

Predictive utility of the P3 event-related potential (ERP) response to alcohol cues for ecologically assessed alcohol craving and use

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Abstract

Neural measures of alcohol cue incentive salience have been associated with retrospective reports of riskier alcohol use behaviour and subjective response profiles. This study tested whether the P3 event-related potential (ERP) elicited by alcohol-related cues (ACR-P3) can forecast alcohol use and craving during real-world drinking episodes. Participants ($N = 262$; $M_{\text{age}} = 19.53$; 56% female) completed a laboratory task in which they viewed images of everyday objects (Neutral), non-alcohol drinks (NonAlc) and alcohol beverages (Alc) while EEG was recorded and then completed a 21-day ecological momentary assessment (EMA) protocol in which they recorded alcohol craving and consumption. Anthropometrics were used to derive estimated blood alcohol concentration (eBAC) throughout drinking episodes. Multilevel modelling indicated positive associations between P3 amplitudes elicited by all stimuli and within-episode alcohol use measures (e.g., eBAC, cumulative drinks). Focal follow-up analyses indicated a positive association between AlcP3 amplitude and eBAC within episodes: Larger AlcP3 was associated with a steeper rise in eBAC. This association was robust to controlling for the association between NonAlcP3 and eBAC. AlcP3 also was positively associated with episode-level measures (e.g., max drinks, max eBAC). There were no associations between any P3 variables and EMA-based craving measures. Thus, individual differences in neural measures of alcohol cue incentive salience appear to predict the speed and intensity of alcohol consumption but not reports of craving during real-world alcohol use episodes.

KEYWORDS

alcohol craving, alcohol use, biomarkers, ecological momentary assessment, LPP, P300

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1 | INTRODUCTION

The Addictions Neuroclinical Assessment (ANA) framework aims to identify new neuroscience-based clinical assessments that can tailor addiction treatments and interventions based on neurobehavioral risk processes.¹ Incentive salience (IS), one of the three ANA domains, refers to the amount of motivational significance attributed to alcohol/drugs and alcohol/drug-associated cues.² Most proposed IS indices are task-based assessments of alcohol/drug cue reactivity (ACR), including cue-elicited attentional orienting, cue-triggered behavioural approach, cue-provoked subjective craving and cue-elicited neurobiological and psychophysiological responses.³ These manifestations of IS are theorized to promote alcohol/drug craving and use behaviour in individuals' natural environments, where alcohol/drug-associated cues and contexts abound.

One important indicator of construct validity for these IS indices is their ability to predict alcohol/drug craving and use behaviours in the natural environment. Findings in this regard have been mixed.^{4,5} Most studies have tested the predictive utility of IS indices against retrospective self-report measures of alcohol/drug craving and use. Such approaches are limited by social desirability⁶ and recall biases.⁷ Additionally, although some prospective studies have shown that IS indices can predict self-reported quantity or frequency of use prospectively,^{8,9} such measures cannot inform alcohol/drug consumption topographies within use episodes as these unfold in real time.

Rather than asking participants to reconstruct their past experiences of alcohol/drug craving and use behaviours from memory, ecological momentary assessment (EMA) protocols use time- and event-based sampling to record alcohol/drug craving and use as they occur, with near-real-time temporal precision, during participants' daily lives.¹⁰ The resulting records can be used to model not only whether substance use occurred but also use topography, such as rates of consumption and estimated intoxication trajectories within and across episodes.^{11,12} Such fine-grained monitoring of within-episode trajectories is particularly important when studying antecedents to long-term alcohol misuse trajectories in nascent drinkers. Specifically, rapid acceleration of blood alcohol concentration (BAC) levels early in drinking episodes (viz., 'front-loading')¹³ increases the likelihood of blackouts,¹⁴ physical altercations¹⁵ and other hazardous behaviours (e.g., consuming 10+ drinks).^{15,16}

There is increasing evidence of a link between IS and front-loading. IS attribution to alcohol manifests as increased motivation to experience alcohol reward and concomitantly invigorated seeking and drinking behaviour (viz., a state of alcohol 'wanting'). In rodent models, front-loading has been observed to increase progressively (i.e., sensitize) over days,^{17,18} leading to the conclusion that front-loading may index alcohol 'wanting'.¹³ Similarly, the frequency of drinking bouts in a rodent alcohol access session, analogous to the number of drinks consumed and/or rate of intoxication in a circumscribed period in humans, also is considered an index of alcohol 'wanting'.¹⁹ Thus, neural and behavioural indices of IS in humans might predict the likelihood of a front-loading drinking topography during real-world drinking episodes.

The magnitude of the P3 (or late positive potential; LPP) component of the event-related potential (ERP) elicited by alcohol/drug cues

provides a promising index of IS. An extensive literature in experimental psychophysiology has established that the magnitude of the P3/LPP component reflects the incentive-motivational value of sensory stimuli.²⁰ Furthermore, the P3/LPP is enhanced for alcohol/drug relative to control cues among alcohol/drug users relative to non-users^{21,22} and among users with higher relative to lower alcohol use disorder (AUD) risk profiles.^{8,23–25} The P3/LPP elicited by alcohol cues (i.e., AlcP3) has shown strong test-retest reliability over 10 months,²⁶ supporting its use as an index of individual differences in IS attribution.

No prior study has examined whether the AlcP3 is associated with alcohol craving and use topographies in the natural environment. One study reported that individuals with greater ventral striatum activation elicited by alcohol beverage pictures (measured via fMRI) showed both stronger average alcohol craving across a 28-day EMA protocol and stronger associations between craving and subsequent consumption in some contexts.²⁷ Although that study's findings suggest a link between neural indices of IS and ecologically assessed alcohol consumption and craving, its EMA protocol consisted of only two surveys per day (morning and evening) and captured only episode-level alcohol craving and use behaviour. Moreover, the reported association between IS and alcohol use was limited to highly circumscribed situations (i.e., when drinking followed a feeling of low purpose in life). Thus, whether neural measures of IS are associated with differences in drinking or craving topographies within drinking episodes, and the generalizability of any associations to a wider range of drinking contexts, remains unknown.

