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Differential brain responses to alcohol-related and natural rewards are associated with alcohol use and problems: Evidence for reward dysregulation

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Abstract

Multiple theoretical perspectives posit that drug use leads to biased valuation of drug-related reward, at the expense of naturally occurring rewarding activities (i.e., *reward dysregulation*). Recent research suggests that the comparative balance of drug-related and nondrug-related reward valuation is a powerful determinant of substance misuse and addiction. We examined differential neurophysiological responses—indexed with the P3 component of the event-related potential (ERP)—elicited by visual alcohol cues and cues depicting natural reward as a neurobiological indicator of problematic drinking. Nondependent, young adult drinkers ($N = 143$, aged 18–30 years) completed questionnaire measures assessing alcohol use and problems, and viewed alcohol cues (pictures of alcoholic beverages), high-arousing natural reward cues (erotica, adventure scenes), nonalcoholic beverage cues, and neutral scenes (e.g., household items) while ERPs were recorded. When examined separately, associations of P3-ERP reactivity to alcohol cues and natural reward cues with alcohol use and problems were weak. However, differential P3 response to the two types of cues (i.e., *reward dysregulation P3*) showed consistent and robust associations with all indices of alcohol use and problems and differentiated high-risk from lower-risk drinkers. The current results support the idea that the differential incentive-motivational value of alcohol, relative to naturally rewarding activities, is associated with increased risk for substance misuse and dependence, and highlight a novel neurophysiological indicator—the reward dysregulation P3—of this differential reward valuation.

KEYWORDS
alcohol cues, cue reactivity, event-related potentials, natural rewards, reward dysregulation P3

1 | INTRODUCTION

Humans evolved to experience reward from activities that promote their survival (see Lende and Smith[1]). For example, eating,[2] exercising,[3] social interaction,[4] and sexual intimacy[5] are all known to stimulate the neurocircuitry of reward and reinforcement learning, thereby motivating their repetition.[6] Drugs of abuse also engage neural reward systems,[7] thus reinforcing efforts to obtain and consume them. Multiple theories posit that repeated use of drugs can alter the neurocircuitry of reward processing in ways

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that bias attention and motivational systems towards drug pursuit,[7,8] at the expense of other, naturally rewarding activities.[9,10]

Consistent with these perspectives, alcohol use disorder (AUD) has been characterized as a disorder of reinforcement pathology.[11] Three theoretical perspectives—the incentive-sensitization theory,[12] reward deficit models,[13,14] and behavioural economic theory[15]—make complementary predictions in this regard. Yet, researchers have largely failed to integrate these theoretical perspectives in empirical work investigating neurobiological indicators of AUD risk. Here, we investigated whether *differential* neural reactivity to alcohol cues versus cues depicting nondrug rewards—an index of individual differences in *reward dysregulation* (i.e., drug overvaluation)—is associated with young adults' alcohol use and problems.

2 | INCENTIVE-MOTIVATIONAL AND REWARD DEFICIT MODELS OF ADDICTION

The incentive-sensitization theory of addiction[7,12] posits that, in vulnerable individuals, contextual cues signalling drug availability take on the incentive value of the drugs themselves, transforming cues into "motivational magnets"[16] that capture attention, elicit craving and approach, and compel consumption. In preclinical models, the expression of aberrant incentive salience to drug-related cues is evident when, following conditioning of cues with drug delivery, animals approach and even attempt to consume those cues.[17] In humans, incentive salience sensitization of drug-related cues can be observed in the magnitude of users' cue reactivity.[18,19] Among heavy drinkers and individuals with AUD, alcohol cues capture attention,[20,21] promote appetitive approach behaviours,[22,23] elicit exaggerated neurophysiological responses,[24,25] and trigger craving.[19,26]

Whereas the incentive-sensitization theory emphasizes the aberrant incentive-motivational value of alcohol-related cues in AUD aetiology,[27] reward-deficit models posit that risk for drug abuse is conferred by blunted motivational significance of natural (i.e., nondrug) reinforcers. The allostatic model of addiction[13] posits that, with repeated drug use, neural reward pathways become sensitized to drug reward, such that incentive-motivational value of nondrug rewards is attenuated.[28] In contrast, the reward deficiency hypothesis[14,29,30] posits that blunted sensitivity to nondrug-related rewards represents a premorbid *liability* factor for substance misuse (i.e., *reward deficiency syndrome*[14,30]), prompting affected individuals to seek activities, such as drug use, that stimulate the reward system.[31]

In support of these perspectives, various addicted populations demonstrate reduced activation in key reward processing regions, such as the medial prefrontal cortex,[32] orbitofrontal cortex,[10] and the ventral striatum,[33,34] when viewing nondrug rewards.[35] Heavy drug and alcohol users also demonstrate blunted neurophysiological responses to highly arousing pleasurable cues (e.g., erotic scenes; food)[36] and reward-related feedback,[37,38] and lesser inhibition of startle-probe reactivity during viewing of natural reinforcers.[39]

3 | DIFFERENTIAL VALUATION OF DRUG AND NONDRUG REINFORCERS: REWARD DYSREGULATION

Whereas the incentive-sensitization and reward-deficit models emphasize the importance of drug-related and nondrug-related reinforcement, respectively, in the aetiology of addiction, neither of these perspectives directly addresses whether the *differential* valuation of these forms of reward might signify risk for substance abuse. However, behavioural theories of choice,[11,40] value-based decision-making models,[41,42] and computational neuroscience-based models of relative reward value[43] suggest that the relative difference between substance-related versus substance-free reward is critical to addiction aetiology. For example, recent studies using demand metrics and concurrent choice tasks in humans[44,45] and rodents[46,47] demonstrate that greater valuation of drugs over substance-free reward is strongly associated with addiction.[48–50] However, no study has tested whether the extent of *differential* valuation of drug cues versus naturally occurring rewards—as indexed by neurophysiological measures of incentive-motivational value—is a marker of risk for substance abuse and dependence.

