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ARTICLE

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Variants of the P3 event-related potential operate as indicators of distinct mechanisms contributing to problematic alcohol use

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Considerable research has linked relative reduction in the amplitude of the P3 event-related potential (ERP) during cognitive task performance (i.e., Target-P3) with increased risk of alcohol-related problems. A separate literature indicates that a relative *increase* in the amplitude of the P3 elicited by cues signaling alcohol availability (i.e., ACR-P3) also is associated with alcohol use and problems. To date, no research has integrated these seemingly discrepant findings. Here, we aimed to demonstrate that P3 amplitudes elicited in different task contexts reflect distinct domains of functioning relevant to problematic alcohol involvement (PAI), and therefore can inform heterogeneity in the etiology of PAI. 156 emerging adults (61% women; 88% White/Non-Hispanic) completed a mental rotation task and a picture-viewing task while ERPs were recorded. Participants also completed questionnaire measures of trait disinhibition, alcohol use, and alcohol-related problems. Findings from regression analyses indicated that (a) Target-P3 was negatively associated and ACR-P3 was positively associated with a PAI latent variable; (b) the two P3s accounted for unique variance in PAI, beyond that accounted for by recent drinking; and (c) the association between Target-P3 and PAI—but not ACR-P3 and PAI—was statistically mediated by trait disinhibition. The present findings highlight the unique contributions of distinct functional domains associated with disinhibition and incentive salience in the etiology of PAI. Moreover, findings are consistent with a nuanced understanding of the P3 ERP, whereby its specific meaning varies according to the task context in which it is elicited.

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INTRODUCTION

Among drugs of abuse, alcohol is the most harmful to society [1]. The use of alcohol becomes problematic when it leads to acute and/or chronic negative consequences [2, 3], as reflected in the diagnostic criteria for alcohol use disorder (AUD; [4]). Clarifying the factors that give rise to AUD is critical to ameliorating the costly toll drinking exacts on society.

Addiction scientists have long recognized that AUD—and problematic alcohol involvement (PAI) more generally—is highly heterogeneous both phenotypically (i.e., manifest symptoms vary considerably across individuals, and within individuals across time) and etiologically (i.e., there are several neurobehavioral mechanisms thought to facilitate PAI; [5–10]). Accounting for PAI's etiologic heterogeneity requires approaches that can characterize distinct neurobehavioral mechanisms within and across individuals and the shared and unique variance in PAI attributable to those mechanisms. The current study research addressed this goal with respect to two posited PAI mechanisms—disinhibition and incentive salience—represented by different variants of the P3 event-related potential (ERP).

Variants of the P3 ERP as indicators of distinct neurocognitive functional domains

Numerous studies have demonstrated that relative reduction in the amplitude of the P3 (or P300) elicited by infrequent targets in cognitive tasks (i.e., Target-P3) is associated with increased AUD risk [11–14]. Other research indicates that reduced Target-P3 reflects a broad liability for externalizing psychopathology [15–17], a dispositional factor involving deficits in inhibitory control (see also [18]). Evidence from prospective [19] and genetically informed designs [20–22] indicates that reduced Target-P3 antedates the onset of substance misuse and that its associations with this and other externalizing problems largely reflect shared genetic influences.

A separate, emerging literature has identified a different variant of the P3 that appears more specific to PAI. In contrast to Target-P3, the P3 elicited by stimuli signaling alcohol availability tends to be *larger* in heavier compared to lighter drinkers [23, 24] and among individuals at heightened AUD risk [25–30]. Variability in this "alcohol cue-reactivity P3" (ACR-P3) is posited to reflect individual differences [31] in the incentive salience of alcohol-related cues [29, 32, 33]. In theory, such differences are acquired through the repeated pairing of alcohol cues with the experience of alcohol-related reward [34, 35], reflecting neuroadaptations in dopaminergic reward processing circuits (e.g., [36–38]). Although limited data suggest elevated neural reactivity to alcohol images among alcohol naïve youth with substance use disorder in their families [39], variation in ACR-P3 and other indices of cue reactivity is posited mainly to reflect *effects* of personal drinking experience, rather than a premorbid liability for AUD.

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Opposing relations of Target-P3 and ACR-P3 with alcohol problems

The opposing relations that Target-P3 and ACR-P3 exhibit with PAI might seem surprising given that both P3s are variants of the same neurophysiological response. Indeed, prior studies have demonstrated that P3s measured in different cognitive tasks are moderately correlated (e.g., [40–42]), and that variance shared among these "cognitive" P3s relates negatively to trait disinhibition [42, 43]. Related work has shown that P3s elicited by drug-related cues and P3s elicited by cues depicting natural reward correlate positively with one another but in opposing directions with substance use and problems [44–47]—including findings from the dataset on which the current report is based [48].