Here, we related AlcP3 amplitude to both within-episode and across-episode alcohol craving and use behaviour in a large sample of emerging-adult drinkers. Emerging adulthood is a developmental period in which heavy and hazardous alcohol use patterns are most prevalent²⁸ and rates of AUD peak.²⁹ Based on prior work linking greater drug cue-elicited P3/LPP amplitude with increased craving^{30,31} and drug use,^{8,32} we hypothesized that a greater AlcP3 response would predict greater alcohol craving and alcohol use in the natural environment. Moreover, based on prior research suggesting a possible link between IS attribution and front-loading,¹³ we hypothesized that a greater AlcP3 would be associated with a steeper rise in estimated BAC (eBAC) within real-world drinking episodes.

2 | METHOD

2.1 | Participants

Data in this report are from the first wave of 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 online eligibility screening survey. Individuals were invited to the laboratory if they were age 18–20 years, reported at least monthly alcohol use in the past year and ≥ 1 binge-drinking episode (4+/5+ drinks in 2 h 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, detailed inclusion–exclusion criteria and compensation. Eligible individuals were invited strategically to stratify the sample for biological sex and terciles of alcohol sensitivity (important to the larger project from which these data were drawn). The final Wave 1 sample consisted of 318 participants. For this report, data were excluded from participants (i) who completed no EMA assessments ($n = 1$); (ii) whose anthropometric data were missing ($n = 6$); (iii) who reported zero alcohol use episodes across the EMA period ($n = 29$); and (iv) whose EEG recording could not be segmented due to missing event markers ($n = 4$) or included fewer than 10 artefact-free EEG segments per image type for ERP derivation ($n = 24$). Some participants met more than one of these data quality-related exclusion criteria. Table 1 summarizes the sociodemographic characteristics of the final analytic sample ($N = 262$).

2.2 | Materials

2.2.1 | Picture viewing task

Participants completed a picture-viewing task similar to those in our previous studies.^{8,23,24} On each of 400 trials, a colour photograph was presented centrally for 1 s. Trials were separated by a jittered inter-trial interval varying from 1 to 2 s. Nonbeverage neutral images (e.g., clothing, tools; ‘Neutral’) from the Internal Affective Picture System³⁵ comprised 80% of trials. Images of alcohol beverages (e.g., beer can, wine glass; ‘Alc’) and nonalcohol beverages (e.g., soft drink can, juice bottle; ‘NonAlc’) from the ‘passive’ subset of the Amsterdam Beverage Picture Set³⁶ each comprised 10% of trials. Participants were instructed to classify beverage images as alcoholic or nonalcoholic via button press as quickly as possible and to withhold responding on all non-beverage trials. Other technical details are provided in [Supporting Information](#).

2.3 | Measures

2.3.1 | EMA measures of alcohol use

Participants were instructed to initiate a diary entry when they consumed the first drink in a drinking episode. Prompted assessments throughout the day (1 prompt per day at user-specified typical wake time before noon plus 4 prompts per day pseudorandomly delivered during equally spaced periods spanning 8 AM to 11 PM) also asked whether alcohol had been consumed in the past 2 h. Reports of drinking via either route triggered periodic follow-up assessments at 30-min intervals.* When drinking was endorsed, the app displayed an

*The route of entry into drinking follow-up assessments (63.4% of drinking follow-up assessments began after a user-initiated first drink report versus 36.6% of drinking follow-up assessments began after alcohol consumption was disclosed on one of the prompted assessments) was not associated with any of the P3 measures, $r = 0.08$ – 0.10 , $p = 0.09$ – 0.19 . Thus, associations between P3 measures and EMA-based alcohol craving and consumption measures are unlikely to be artefacts related to procedural assessment biases.

TABLE 1 Characteristics of final sample used in current analyses ($N = 262$).

	N (%)	M (SD)
Age	–	19.53 (0.76)
Undergraduate student status	255 (97)	
Biological sex (female)	148 (56)	
Gender identity		
Man	105 (45)	
Woman	123 (53)	
Other	5 (2)	
Hispanic/Latinx	20 (8)	
Race		
White/Caucasian	232 (89)	
Black/African American	6 (2)	
Asian	8 (3)	
Native American Indian	2 (<1)	
Multiple	12 (5)	
AUDIT	–	10.30 (5.04)
DSM-5 AUD diagnoses		
None	117 (45)	
Mild	74 (29)	
Moderate	44 (17)	
Severe	24 (9)	
EMA report characteristics		
Drinking moments per user		6.1 (5.6)
Drinking episodes per user		3.0 (2.3)
Drinks per drinking episode		2.9 (1.9)
Momentary cigarette use prior 2 h	28 (1.8)	
Momentary cannabis use prior 2 h	85 (5.4)	

Note: AUDIT = Alcohol Use Disorder Identification Test.³³ DSM-5 AUD Diagnoses were derived from the Mini International Neuropsychiatric Interview (MINI).³⁴ MINI hardcopies and audio recordings were unavailable for three participants; hence, AUD diagnostic information is reported for only $N = 259$ individuals. Participants were not required to respond to the gender identity question and 29 chose not to respond; hence, gender identity information is reported for only $N = 233$ individuals.

infographic reminder concerning standard drink sizes for different beverage types. Following this screen, the number of standard drinks (14 g ethanol equivalents) consumed and time since consumption were assessed during all first-drink reports, drinking follow-ups and random prompts/morning reports in which participants reported any alcohol consumption within the past 2 h. The drink count item presented options corresponding to 0–5.5 in 0.5 increments as well as a ‘6 or more’ option.† These data were combined with anthropometric data gathered at baseline (i.e., weight, sex) to calculate estimated blood alcohol concentrations (eBACs) according to the Matthews and Miller formula, which prior work has indicated correlate strongly with

†This upper limit was endorsed during 1.1% of drinking moments.

actual breath alcohol concentrations (BrAC).³⁷ In rare instances (4.0% of all drinking moments), eBAC exceeded 0.20 g/dL. Because such instances were rare and a possible result of entry error or incomplete physiological absorption, they were excluded. Analyses were limited to moments occurring on the ascending limb of the biphasic BAC time course ($n = 1611$), assessed by change in eBAC from the previous moment. Given drinking episode reports were limited to 2 h to reduce participant burden, descending limb moments were removed ($n = 501$) as they (a) occurred primarily during short, light drinking episodes, (b) were more likely to occur in a subsample of lighter drinkers and (c) occurred infrequently.