Results from previous electrophysiological studies are suggestive in this regard.[36,51,52] For example, Dunning et al.[52] demonstrated that individuals with cocaine use disorder show enhanced event-related potential (ERP) reactivity to cocaine-related cues but blunted reactivity to nondrug-related pleasant cues. Parvaz et al.[51] showed that this profile can be reversed with abstinence. Furthermore, recent work by Versace et al.[53] showed that, compared to smokers who demonstrated relatively high ERP reactivity to both smoking-related cues and to nondrug-related pleasant images, smokers who demonstrated low ERP reactivity to nondrug-related pleasant images but high reactivity to smoking-related cues were more likely to relapse after a quit attempt. Yet, none of these prior studies has quantified the *difference* in neurophysiological responses to drug cues versus naturally occurring rewards as an indicator of substance abuse and dependence.

4 | THE CURRENT STUDY

Prior research has demonstrated the utility of enhanced neural reactivity to substance-related and blunted reactivity to natural reward cues for understanding addiction pathology in cocaine users[51,52] and smokers attempting to quit.[36] In addition, behavioural economics work has shown that greater self-reported valuation of alcohol over substance-free rewarding activities is associated with problematic alcohol use in young adult drinkers.[50] Here, we examined whether the extent of *differential* neurophysiological reactivity to alcohol-related versus natural reward cues (i.e., *reward dysregulation*) is associated with alcohol use and problems in young adults with no history of AUD-like symptoms. *Reward dysregulation* was quantified as the difference in amplitude of the P3 ERP elicited by alcohol-related versus natural reward cues. The P3 (or P300) is known to increase in

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amplitude in relation to the motivational significance or incentive value of eliciting stimuli,[54–56] and enhanced amplitude of the P3 elicited by alcohol cues (ACR-P3) has been shown to predict alcohol use and heavy drinking.[57] In contrast, blunted amplitude of the P3 elicited by natural, nondrug reward cues (Reward-P3) has been demonstrated in AUD[58] and persistent users of nicotine[36] and cocaine.[59]

Following from this work, we hypothesized that the amplitude of the ACR-P3 would be positively associated with alcohol use and problems (H1) and that the amplitude of the Reward-P3 component would be negatively associated with alcohol use and problems (H2). Most critically, we posited that the *difference* in the ACR-P3 relative to the Reward-P3 (i.e., *reward dysregulation P3*) would be more strongly associated with alcohol use and problems (H3i) and, therefore, would better differentiate problem from nonproblem drinkers than either of its constituent components (H3ii).

5 | METHODS

5.1 | Participants

Participants were 156 young adults (ages 18–30 years) recruited from a large, public university and surrounding community via flyers and informational emails. Study candidates were prescreened using a questionnaire; individuals were excluded if they reported any attempts to quit drinking, history of alcohol withdrawal symptoms, or history of head trauma or other neurological disorder. The current report includes data from 143 individuals (see online Supplementary Materials for exclusions), the majority of whom were female (61%), White (88%), university students (79.7%), and relatively young (M_{age} = 21.9, SD = 2.97 years) (see Table S1 for more details). Participants were compensated at $10/h. The University of Missouri's Institutional Review Board approved the study's materials, protocol, and procedures.

5.2 | Measures and materials

5.2.1 | Alcohol use and problems

Participants reported on their typical *alcohol use*, frequency of *binge drinking*, and the largest number of drinks in a 24-h period over the past year (*max drinks*) using items recommended by the NIAAA Task Force.[60] A subset of participants (N = 103; 66%) also reported past-year negative alcohol-related consequences using the Young Adult Alcohol Consequences Questionnaire (YAACQ[61,62]).1 Details on these measures are in the online supplementary materials; Table S2 provides descriptive data from these measures.

To address a secondary goal of the study (testing the problem-drinking classification performance of ACR-P3 and Reward-P3), the subset of participants who completed the YAACQ were categorized as either low/moderate risk (YAACQ score ≤ 15; n = 77) or high risk (YAACQ total score ≥ 16; n = 26) for alcohol problems, applying cut-scores suggested by Read et al.[63]

5.3 | Picture-viewing task

The ACR-P3 and Reward-P3 were elicited in the context of a picture-viewing 'oddball' task[64,65] (see Figure 1). Participants viewed infrequent (4% each) pictures of alcoholic beverages (e.g., beer), nonalcoholic beverages (e.g., milk), adventure scenes (e.g., people skydiving), and erotic scenes (e.g., partial nudity) amid more frequently presented (84%) neutral pictures (e.g., a bus). Images were presented against a black background one at a time in sequences of five, at least four of which were from the neutral category. A total of 100, five-trial sequences (500 total viewed images) were presented, such that participants viewed each type of target image 20 times. To prevent the influence of participants' expectations and anticipatory neural responses, and to ensure that at least three neutral images occurred

