item-specific variance to be modeled explicitly using a random intercept term, giving greater confidence that results do not depend upon the specific stimuli used in a given implementation of the task. Modeling trial-by-trial data represents an important future direction that would permit examination of within-task behavioral and neural response dynamics as well as the relationship between P3 or N450 amplitude and behavior on any given trial [106, 107]. Fifthly, there is considerable debate regarding the types of laboratory paradigms that best translate the tenets of pre-clinical models of the ISTA to humans [6, 108, 109]. The extent to which pulling and pushing a joystick is analogous to cue-elicited approach/avoidance behaviors observed in pre-clinical models is unclear, and it remains to be determined whether homologous neural circuits across species impel these ostensibly different behaviors [32]. Sixthly, there are concerns about low reliability and limited validity of approach bias measures from tasks in which participants respond to ostensibly irrelevant stimulus features [22, 110]. However, it is also possible that inconsistent associations between approach bias and alcohol use reflect that only

some individuals' use is related to cue-reactivity and incentive salience [1–3, 5].

## CONCLUSION

By highlighting individual differences in behavioral and neurophysiological responses to reward-related cues, the current study contributes to ongoing attempts to translate tenets of the ISTA to a human model of addiction risk [6, 108, 109]. The current findings add to growing evidence implicating individual differences in alcohol sensitivity as a candidate indicator in humans of the propensity to over-attribute incentive salience to alcohol cues and consequent susceptibility to alcohol use-related incentive-sensitization [3].

## DECLARATION OF INTERESTS

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## AUTHOR CONTRIBUTIONS

**Roberto Cofresí:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization. **Courtney Motschman:** Conceptualization. **Reinout Wiers:** Conceptualization; methodology; resources; supervision. **Thomas Piasecki:** Conceptualization; funding acquisition; methodology; resources; supervision. **Bruce Bartholow:** Conceptualization; funding acquisition; methodology; resources; supervision.

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