2.3.2 | EMA measure of alcohol craving

Craving for alcohol was assessed in every report type with two items ('urge to drink'; 'craving a drink') to which participants responded using a visual analogue scale anchored at 1 (*not at all*) and 7 (*extremely*). Following Nezlak's approach to estimating internal consistency with highly nested data,³⁸ these two items had excellent internal consistency ($\alpha = 0.99$). Thus, a mean of the two items was used as the measure of momentary craving. Three measures were extracted from these craving reports: (1) tonic or baseline craving during nondrinking moments; (2) maximum craving within drinking episodes and (3) changes in craving over the course of drinking episodes. Note that, because maximum craving nearly always occurred at the beginning of drinking episodes, this craving measure likely reflects craving induced by or in anticipation of a priming dose of alcohol and as eBAC was ascending.

2.3.3 | EMA measures of contextual factors

Timestamps for the time of day and the day of the week were generated automatically for each submitted report and used to create a weekend/weekday variable. Weekends were defined as 6:00 PM Thursday to 6:00 PM Sunday (coded 1) whereas weekdays spanned from 6:00 PM Sunday to 6:00 PM Thursday (coded 0). A dummy-coded variable indicated the presence/absence of peers (i.e., a friend, partner/spouse or coworker; coded 1). A dummy-coded variable indicated the current location as in a bar/restaurant (coded 1) or other (coded 0). Additionally, separate dummy-coded variables indicated cannabis and cigarette use since the last recording (coded 1) or not (coded 0).

2.3.4 | Electrophysiological recording, ERP derivation, and P3 component scoring

EEG was recorded at 512 Hz from 32 Ag/AgCl electrodes (mastoid reference) arranged in the expanded 10–20 system. Impedance was kept below 10 k Ω . Offline, the EEG was re-referenced to the average of the two mastoids, resampled at 256 Hz and bandpass filtered

(second-order Butterworth with half-amplitude cut-offs: 0.1–30 Hz). Independent components analysis was used to identify and remove components corresponding to blinks, eye movements and other artefacts. The EEG was then segmented into stimulus-locked epochs and underwent additional artefact detection and rejection routines. EEG data from error trials (i.e., misclassifying beverage type; responding to non-beverage images) were discarded. Additional technical details are in Supporting Information.

P3 mean amplitudes were quantified at nine parietal/occipital electrodes over which the P3 was maximal (see Figure S1), which improves psychometrics.²⁶ As enhanced P3 reactivity to alcohol cues relative to non-drug reward cues is maximal at the start of the picture viewing task and decreases as the task unfolds,³⁹ P3 mean amplitudes were scored using only EEG data from the first half of the task.[‡] The time-window used for P3 quantification is indicated on the grand average ERP waveforms shown in Figure 1. P3 scores exhibited excellent internal consistency ($\alpha = 0.91$ – 0.94) and evinced bivariate correlations with one another ranging from moderate ($r = 0.47$ for AlcP3 with NeutralP3) to large (0.84 for AlcP3 with NonAlcP3). A difference score aiming to capture alcohol cue-specific P3 reactivity also was derived (AlcP3 – NonAlcP3 difference score [ACRP3]) but exhibited poor internal consistency ($\alpha = 0.27$). The residualized ACRP3 score (i.e., residual from regressing AlcP3 on NonAlcP3) exhibited slightly better internal consistency ($\alpha = 0.36$), so it was used in analyses in place of the raw ACRP3 score. Descriptive statistics for all P3 scores are provided in Table 2.

2.4 | Procedure

Upon arrival, participants provided informed consent, sobriety was verified using a breathalyser (Alco-Sensor IV, Intoximeters, St. Louis, MO) and anthropometric data were recorded. Participants were prepared for EEG recording and then completed the picture-viewing task, after which they completed other tasks and self-report measures. See Supporting Information for additional details about procedures during the laboratory visit. At the end of the lab visit, the EMA app was downloaded onto participants' smartphones, and instructions for the EMA period were provided. The 21-day EMA protocol began the following day.

2.5 | Analytic approach

The following P3 measures were tested for predictive utility: AlcP3 amplitude, NonAlcP3 amplitude, NeutralP3 amplitude and the

[‡]Some may argue that P3 mean amplitude measures derived from the entire task would be preferable as indices of between-person variation here, because such measures draw on more trials and are thus more likely to provide a stable person-level estimate of differential alcohol cue reactivity. Consequently, all analyses reported in this manuscript were repeated using P3 mean amplitude measures derived from the entire task rather than only its first half. Effect sizes were generally smaller than those in the original analyses, but effects that were significant in the original analyses also emerged as significant ($p < 0.05$) in these ancillary analyses. Since the pattern of results did not change, we present only the original analyses.