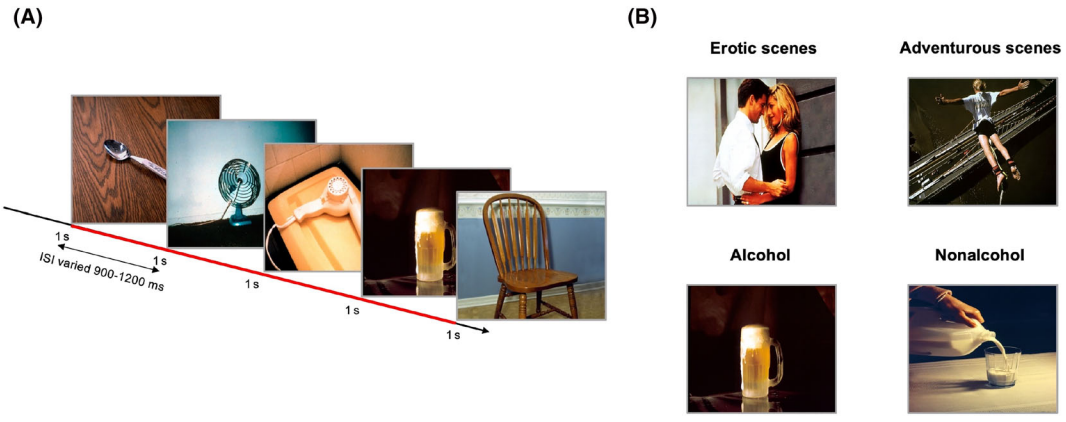

FIGURE 1 (A) Example of a trial sequence from the picture-viewing 'oddball' task, in which more frequent neutral images form a context in which the 'target'/oddball image (e.g., a picture of beer) appears in the fourth position. (B) Exemplars of the oddball stimuli used in the current study: erotic scenes, adventurous scenes, Alcoholic beverages, and Nonalcoholic beverages

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between any two presentations of images from target categories, target images appeared in the fourth or fifth position in the trial sequence and some of the trial sequences consisted exclusively of neutral pictures. Participants categorized each image as "neutral" or "pleasant" by pressing one of two buttons; response mapping was counter-balanced across participants. Images were presented for 1000 ms, followed by a 900- to 1200-ms interstimulus interval that varied randomly. Trial sequences were separated by a 500-ms intertrial interval during which the word "pause" appeared on the screen. Images were selected either from the Normative Appetitive Picture System (NAPS,[66,67] or the International Affective Picture System (IAPS,[68]; see Supporting Information for details).

5.4 | Neurophysiological recording and data processing

The electroencephalogram (EEG) was recorded from 27 Ag/AgCl electrodes fixed in a spandex cap (Electro-Cap International, Eaton, OH) and positioned according the 10–20 system.[69] EEG was digitized at 1000 Hz and band-pass-filtered online at 0.01–0.40 Hz. Scalp electrodes were referenced online to the right mastoid; an average mastoid reference was derived offline. Ocular artefacts (e.g., blinks) were recorded with additional electrodes placed 1 in below and above the left eye and 1 cm lateral to the outer canthi of the eyes, and were removed from the EEG using a regression-based algorithm (see Gratton et al.[70]). Electrode impedances were kept below 10 kΩ. Stimulus-locked epochs of 1300 ms (200-ms baseline) were extracted and then baseline-corrected before rejecting artefact-contaminated trials with voltage ±75 μV; the average number of rejected trials per subject for those subjects included in the subsequent analyses was $M = 3.72$ for alcoholic beverages; $M = 3.52$ for adventure scenes; and $M = 3.19$ for erotic scenes. Accepted trials ranged from 5 to 20 for alcoholic beverages and adventure scenes and 6 to 20 for erotic scenes.

5.4.1 | P3 quantification

Figure 2 presents grand-average waveforms for each picture type; Figure 3 presents grand-average waveforms elicited by alcohol and nonalcohol reward pictures separately for the two problem-drinking risk groups; and Figure 4 presents topographic distribution of the P3 measures. Consistent with previous reports using a similar picture-viewing task,[57,65] P3 amplitude was largest at posterior and occipital electrode sites, especially Pz, and peaked 400–600 ms following image onset. Thus, P3 amplitudes were quantified as the mean voltage 400–600 ms post-stimulus at P3, Pz, P4, P7, P8, O1, and O2, averaged across trials for each image category separately. ACR-P3 was quantified as the mean P3 amplitude elicited by alcohol cues; the Reward-P3 was computed as the average of the standardized (z-scored) mean P3 amplitudes elicited by erotic and adventurous scenes. As an appetitive control condition, we also

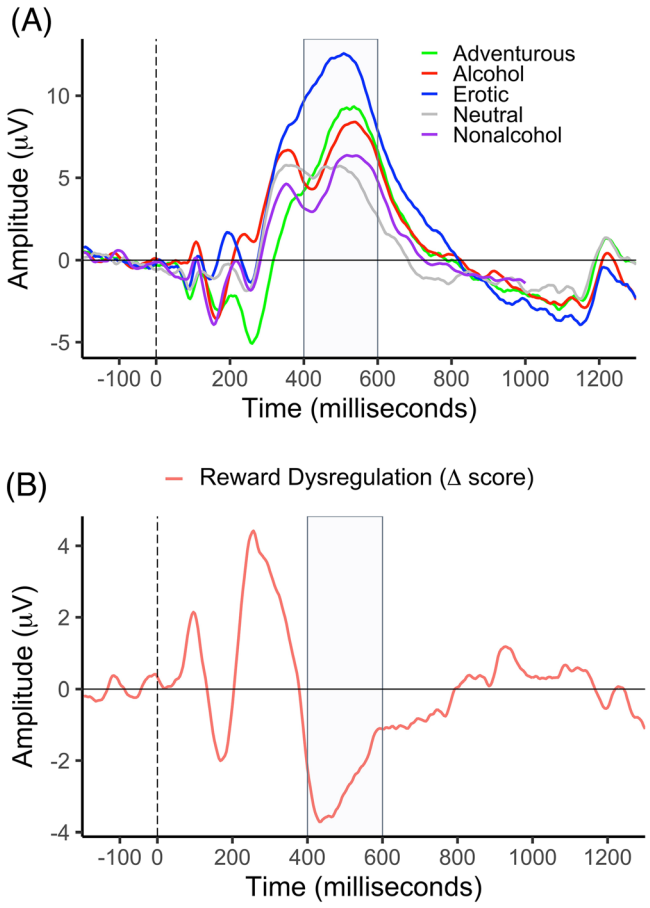

FIGURE 2 (A) Grand-averaged, stimulus-locked ERP waveforms recorded at channel Pz as a function of image type. (B) Difference waveform (ACR-P3 minus Reward-P3) recorded at channel Pz. Shading represents the time window (400–600 ms post-stimulus) used for P3 mean amplitude quantification