We argue that these seemingly divergent patterns of findings might be explained in terms of PAI's etiologic heterogeneity [6, 7, 9] and differing influences on P3 amplitude. In general, P3 amplitude reflects the perceived salience (significance) of the eliciting stimuli [49, 50]. Whereas affective images (including alcohol cues) convey salience via bottom-up motivational features, stimulus salience in cognitive tasks is conveyed by top-down relevance to task responding.

Considered within this framework, reduced Target-P3 can be viewed as a disinhibition-related failure to sufficiently attribute (top-down) significance to stimuli requiring goal-directed action, whereas enhanced ACR-P3 reflects over-attribution of (bottom-up) significance to stimuli representing the promise of alcohol reward.

Extending this reasoning, we argue that Target-P3 and ACR-P3 index distinct domains of functioning posited to confer vulnerability for PAI. Specifically, we theorize that Target-P3 reflects the cognitive/executive control domain, whereas ACR-P3 reflects the incentive salience domain [7, 9]. To the extent that Target-P3 and ACR-P3 reflect divergent etiologic mechanisms, both should account for unique variance in PAI. Recent research provides provisional support for this idea, in that ACR-P3 and Target-P3 contribute separately to prediction of relapse in AUD [51].

Study aims and hypotheses

Operating from the general theory that Target-P3 and ACR-P3 represent distinct PAI- related etiologic mechanisms, we hypothesized that (1) Target-P3 would relate negatively and ACR-P3 positively to a latent PAI variable, replicating extant research; (2) Target-P3 and ACR- P3 would mutually suppress one another [51], such that their unique effects would be larger than their zero-order correlations with PAI [48]; (3a) the association between Target-P3 and PAI would be mediated by trait disinhibition, but (3b) the association between ACR-P3 and PAI would be independent of disinhibition; (4a) P3s elicited by infrequent, alcohol-unrelated stimuli across tasks would jointly define a single latent factor (*general P3*), (4b) ACR-P3 would exhibit a robust positive association with this general P3 factor, but separately from this (i.e., independent of its association with general P3), (4c) ACR-P3 would also show a significant positive association with PAI.

MATERIALS AND METHODS

Participants

One hundred fifty-six emerging adults ($M_{age} = 21.8$, SD = 3.0; 61% women; 88% White/Non-Hispanic), recruited from a large public university and its surrounding community, were paid $10/hr for participation. All had prior drinking experience (at least monthly use and at least one binge-drinking episode in the past year) but no history of AUD treatment or quit attempts and no current withdrawal symptoms. Due to the nature of the neurophysiological measures, individuals reporting a history of head trauma resulting in loss of consciousness for >2 min or a neurological disorder were excluded from participation. All procedures were approved by the University of Missouri Institutional Review Board.

Self-report measures

Problematic alcohol involvement (PAI). Four measures of problematic drinking were used to define a latent PAI factor, consisting of: (1) the number of negative consequences arising from alcohol use within the past year, quantified via total scores on the 48-item Young Adult Alcohol Consequences Questionnaire (YAACQ [52, 53]; current study alpha reliability [α] = 0.97);[1] (2) the maximum number of drinks consumed within one drinking episode in the past year and (3) over the participant's lifetime, assessed using items recommended by the National Institute on Alcohol Abuse and Alcoholism [54]; and (4) scores on the Alcohol Problems subscale of the Externalizing Spectrum Inventory (ESI [55]; current study $\alpha = 0.78$).

In addition, current alcohol use, defined as the product of quantity (typical number of drinks on drinking days) and frequency (typical number of drinking days per week) over the past 30 days, was computed for use as a covariate.

Trait disinhibition. The general propensity toward disinhibited behavior was operationalized using the 30-item Disinhibition scale of the ESI (22; current $\alpha = 0.97$), a measure that has been validated against various criterion outcomes [21, 42, 56].

P3 Variants

ACR-P3 along with P3s elicited by other appetitive images (nonalcoholic beverages; high-arousal pleasant scenes) were recorded during a picture-viewing task in which beverage [40 trials; half alcohol, half non-alcohol] [57, 58] and other appetitive images [40 trials] [57] constituted infrequent "oddballs" presented amid more frequent affectively neutral scenes (cf. [26, 48]). A separate visual "oddball" task requiring mental rotation of stimulus images (cf., [11, 16]) was used to elicit the Target-P3 response. Details regarding the two visual oddball tasks and acquisition/processing of EEG data for these tasks are provided in the article Supplement.

Representative ERP waveforms highlighting the Target-P3, ACR-P3, and neutral images P3 are depicted in Fig. 1.