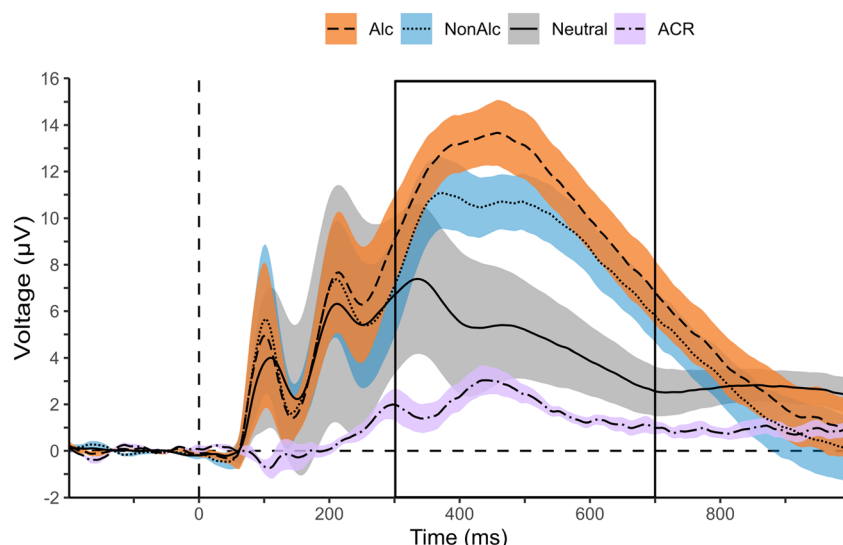


FIGURE 1 ERP waveforms as a function of stimulus category. Cue onset and offset occurred at 0 and 1000 ms, respectively. Grand average ERP waveforms from the first half of the picture viewing task averaged over an occipitoparietal electrode cluster (PZ, P3, P4, P7, P8, PO7, PO8, O1 and O2) are shown for different cue types: alcohol beverage images (Alc; light orange ribbon with dashed line at its centre), nonalcohol beverage images (NonAlc; sky blue ribbon with densely dotted line at its centre) and neutral non-beverage images (neutral; light grey ribbon with solid line at its centre). Also shown is a difference ERP waveform capturing alcohol cue-specific reactivity (ACR: Alc – NonAlc; lilac ribbon with dashed-dotted line at its centre). Line at the centre of each ribbon represents the *M* across participants. Ribbon thickness represents ± 1 SD across participants. The time-window (300–700 ms) used for P3 response mean amplitude measurement is indicated on the plot by the tall rectangular box (black outline, no fill) placed on the x-axis. Data shown are from *N* = 262 persons who contributed to the P3-EMA analyses

TABLE 2 Descriptive statistics for P3 mean amplitude measures (μ V).

Score	M	SD	SME
AlcP3	11.24	4.78	0.66
NonAlcP3	9.39	4.74	0.66
NeutralP3	4.96	2.61	0.25
raw ACRP3 diff.	1.84	2.70	0.81
res. ACRP3 diff.	0.00	2.60	-

Note: On average, 18 ± 3 trials were accepted for AlcP3 and NonAlcP3 and raw ACRP3 difference scores, whereas 145 ± 25 trials were accepted for NeutralP3. The standardized measurement error (SME)⁴⁰ was computed for each score and each person as the SD of the P3 score divided by the square root of the number of accepted trials and then aggregated across people using the root mean square so that it is in the natural units of P3 mean amplitude (μ V). SME could not be computed for the residualized ACRP3 score because, unlike the raw ACRP3 score, the residualized ACRP3 score is not derived directly from the ERPs.

residualized ACRP3 amplitude variable. Each P3 measure's predictive utility was tested while adjusting for other explanatory factors such as biological sex and drinking context (e.g., peers, weekend, recent cannabis or tobacco use). All non-P3 explanatory factors were entered as dummy-coded categorical predictors. The P3 predictor variables were entered as continuous predictors in their natural units (μ V). EMA outcome variables were analysed using generalized linear mixed models (GLMMs). As eBAC, drink count and craving were positively skewed, continuous and bounded by zero, GLMMs predicting these variables used the gamma distribution with a log link function. To make the

eBAC variable appropriate for use with the gamma distribution, 0.0001 was added to all eBAC values as all values must be nonzero and positive. For episode-level analyses (peak eBAC, max drinks and max craving per episode), two-level GLMMs were used in which drinking episodes (level 1) were nested within participants (level 2) with a random intercept for participants. For within-episode analyses (eBAC, drinks and craving over time within episodes), three-level GLMMs were used in which moments (level 1) were nested within drinking episodes (level 2), which were nested within participants (level 3). Within-episode GLMMs included random intercepts for participants and for drinking episodes nested within participants as well as random slopes for episode time.[§] All within-episode follow-up analyses were focused on interactions of P3 scores with change over linear time, and the Johnson-Neyman approach⁴¹ was used to identify the periods within episodes during which estimated slopes differed significantly. Episode-level (i.e., between-episodes) follow-up analyses were conducted in order to examine the relationship between measures of P3 and the presence of front-loading. For current purposes, front-loading was defined as any episode in which eBAC was ≥ 0.080 g/dL within 1 h of drinking initiation (i.e., half the time required to qualify as a 'binge' episode). Two-level binomial GLMMs, with episodes (level 1) nested within participants (level 2) and a random intercept for participant, used P3 measures to predict the

[§]For all within-episode models of eBAC, other than the model with NonAlcP3 as a predictor, the intercept slope correlations for level 2 (drinking episode nested within participant) were set to zero. Intercept-slope correlations at the same level were also set to zero for the models predicting eBAC and cumulative drink total as a function of AlcP3 controlling for the interaction between NonAlcP3 and linear time.

TABLE 3 Summary of P3 score predicting alcohol use and craving across EMA drinking episodes.