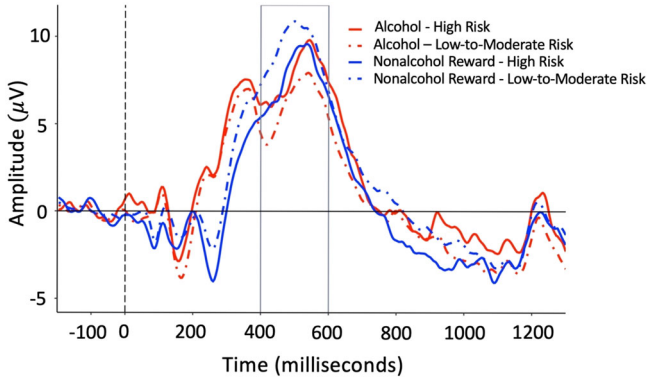

FIGURE 3 Grand-averaged ERP waveforms elicited by alcohol and nonalcohol reward images (recorded at channel Pz), separately for individuals at Low/Moderate Risk (YAACQ score ≤15) and High Risk (YAACQ score ≥ 16) for harmful and hazardous drinking. Shading represents the time window (400–600 ms post-stimulus) used for P3 mean amplitude quantification

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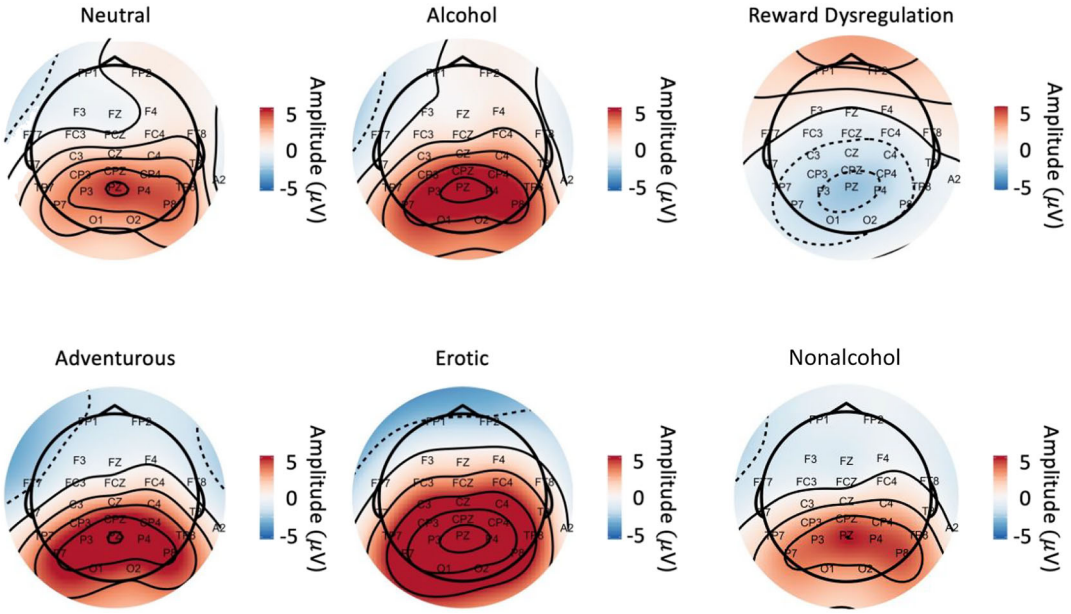

FIGURE 4 Topographic distribution of mean P3 amplitude 400–600 ms post-stimulus as a function of image type

computed the P3 elicited by nonalcoholic beverage images (Nonalc-P3). Both ACR-P3 and Reward-P3 showed adequate Spearman-Brown corrected split-half reliability (*rs* = 0.73 and 0.86, respectively), whereas the Nonalcohol-P3 showed lower reliability (*r* = 0.62). As is common with many ERP difference scores,[71,72] the reward dysregulation P3 (ACR-P3 minus Reward-P3) demonstrated lower reliability (*r* = 0.54), which nevertheless was comparable to estimates of reliability reported for other reward sensitivity neural difference score measures.[37,73,74]2

5.5 | Procedure

Upon providing informed consent, participants completed questionnaires assessing alcohol use and problems, and then were fitted with an electrode cap. Participants completed the picture-viewing task, after which they were shown to a private restroom to clean electrode gel from their face and hair. Finally, participants were debriefed, thanked for their participation, and dismissed.

5.6 | Data analytic approach

Participant exclusions: Two participants withdrew before EEG data collection was completed. Data from four other participants were not properly acquired due to experimenter error (*n* = 2) or equipment malfunction (*n* = 2), and data from seven additional participants were excluded because their EEG contained excessive artefact (<25% valid trials).3 The final sample included 143 participants.