P3 measure	Episode level analyses: P3 effects		
	Maximum eBAC	Maximum drink Total	Maximum craving
AlcP3	0.026 (0.007)***	0.020 (0.007)**	0.006 (0.006)
NonAlcP3	0.012 (0.008)	0.008 (0.007)	0.003 (0.006)
NeutralP3	0.026 (0.014)	0.018 (0.013)	0.010 (0.011)
ACRP3	0.049 (0.013)***	0.040 (0.012)**	0.009 (0.012)
P3 measure	Within-episode analyses: P3 × Linear time effects		
	eBAC	Drink Total	Craving
AlcP3	0.045 (0.011)*** ^a	0.029 (0.008)***	−0.004 (0.009)
NonAlcP3	0.048 (0.012)*** ^a	0.033 (0.009)***	−0.016 (0.010)
NeutralP3	0.044 (0.021)*	0.032 (0.015)*	−0.031 (0.017)
ACRP3	0.025 (0.018) ^a	0.015 (0.013)	0.022 (0.015)

Note: Cells show beta coefficients with SE given in parentheses. Because a GLMM with the gamma distribution uses the log link function, the coefficients are on the log scale. Episode-level parameter estimates represent the slope for P3 score from GLMMs controlling for biological sex and the episode-level contextual factor of weekend versus weekday. Within-episode parameter estimates represent the interaction between P3 score and linear time from GLMMs controlling for biological sex and the following moment-level contextual factors: weekend versus weekday, bar/restaurant versus any other location, presence of peers, recent consumption of tobacco cigarettes and recent consumption of cannabis products. All of these factors were entered as dummy-coded categorical predictors. In all alcohol craving analyses, tonic (baseline) craving was controlled for by entering as a person-level predictor the average craving level across all moments outside of alcohol use episodes in which participants also reported no alcohol cue exposure in the past 15 min. Other approaches to controlling for tonic craving produced similar results. ACRP3: residualized difference score (AlcP3 – NonAlcP3). To make the eBAC variable appropriate for use with the gamma distribution, 0.0001 was added to all eBAC values as all values must be nonzero and positive. All alcohol consumption-related models drew upon 1588 observations within 793 drinking episodes across 262 participants. All alcohol craving models drew upon 1468 observations within 731 drinking episodes across 245 participants. See Table S1 for tests of P3 score interactions with Quadratic Time in the within-episode analyses.

^aIntercept/slope correlations for time and drinking episode nested within participant were set to 0 to ensure model fit.

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

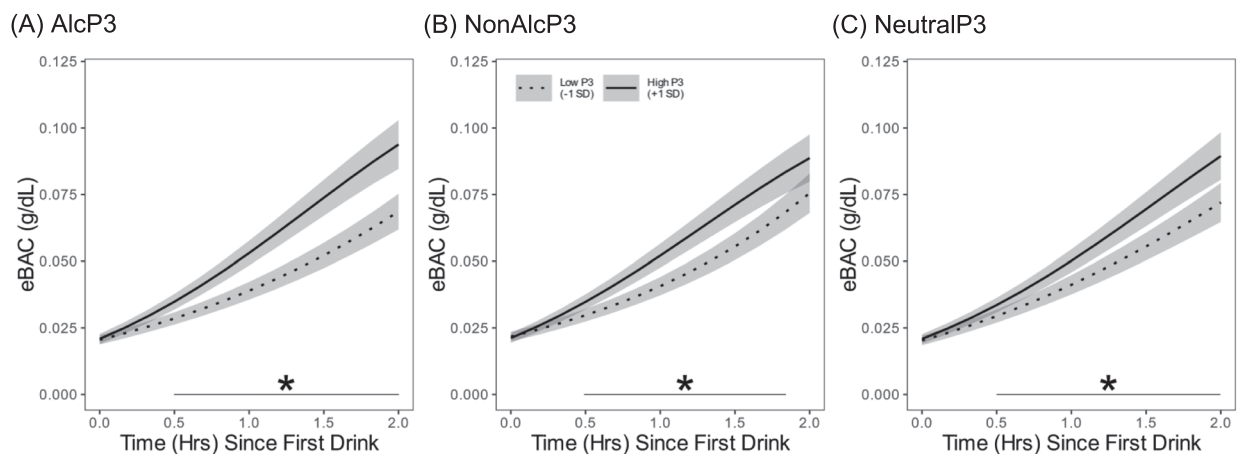


FIGURE 2 Model-estimated eBAC during drinking episodes as a function of time and P3 score. eBAC = estimated blood alcohol concentration; low P3 = mean P3 score – 1 SD; high P3 = mean P3 score + 1 SD. Lines inside each plot depict back-transformed, model-estimated means; the grey area around each line shows ± 1 SE. All graphs represent model-estimated means of gamma GLMMs controlling for biological sex and the following moment-level contextual factors: weekend versus weekday, bar/restaurant versus any other location, presence of peers, recent consumption of tobacco cigarettes and recent consumption of cannabis products. Models for cumulative drink total not pictured as they are very similar (see Figure S2). Horizontal line with asterisk along the x-axis indicates the period of significant difference between eBAC time courses estimated for people with low versus high P3 scores, as identified using the Johnson-Neyman technique.⁴¹ All models based on 1588 observations within 793 drinking episodes.

occurrence of a front-loading episode (coded 1 for front-loading and 0 for no front-loading).

3 | RESULTS

3.1 | Alcohol consumption across episodes

Table 3 shows that AlcP3 and ACRP3 scores were positively associated with max eBAC reached per episode and maximum drink total reached per episode, whereas NonAlcP3 and NeutralP3 scores were not.

3.2 | Within-episode alcohol consumption over time

Table 3 also shows that AlcP3, NonAlcP3 and NeutralP3 amplitudes were positively associated with an increase in eBAC over time (i.e., significant $P3 \times$ Linear Time effects; see Figure 2), whereas

ACRP3 scores were not. ($P3 \times$ Quadratic Time effects are reported in Table S1.) Applying the Johnson-Neyman technique⁴¹ to the $P3 \times$ Linear Time interactions effect on eBAC over time indicated that people with larger compared to smaller P3 scores had a larger eBAC as early as 30 min into drinking episodes. For AlcP3 and NeutralP3 (but not NonAlcP3), these differences remained significant throughout the recording period (2 h; see Figure 2). Models testing cumulative drink total over time produced very similar results (i.e., $P3 \times$ Linear Time, $P3 \times$ Quadratic Time; see Figure S2).