5.6.1 | Regression analyses

To determine the extent to which the ACR-P3, Reward-P3, their difference (reward dysregulation P3), and the appetitive control condition (ACR-P3 minus Nonalc-P3) were associated with typical alcohol use, frequency of binge drinking, and heavy episodic drinking, a series of ordinary least squares (OLS) multivariate linear regression models were estimated using the R statistical package.[75] Distributional properties indicated that the distribution of these outcomes did not deviate dramatically from normality (all skew <2.0 and kurtosis <7.0). Separate regression models—accounting in each case for the effects of age, gender (0 = females; 1 = males), and race (0 = Non-White; 1 = White)—were used to examine associations for the three P3 response variables with each drinking outcome measure. For each drinking outcome measure, two of the regression models included either ACR-P3 or Reward-P3 as the ERP predictor, a third model included both ACR-P3 and Reward-P3 as ERP predictors, the fourth model included the reward dysregulation P3 as the ERP predictor, and a final model included the appetitive control P3 as the ERP predictor. In addition, a series of negative binomial multivariate (NB) regression models4 were estimated in R[75] using the *MASS* package[78] to determine the extent to which each P3 response measure was associated with alcohol problems. Each NB regression model separately examined the association between each P3 response measure and alcohol problems, while accounting for the effects of age, gender, race, and a composite alcohol use/heavy drinking measure created by averaging responses to the typical alcohol use, binge drinking, and max drinks measures (mean *r* value = 0.70; range = 0.65 to 0.77). All models indicated low multicollinearity (all VIFs <2).

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5.6.2 | ROC curves

Another goal of this work was to investigate the classification performance of each P3 response measure for identifying individuals at risk for harmful or hazardous drinking. Comparing the classification performance of the neural response measures to that of a more common self-report measure (e.g., alcohol use) provides validity information for the clinical utility of the neural measures. To address this goal, we estimated a series of receiver operating characteristic (ROC) curves in R[75] using the *pROC* package[79] quantifying how well each P3 measure classifies participants as low/moderate risk versus high risk for alcohol problems based on their YAACQ scores. The area under the curve (AUC) is used to quantify the classification precision and utility of a classifier. Values of AUC can vary between 0 and 1, where AUC = 0.5 indicates random classification performance. Higher AUC values indicate better classification accuracy and diagnostic performance.

6 | RESULTS

6.1 | Associating P3 responses with alcohol use and problems: Regression analyses

Table S3 summarizes bivariate correlations between ACR-P3, Reward-P3 and their difference score variable (reward dysregulation P3) with all drinking-related outcomes. Results from the five OLS regression models associating all P3 measures with drinking-related outcomes are summarized in Table 1. Although the ACR-P3 and Reward-P3 were positively correlated ($r = 0.59$, $p < 0.001$), when tested individually as predictors of alcohol outcomes (Models 1 and 2) they showed small and largely nonsignificant associations with those outcomes. When included together as predictors (Model 3), their relations with alcohol outcomes became stronger in all cases—and in opposing directions—and statistically significant in some. More importantly, the reward dysregulation P3 (Model 4) showed robust and consistent associations with all alcohol outcome measures, consistently accounting for a higher proportion of variance than either of its constituent P3 measures or the appetitive control P3 difference score (Model 5).

6.2 | Classification of problem drinking risk: ROC curve analyses

ROC curves (Figure 5) showed that classification performance for each ERP measure alone was no better than chance. For ACR-P3, AUC = 0.61 ($SE = 0.07$, 95% CI = 0.48–0.74), positive predictive value (PPV) = 0.38, and negative predictive value (NPV) = 0.82. For Reward-P3, AUC = 0.62 ($SE = 0.06$, 95% CI = 0.50–0.74), PPV = 0.35 and NPV = 0.86. However, reward dysregulation P3 successfully differentiated high-risk from low/moderate-risk drinkers (AUC = 0.72, $SE = 0.05$, 95% CI = 0.61–0.83), PPV = 0.40 and NPV = 0.93, and did so nearly as well as a composite alcohol use/heavy drinking measure (AUC = 0.85; $SE = 0.05$, 95% CI = 0.76–0.94), PPV = 0.55 and NPV = 0.92. Indeed, the reward dysregulation P3 and alcohol use/heavy drinking composite variable were similar in their classification performance: AUCs = 0.72 versus 0.85; $D = -1.98$, $p = 0.05$. However, the AUC for the reward dysregulation P3 did not differ statistically from the AUCs for both ACR-P3 (AUCs = 0.72 vs. 0.61; $D = 1.65$, $p = 0.098$) and Reward-P3 (AUCs = 0.72 vs. 0.62; $D = 1.61$, $p = 0.107$), suggesting that the incremental classification precision of the reward dysregulation P3 over its constituents is essential for achieving a classification accuracy and diagnostic performance better than random guessing.

7 | DISCUSSION

Conceptualizing addiction as a brain disease[80] has led researchers to search for neurobiological indicators of addiction vulnerability.[81] The current study examined reward dysregulation P3—a neurophysiological response representing the differential incentive value of alcohol vs. natural reinforcers—as a potential neurobiological indicator of risky drinking and adverse consequences. The notion that differential valuation of drug versus nondrug reward is an indicator of addiction risk is congruent with multiple theoretical perspectives[12–14,82] and with recent neuroimaging research showing that addiction is characterized by enhanced responses to drugs cues, coupled with blunted responses to cues representing natural reinforcers (e.g., previous works[9,10,51,52]).