The previous models (Table 3, Figure 2) provide little information concerning the predictive utility of differential neural reactivity to alcohol relative to nonalcohol cues. Moreover, the low reliability of the ACRP3 difference scores undermines their utility for this purpose. Thus, as an alternative approach, we tested models of the AlcP3 \times Linear Time effect on within-episode alcohol use measures (eBAC, drink total) while simultaneously covarying the NonAlcP3 \times Linear Time effect (and person-level and contextual covariates). As shown in Table 4, the AlcP3 \times Linear Time effect on eBAC during drinking episodes was robust to covarying the NonAlcP3 \times Linear Time effect, indicating that neural reactivity to alcohol cues has

TABLE 4 Fixed and random effects from multilevel regression analyses predicting eBAC as a function of linear time and AlcP3 score, controlling for the interaction between NonAlcP3 score and linear time.

	Estimate	SE	p
Intercept	-3.978	0.103	<0.001
Covariates			
Biological sex	-0.087	0.060	0.145
Weekend	0.034	0.051	0.502
Bar/restaurant	0.036	0.050	0.477
Peers	0.163	0.058	0.005
Recent cigarette use	0.048	0.121	0.691
Recent cannabis use	-0.067	0.080	0.402
Hypothesized predictors			
Linear Time	0.509	0.066	<0.001
NonAlcP3	0.001	0.011	0.932
AlcP3	0.011	0.011	0.322
NonAlcP3 \times Time	-0.012	0.009	0.206
AlcP3 \times Time	0.021	0.009	0.021
Random effects			
Dispersion estimate	0.151		
Random intercept SD	0.604 _{episode participant}		
	0.144 _{participant}		
Random slope SDs	0.169 _{time drinking episode : participant}		
	0.184 _{time participant}		
Random intercept-slope correlations	0.00 _{time drinking episode : participant}		
	0.06 _{time participant}		
ICC	0.760		
Fixed Effects R^2 /Total R^2	0.298/0.821		

Note: Because a GLMM with the gamma distribution uses the log link function, the coefficients are on the log scale. All of covariates were entered as dummy-coded categorical predictors. The model is based on 1588 observations within 793 drinking episodes across 262 participants.

predictive utility above and beyond neural reactivity to reward cues generally. This was not the case for cumulative drink total over time (see Table S2). Applying the Johnson-Neyman technique⁴¹ to the AlcP3 × Linear Time interaction effect on eBAC over time indicated that people with larger compared to smaller AlcP3 scores had a larger eBAC as early as 30 min into drinking episodes (see Figure 3). In addition, follow-up analyses (Table 5) indicated that AlcP3 and ACRP3 scores were positively associated with the likelihood of a front-loading episode, whereas NonAlcP3 and NeutralP3 scores were not.

3.3 | Alcohol craving

As shown in Table 3, none of the P3 amplitude measures were associated with maximum craving level per drinking episode, nor with fluctuations in craving over time within drinking episodes. These analyses controlled for individual differences in tonic alcohol craving levels (i.e., moments in which participants reported neither alcohol cues nor alcohol use). These tonic alcohol craving levels also were unrelated to P3

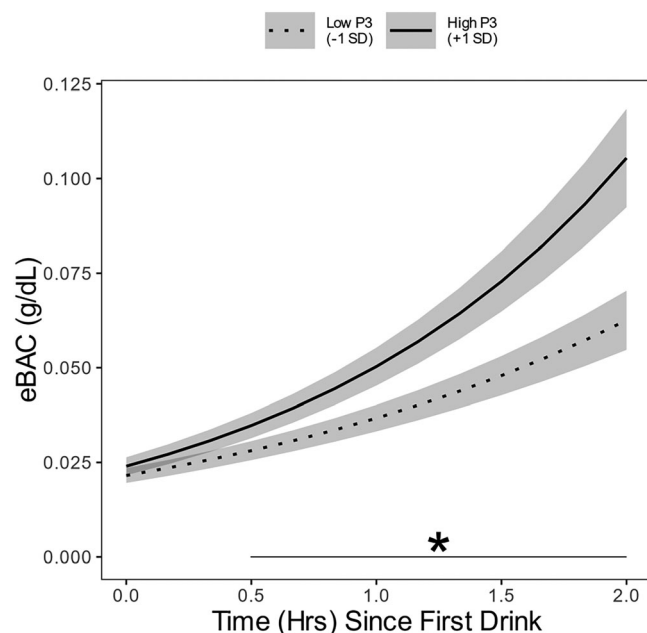


FIGURE 3 Model-estimated eBAC during drinking episodes as a function of time and AlcP3 score, controlling for NonAlcP3 × Time. eBAC = estimated blood alcohol concentration; low P3 = mean P3 score – 1 SD; high P3 = mean P3 score + 1 SD. Lines inside plot depict back-transformed, model-estimated means; the grey area around the line shows ±1 SE. Graph represents model-estimated means of gamma GLMM also controlling for biological sex and the following moment-level contextual factors: weekend versus weekday, bar/restaurant versus any other location, presence of peers, recent consumption of tobacco cigarettes and recent consumption of cannabis products. Line with asterisk along the x-axis indicates the period of significant difference between eBAC time courses estimated for people with low versus high P3 scores, as identified using the Johnson-Neyman technique.⁴¹ Model based on 1588 observations within 793 drinking episodes.

measures, $r_s = -0.05$ – 0.10 , $p_s = 0.12$ – 0.97 . To probe the validity of the craving assessments, we performed a supplemental analysis examining the association between peak craving within an episode and subsequent number of drinks consumed in that episode after the moment of peak craving. This model also included sex, day of the week and tonic/baseline craving as covariates. This analysis confirmed that peak intra-episode craving was associated with consuming a larger number of subsequent drinks in the remainder of the episode, $b = 0.13$, $z = 4.23$, $p < 0.001$ (for detailed model description and full results, see Table S3).

4 | DISCUSSION

Previous studies have reported positive associations between neurophysiological indices of IS attribution to alcohol cues and reports of alcohol use aggregated across drinking episodes.^{8,9} The primary aim of this study was to provide initial evidence regarding the utility of a common neurophysiological index for IS attribution to alcohol cues, the AlcP3, for understanding the within-episode dynamics of real-world drinking episodes among emerging-adult drinkers. Our findings support the utility of AlcP3 for explaining variance in rates of alcohol consumption *within* drinking episodes, such that larger AlcP3 is associated with a more rapid rise in eBAC (viz., front-loading). This relationship is robust to covarying the similar association that emerged between NonAlcP3 and eBAC within episodes, indicating an explanatory role for alcohol cue-specific neural reactivity. People with larger AlcP3 or ACRP3 also were found to engage in more intense alcohol use *across* drinking episodes, consistent with previous studies showing that people who report engaging in front-loading within drinking episodes also report heavier and more hazardous alcohol use across drinking episodes.^{15,16} Thus, the hypothesis that larger AlcP3, as an index of alcohol cue IS, should predict greater alcohol use in the

TABLE 5 Summary of P3 score predicting classification of EMA drinking episodes as ‘front-loading’ episodes.

P3 measure	Episode level analyses: P3 effects ‘Front-loading’ episode vs. not
AlcP3	0.070 (0.025)**
NonAlcP3	0.042 (0.025)
NeutralP3	0.070 (0.043)
ACRP3	0.104 (0.044)*

Note: Cells show beta coefficients with SE given in parentheses. Because a GLMM with the binomial distribution uses the logit link function, the coefficients are on the logit scale. Parameter estimates represent the slope for P3 score from GLMMs controlling for biological sex and the episode-level contextual factor of weekend versus weekday, both as dummy-coded categorical predictors. ACRP3: residualized difference score (AlcP3 – NonAlcP3). The models are based on 793 drinking episodes across 262 participants. Front-loading was defined as any episode in which eBAC was ≥ 0.080 g/dL within 1 h of drinking initiation (i.e., half the time required to qualify as a ‘binge’ episode). Given this criteria, 108 episodes were identified in which front-loading occurred.

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

natural environment was confirmed, including the specific prediction of greater front-loading. In contrast, our results did not support the hypothesis that larger AlcP3 should predict greater alcohol-primed craving in the natural environment.

4.1 | On the relationship between alcohol cue IS and alcohol use behaviour

Evidence from both humans and other species supports IS as a neural mechanism in alcohol use behaviour.^{3,13} Here, greater IS attribution to alcohol cues in the laboratory predicted greater front-loading of alcohol within drinking episodes in the natural environment. Front-loading is thought to reflect the motivational impetus to experience alcohol reward (viz., alcohol 'wanting'). Behaviourally, such an impetus could arise from the chaining of cue-elicited responses alone. For example, the smell of the beverage or the sight of the beverage container might elicit reaching for and handling the container, increasing the likelihood of sipping. In turn, the sensations produced by an initial sip (viz., orosensory and other interoceptive cues) might stimulate larger or longer sips or a rapid succession of sips from the container before it is put down, at which point the cycle can repeat. The ability of alcohol cues to drive this cycle depends on individual differences in IS attribution to alcohol cues (which is in part a function of the extent to which sensitization has taken place across the individual's alcohol use history).³

Individual differences in the relevance of IS to alcohol use are consistent with the contemporary consensus view that heterogeneity in the clinical presentation of alcohol and other substance use disorders (AUD/SUD) entails heterogeneity in their etiological (causal) mechanisms.¹ Any given theorized mechanism (e.g., incentive sensitization, hedonic allostasis) may account for only a subset of AUD/SUD risk phenotypes. Our prior work has found that AlcP3 is selectively associated with trait-like lower sensitivity to the acute effects of alcohol (LS), an established AUD risk phenotype,⁴² rather than being associated with reports of heavier or more hazardous alcohol use aggregated across drinking episodes.^{8,43} In keeping with that prior work, in the present study, AlcP3 was not associated with reports of alcohol use aggregated across drinking episodes in the month preceding the lab visit (see Table S4). Furthermore, our prior EMA studies of alcohol use in the natural environment have found that people with the LS phenotype are more likely to engage in front-loading.^{11,44} Taken together, our body of work strongly suggests that, with respect to heterogeneity in AUD risk phenotypes, the neural mechanism of IS may account for the LS phenotype at the between-person level and front-loading, as an LS-typical drinking pattern, at the within-person level.

Nonetheless, since there was limited temporal separation between brain and drinking behaviour measurements in the present study (i.e., EMA of alcohol use began the day following measurement of AlcP3), there are at least two possible explanations for the observed brain-behaviour association. First, trait-like individual differences in the propensity to attribute IS to alcohol/reward cues,⁴⁵ which entail individual differences in mesocorticolimbic dopamine system structure and/or function, may predispose individuals to within-

episode alcohol consumption patterns like front-loading because these patterns more rapidly expose the brain to higher ethanol concentrations and their known pharmacological effects,⁴⁶ including dopamine release across the mesocorticolimbic system. This account specifies the direction of causality as brain \rightarrow behaviour. Second, a history of repeated front-loading may 'stamp in' IS attribution to antecedent environmental stimuli (i.e., cues like the sight, smell and taste of alcohol beverages) because more rapid brain exposure to higher ethanol concentrations (and thus pharmacological effects) shortens the lag between the cue and the cue-predicted outcome, which facilitates their learned association. This account specifies the direction of causality as behaviour \rightarrow brain. A long-term prospective study involving AlcP3 measurement in alcohol-naïve youth would be necessary to distinguish these two causal accounts. Applied to such a study, the brain \rightarrow behaviour account predicts that alcohol-naïve youth with larger compared to smaller AlcP3 before alcohol use onset will be more likely to engage in front-loading once they have initiated alcohol use. The behaviour \rightarrow brain account instead predicts that AlcP3 measured in alcohol-naïve youth will fail to forecast their later drinking patterns. These two accounts might not be mutually exclusive, and alternative accounts posit a bidirectional or cyclic relationship.³ Conclusively determining the direction or nature of causality in humans is challenging, but the ongoing prospective study from which these Wave 1 data were drawn ultimately will permit us to assess how changes in alcohol involvement between annual assessments influence the AlcP3.