In line with our hypotheses, ACR-P3 was positively associated with binge drinking and alcohol problems (H1), the latter independently of alcohol use, and Reward-P3 was (modestly) negatively associated with heavy drinking (H2). More importantly, attesting to its potential as a neurobiological indicator of problematic drinking, reward dysregulation P3 showed robust and consistent associations with alcohol-related outcomes, accounting for a greater proportion of variance in those outcomes than its constituent responses (H3i). Furthermore, reward dysregulation P3 showed better utility in discriminating at-risk from lower-risk individuals than did ACR-P3 or Reward-P3 alone (H3ii)—and did so essentially as well as an alcohol use/heavy drinking composite measure, the "gold standard" indicator of risk for alcohol-related problems.[83] These findings are consistent with recent studies demonstrating that a neurophysiological response profile involving low reactivity to nondrug-related, natural reward images and high reactivity to drug-related cues is associated (positively) with risk for relapse among smokers[36,53] and (negatively) with abstinence in cocaine use disorder.[51,52] The current findings extend prior reports by demonstrating that differential incentive valuation of cues for drug and nondrug reward is associated with heavier, more problematic use of alcohol—a substance far more commonly used than either nicotine or cocaine[84]—and is evident in a nonclinical young adult sample. Thus, the current results highlight that the reward dysregulation phenomenon is evident even among a nonaddicted, more typical substance-using population, and suggest that the reward dysregulation profile could be a premorbid liability for addiction rather than a consequence of neuroadaptations resulting from it.

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TABLE 1 Ordinary least squares (OLS) regression and negative binomial (NB) models predicting alcohol use measures from ACR-P3, Reward P3, and Reward Dysregulation P3 quantified by averaging stimulus-locked EEG activity measured at electrodes P3, Pz, P4, P7, P8, O1, and O2

	Alcohol use					Binge drinking					Max drinks					Alcohol problems				
Model	Adj. R^2	AIC	*b*	*SE b*	*p*	Adj. R^2	AIC	*b*	*SE b*	*p*	Adj. R^2	AIC	*b*	*SE b*	*p*	Adj. pseudo-R^2	AIC	*b*	*SE b*	*p*
Model 1: ACR-P3	0.10	1220.4				0.07	624.65				0.06	921.91				0.15	655.58			
Age			−0.35	0.55	0.522			−0.05	0.06	0.385			−0.22	0.19	0.248			0.03	0.02	0.152
Gender			**11.30**	**3.38**	**0.001**			0.53	0.39	0.174			**3.33**	**1.15**	**0.005**			−0.07	0.14	0.603
Race			**10.77**	**5.33**	**0.046**			1.16	0.60	0.055			2.61	1.82	0.155			**0.54**	**0.28**	**0.023**
Alcohol use/heavy drinking																		**0.06**	**0.01**	**<0.001**
ACR-P3			0.41	0.39	0.298			**0.11**	**0.05**	**0.015**			0.10	0.13	0.456			**0.04**	**0.02**	**<0.001**
Model 2: Reward-P3	0.10	1219.6				0.03	630.41				0.08	919.47				0.14	661.45			
Age			−0.51	0.55	0.356			−0.08	0.06	0.235			−0.27	0.19	0.147			0.04	0.02	0.133
Gender			**9.06**	**3.53**	**0.011**			0.28	0.41	0.501			**2.49**	**1.20**	**0.040**			−0.10	0.15	0.516
Race			**12.45**	**5.27**	**0.020**			**1.45**	**0.60**	**0.018**			3.15	1.79	0.081			**0.73**	**0.28**	**0.010**
Alcohol use/heavy drinking																		**0.06**	**0.01**	**<0.001**
Reward-P3			−0.59	0.43	0.168			−0.03	0.05	0.524			−0.25	0.15	0.088			0.01	0.02	0.623
Model 3: ACR-P3 + Reward-P3	0.13	1216.3				0.11	620.08				0.10	916.83				0.16	654.86			
Age			−0.45	0.54	0.409			−0.07	0.06	0.287			−0.25	0.18	0.173			0.03	0.02	0.196
Gender			**8.75**	**3.48**	**0.013**			0.23	0.40	0.568			**2.39**	**1.18**	**0.045**			−0.12	0.14	0.399
Race			**10.93**	**5.24**	**0.039**			1.16	0.59	0.049			2.67	1.78	0.137			**0.61**	**0.28**	**0.030**
Alcohol use/heavy drinking																		**0.06**	**0.01**	**<0.001**
ACR-P3			**1.06**	**0.47**	**0.025**			**0.19**	**0.05**	**<0.001**			**0.34**	**0.16**	**0.036**			**0.06**	**0.02**	**<0.002**
Reward-P3			**−1.25**	**0.51**	**0.016**			**−0.15**	**0.06**	**0.012**			**−0.46**	**0.17**	**0.009**			−0.04	0.02	0.102
Model 4: Reward Dysregulation P3	0.13	1214.5				0.11	618.69				0.11	915.45				0.15	655.53			
Age			−0.42	0.53	0.435			−0.07	0.06	0.240			−0.23	0.18	0.201			0.03	0.02	0.201
Gender			**1.18**	**3.31**	**<0.006**			0.14	0.38	0.717			**2.66**	**1.13**	**0.020**			−0.17	0.14	0.238

(Continues)

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TABLE 1 (Continued)

Model	Alcohol use					Binge drinking					Max drinks					Alcohol problems				
	Adj. R^2	AIC	*b*	*SE b*	*p*	Adj. R^2	AIC	*b*	*SE b*	*p*	Adj. R^2	AIC	*b*	*SE b*	*p*	Adj. pseudo-R^2	AIC	*b*	*SE b*	*p*
Race			**10.61**	**5.17**	**0.042**			**1.23**	**0.58**	**0.035**			2.47	1.76	0.164			**0.65**	**0.28**	**0.020**
Alcohol use/heavy drinking																		**0.06**	**0.01**	**<0.001**
Reward Dysregulation P3			**1.13**	**0.43**	**0.009**			**0.17**	**0.05**	**<0.001**			**0.39**	**0.15**	**<0.009**			**0.05**	**0.02**	**0.010**
Model 5: ACR-P3-Nonalcohol P3	0.09	1221.0				0.04	629.41				0.07	921.18				0.15	658.18			
Age			−0.40	0.55	0.470			−0.07	0.06	0.286			−0.22	0.19	0.234			0.04	0.02	0.228
Gender			**10.59**	**3.34**	**0.002**			0.34	0.39	0.378			**3.12**	**1.14**	**0.007**			−0.17	0.14	0.252
Race			**11.08**	**5.34**	**0.040**			**1.30**	**0.61**	**0.034**			2.51	1.82	0.169			**0.69**	**0.28**	**0.016**
Alcohol use/heavy drinking																		**0.06**	**0.01**	**<0.001**
ACR-P3-Nonalcohol P3			0.35	0.49	0.471			0.07	0.06	0.242			0.19	0.17	0.263			0.04	0.02	0.059