4.2 | On the relationship between alcohol cue IS and alcohol craving

Prior work has linked larger alcohol/drug cue-elicited P3/LPP amplitude to greater cue-induced subjective craving for alcohol/drugs in the laboratory environment,^{30,31} and lab-based measures of craving reactivity have been shown to predict craving in the natural environment captured via EMA.⁴⁷ Additionally, individual differences in ventral striatum response to alcohol cues (measured via fMRI) have been shown to correlate with person-level, EMA-based measures of alcohol craving. Thus, the null findings in the present study are unexpected and could be considered problematic for the incentive sensitization theory of addiction.²

However, several factors specific to this study likely influenced our failure to find this predicted association, and thus, the present finding should not be considered conclusive. First, meta-analysis indicates that the average size of the correlation between P3/LPP amplitude and craving is modest in size ($r = 0.26-0.46$) and might more easily be observed when cue exposure induces high rather than low intensity craving.⁴⁸ As reported elsewhere,⁴⁴ cue exposure induced only modest increases in craving in this sample, especially outside of drinking episodes, likely because 73% of the sample endorsed only mild (or no) AUD symptoms. Future studies should test for this predicted association among individuals more likely to experience stronger craving reactivity to alcohol and its cues (e.g., people with severe AUD).

Second, unlike in lab-based studies, obtaining ‘pure’ measures of tonic (baseline) alcohol craving (i.e., craving not provoked by cues or drinking) with EMA can be challenging. Participants might not always correctly recall or be consciously aware of cue exposures, which would be expected to influence tonic craving and thereby add noise to craving reports. Moreover, alcohol craving during drinking episodes likely represents a mixture of contributory factors beyond IS attribution to alcohol reward and its cues, factors that generally are not present when neurophysiological cue reactivity is assessed. For example, alcohol consumption may evoke conscious craving directly or indirectly via its psychopharmacological effects. Additionally, satiety signals may emerge as the drinking episode progresses that dampen conscious craving and/or IS. Furthermore, attribution or labelling of certain thoughts and feelings as craving or desire for alcohol may vary between and within individuals. Thus, the likely small portion of the variance in conscious craving that is attributable to IS might be masked by other contributory factors.³

Finally, neural indices of IS attribution to alcohol cues may relate to conscious craving for alcohol only in some situations. For example, when alcohol beverages are readily available for consumption, IS attribution to alcohol beverage cues may translate into cue-triggered self-administration behaviour in the absence of craving.⁴⁹ Thus, neural indices of IS attribution to alcohol cues might be found to predict alcohol use but not craving. However, one might see neural indices of IS attribution to alcohol cues predict alcohol craving outside of drinking episodes, in situations when alcohol cues attract attention and activate automatic approach tendencies that are thwarted by immediate situational constraints, including the non-availability of alcohol for consumption.³ In another large EMA study using a similar design, we found that the LS phenotype was unrelated to craving intensity during drinking episodes.¹¹ Analysis of data from the non-drinking moments in the same study found consistent evidence that contexts and subjective states statistically related to drinking were accompanied by small-magnitude elevations in self-reported craving and that this association was larger among LS drinkers.⁵⁰ It is possible that neural indices of IS will emerge as better predictors of cued craving in the absence of drinking when cued wanting may be more subtle but better isolated from other instigators. This is an important question for future research.

5 | LIMITATIONS

Several caveats should be considered when interpreting the present findings. First, the sample was primarily non-Hispanic white, so findings may not generalize to other ethnic/racial groups and must therefore be interpreted as limited in their scope and generalizability. Second, the ability to detect associations with ACRP3 scores was limited by their poor reliability, as we cautioned in our prior work.²⁶ There also are several limitations inherent to the EMA protocol. For example, in efforts to limit participant burden, queries during drinking reports ceased 2 h following the initiation of a *first-drink report*. As a result, the full scope of drinking during episodes likely was not captured. Additionally, eBACs are less accurate than objective

measurements of alcohol intoxication such as BrAC.³⁷ eBACs and standard drink counts used in this study do not take into account between-drink variation in ethanol concentration and volume, consumption of other foods and liquids during drinking episodes, bodyweight fluctuations across days in the EMA period and between-person variation in alcohol pharmacokinetics (beyond variance contributions of bodyweight and biological sex). Finally, the frequency of exposure to alcohol use-associated cues and contexts, as well as the frequency of alcohol use itself during the EMA period, varies in an uncontrolled fashion across participants.

6 | CONCLUSION

The AlcP3 response forecasted the intensity of alcohol use but not craving reports captured during active drinking in the natural environment. These findings are consistent with the notion that the P3/LPP response to drug cues, as an index of IS attribution, reflects a liability towards drug seeking and taking in the natural environment, where drug cues abound. Additionally, they suggest that, in some situations, IS attribution to drug cues may drive drug use behaviour independently of cue-elicited conscious drug craving.

AUTHOR CONTRIBUTIONS

BDB and TMP designed the project and procured its funding. BDB, TMP and RUC formulated the research questions. BDB, CK, RUC and TMP wrote the manuscript together. CK and RUC processed and analysed the data and prepared the figures and tables.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest with regard to this research.

DATA AVAILABILITY STATEMENT

Materials, data and analysis code for this study are available by emailing the corresponding author.

ETHICS STATEMENT

All procedures were approved by the University of Missouri Institutional Review Board. Informed consent was gathered from all participants.

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SUPPORTING INFORMATION

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