Note: Analyses were based on $N = 143$, except models using alcohol problems as the outcome, which were based on $N = 103$. ACR-P3 = P3 amplitude elicited by alcohol cues; Reward-P3 = P3 amplitude elicited by natural reward cues; Reward dysregulation P3 = ACR-P3 minus Reward-P3; alcohol use = product of typical drinking frequency (number of drinking days/week) and drinking quantity (number of drinks/drinking day) in the past year; binge drinking = number of days in the past year in which four or more (women) or five or more (men) drinks were consumed within a 2-h period; max drinks = largest number of drinks consumed within a 24-h period in the past year; alcohol use/heavy drinking = composite created by averaging responses to alcohol use, binge drinking, and max drinks measures. Adj. R^2 = adjusted proportion of variance explained (McFadden's adjusted pseudo-R^2 for NB models). AIC = Akaike's information criterion; *b* = unstandardized regression coefficient; *SE b* = standard error for *b*. All regression coefficients (and associated *SE*, test statistics, and *p* values) significant at the level of $p < 0.05$ are shown in bold.

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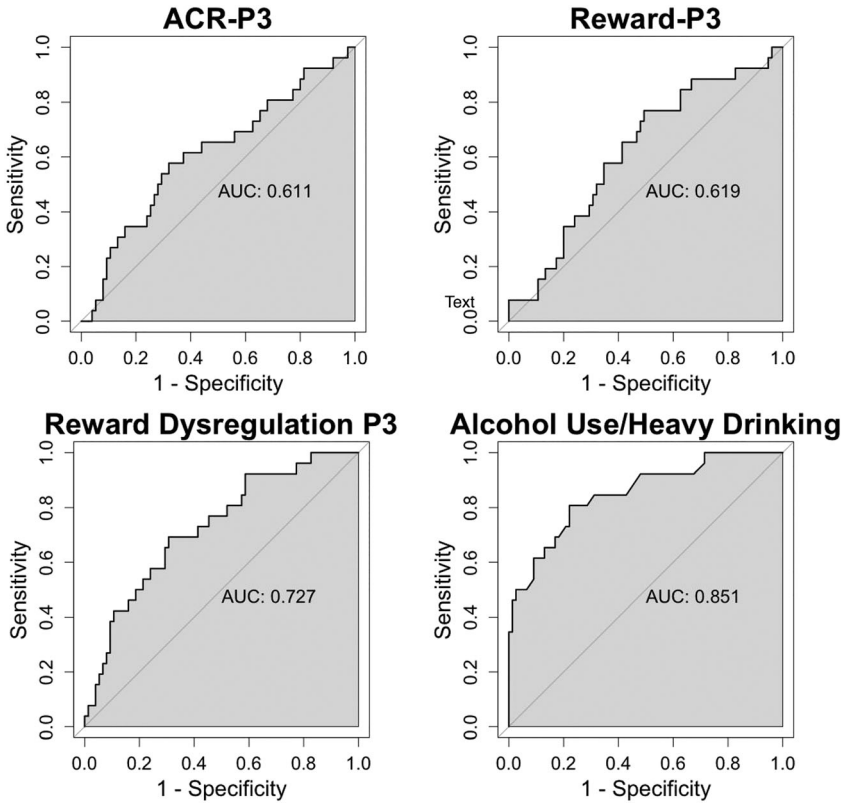

FIGURE 5 Receiver operating characteristic (ROC) curves summarizing classification precision of P3 response measures and a composite alcohol use/heavy drinking measure in discriminating individuals at risk for harmful and hazardous drinking. ACR-P3 = P3 amplitude elicited by alcohol-related cues; Reward-P3 = P3 amplitude elicited by natural reward cues; Reward dysregulation P3 = differential P3 reactivity to alcohol and natural reward cues. Alcohol use/heavy drinking = composite created by averaging scores from typical alcohol use, binge drinking and heavy episodic drinking measures. AUC = area under the curve; the diagonal line denotes an AUC value of 0.5, which indicates random classification performance

The current findings have implications for understanding the utility of neurophysiological indicators of addiction risk. Although ACR-P3 and Reward-P3 were moderately positively correlated ($r = 0.59$, $p < 0.001$), the regression model including both as simultaneous predictors showed that both were independently associated—but in opposite directions—with alcohol use and heavy drinking. These findings underscore the importance of accounting for multiple sources of variance in reward-related processing when interpreting neurophysiological responses to drug-related stimuli[53]; such responses share variance with a general responsivity to reward, but their unique utility for elucidating substance use and related phenomena depends on parsing that shared variance, thereby allowing nonshared variance to contribute uniquely to variance in substance use-related outcomes.

Additionally, both ACR-P3 and reward dysregulation P3 accounted for unique variance in alcohol-related problems beyond that associated with alcohol use. This finding suggests that neurophysiological measures can provide incremental utility for clinical diagnosis and vulnerability assessment, beyond that provided by self-report measures of behaviour.[85–87] This finding also suggests that although the incentive salience of both drug-related and natural reward cues can be affected by substance involvement,[13,88] substance use does not wholly determine neural indicators of the incentive salience construct or fully mediate their associations with criterion measures. This suggests the possibility that a tendency to attribute aberrant incentive salience to drug-related versus natural reinforcers might antedate heavy substance use, perhaps reflecting a (possibly heritable) neurobiological vulnerability.[89,90]

This possibility is directly posited by the reward deficiency hypothesis,[14] which holds that a genetically determined deficiency in dopamine DRD_2 receptor availability[30,91] causes blunted neural reward system responding to natural rewards. This deficient reward response is thought to predispose affected individuals to seek out drugs of abuse. Alternatively, the allostasis model[13] holds that persistent, heavy substance use causes neuroadaptations that alter the balance of responding by reward neurocircuits, such that those circuits become hypoactive in the absence of drugs and hyperactive to drugs and drug-related cues.[8] Thus, both models posit blunted responding to natural reward as key to understanding the attribution of incentive salience to drug-related cues,[36,53] but they differ in ascribing a causal role for this blunted responding to persistent drug use (allostasis) versus premorbid dopamine DRD_2 receptor availability (reward deficiency). Given the relative youth of the current sample and their nonclinical status, and the finding that reward dysregulation P3 amplitude accounted for incremental variance in alcohol-related problems (beyond that associated with heavy drinking), it seems likely that at least part of the reward dysregulation P3 phenotype reflects premorbid vulnerability rather than neuroadaptations resulting from heavy alcohol use. It is important to underscore, however, that the design of the current study does not permit direct inferences regarding the aetiology of the reward dysregulation P3 response.

Future work should seek to clarify the ontogeny of the reward dysregulation P3 phenotype using longitudinal and/or genetically informed designs (i.e., twin studies). Indirect evidence has been provided by several lines of work. For example, reduced dopamine D_2 receptor availability is associated with cue-elicited, dopamine-

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mediated activation of brain reward regions,[92] cue-elicited craving,[92,93] and AUD severity.[94] Preclinical research offers complementary evidence in that dopamine D_2 receptor knock-out rats show increased incentive motivation for drugs,[95,96] and reduced dopamine D_2 receptor availability modulates alcohol preference[97] and is present in rats who attribute incentive value to reward-predictive cues (i.e., expressing the *sign-tracking* phenotype; see Flagel et al.[98] and Tournier et al.[99]).

In addition to the inability to resolve the aetiology of the reward dysregulation P3 response, the current study's design was limited in other ways. First, although P3 amplitude is a clear indicator of the incentive-motivational significance of eliciting stimuli,[54,56] its neural generators are diffuse[100] and modality-dependent,[101] and although some work is suggestive of such a link,[102] the extent to which P3 amplitude reflects engagement of reward neurocircuitry is not clear. Future research using combined ERP and fMRI paradigms[102] can help to resolve whether the Reward-P3 and ACR-P3 share neural sources in the reward processing circuits known to underlie reward deficiency and/or incentive salience attribution. Second, the sample was homogenous in terms of demographic characteristics, and the picture stimuli used to evoke reward-relevant brain responses were limited in number and content. Future work should examine reward dysregulation P3 and its relation to drinking outcomes in more diverse populations and should expand the types of reward-relevant cues (e.g., food, money, and social intimacy) used to elicit its constituent P3 responses. It also is not clear whether the current findings would generalize to older or alcohol-addicted populations. Finally, future work should seek to evaluate the specificity versus generality of these effects—in particular, whether reward dysregulation P3 indexes risk for alcohol use and problems specifically or is associated with broader, transdiagnostic traits (e.g., externalizing proneness[37]) that also increase risk for alcohol problems.

In conclusion, the current results provide the first evidence that differential valuation of alcohol versus natural rewards (i.e., reward dysregulation) is associated with increased risk for alcohol misuse and problems in a nonclinical sample of drinkers. Findings also underscore the added clinical utility of neurophysiological measures for classifying risk, beyond self-report measures of behaviour. Given evidence that dysregulated response to drug versus natural reinforcers can be reversed,[103] the current results can contribute to development of intervention efforts aimed at reducing the burden of alcohol misuse and its adverse consequences.

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CONFLICT OF INTEREST

The authors declare no competing financial interests in relation to this research.

AUTHOR CONTRIBUTIONS

JSM was primarily responsible for data analyses, contributed to interpretation of the results, and was a major contributor to manuscript preparation. KJJ assisted with data analysis and interpretation and contributed to manuscript preparation. DMM provided funding for the study; DMM and DHM designed the study with help from BDB and made critical revisions of the manuscript for intellectual content. CJP contributed to interpretation of results and provided revisions for intellectual content. BDB assisted with study design, contributed substantially to manuscript preparation and critical revision, and provided the laboratory for data collection.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the 1st author.

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ENDNOTES

[1] The YAACQ was added to the questionnaire battery after data collection had started.

[2] In many situations, a regression residual approach is preferred over a difference score approach when using ERPs as individual difference measures.[71] We essentially adopted both approaches here. Our regression models that include both P3 predictors simultaneously are functionally equivalent to the residual score approach. Also, the most important metric for evaluating a difference score is not its reliability per se, but the extent to which it relates to a theoretically relevant criterion.[74] As our models show, the reward dysregulation P3 is more strongly associated with alcohol problems than either of its constituent P3 responses, supporting its validity as a reliable individual difference measure.

[3] Only five participants were at or near this 25% threshold in any image categories; no participant had only 25% valid trials in multiple image categories.

[4] Overdispersion in the observed distribution of nonnegative count variables is commonly observed in substance use data.[76,77] NB models were found to be more adequate and statistically superior to alternative regression models typically used for modeling count data, including Poisson, zero-inflated Poisson (ZIP), zero-inflated negative binomial (ZINB), Poisson Hurdle (PH), and negative binomial Hurdle (NBH) models.

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