Procedure

Upon arrival, participants provided informed consent and then completed the self-report questionnaires. Next, participants were moved to an EEG recording suite and fitted with an electrode cap. After electrode placement and testing, EEG was recorded while participants completed the two oddball tasks in a counterbalanced order. Following task completion, electrodes were removed, and participants were escorted to a private restroom to wash off the electrode gel. Finally, participants were debriefed about the study's purpose, paid and thanked, and then dismissed. Each session took ~2.5 h.

Data analyses

For the self-report measures, outlying values exceeding the median by ±2.5 interquartile ranges were winsorized to the highest non-outlying value. Confirmatory factor analysis was used to define a latent PAI factor reflecting variance shared among the four alcohol scale measures. Because maximum drinks within the past 12 months and over the lifetime shared method-specific variance, residual covariances between these two indicators were specified a priori. Absolute model fit was evaluated based on chi-square, RMSEA, and Standardized Root Mean Square Residual (SRMR). Relative/incremental fit was evaluated based on the Comparative Fit Index (CFI) and Tucker–Lewis Index (TLI).

Having evaluated this model, further structural equation models were run in which the latent PAI factor was regressed onto both the Target-P3 from the rotated-heads oddball task and the ACR-P3 from the picture viewing task, controlling for current (past month) drinking. Next, the indirect effects of Target-P3 and ACR-P3 on PAI via ESI-Disinhibition were evaluated, also controlling for current drinking levels. Following this, a latent "general P3" factor was modeled using indicators consisting of Oddball-Target-P3, Neutral-Nonbeverage-P3 (NNB-P3), and Nonalcohol-Beverage-P3 (NAB-P3) to test the hypothesis that the ACR-P3 contains two distinct components of variance—one of them shared with P3s evoked by non-alcohol stimuli, and the other uniquely indicative of

[1]The YAACQ was added part-way into the study, and thus scores for this measure were available for 103 rather than all participants.

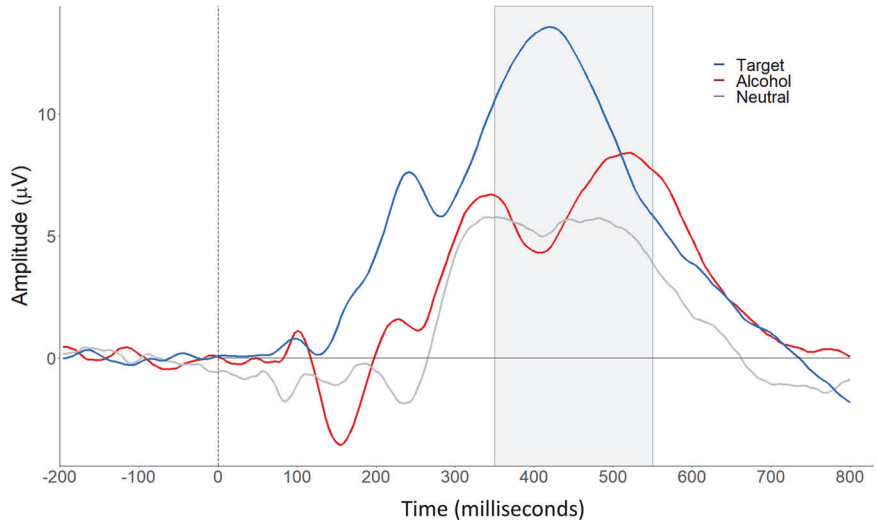

Fig. 1 Waveform plots for variants of the P3 brain response from the picture-viewing and rotated heads oddball tasks. The Target-P3 response is from a different task (i.e., rotated heads oddball task) than the Alcohol and Neutral picture P3s but is presented on the same waveform plot axes to facilitate visual comparisons.

alcohol-cue incentive salience attribution. This hypothesis was tested by regressing the ACR-P3 measure onto both the general P3 factor and the latent PAI factor, with the prediction being that the ACR-P3 would relate independently to each. All analyses included sex as a covariate. The datasets generated and analyzed during the present study are available on Open Science Framework: https://osf.io/9xjt2/.

RESULTS

Co-prediction, and mutual suppression, of Target-P3 and ACR-P3 in relation to PAI

The individual alcohol involvement measures loaded strongly onto the latent PAI variable (YAACQ total, $\lambda = 1.00$;[2] past-year max drinks, $\lambda = 0.52$; lifetime max drinks, $\lambda = 0.54$; ESI- Alcohol Problems, $\lambda = 0.67$). A structural equation model (SEM) in which this latent variable was regressed simultaneously onto the Target-P3 and ACR-P3 variables—which covaried to a moderate positive degree (bivariate $r = 0.42$)—along with current/recent drinking and sex exhibited acceptable fit: CFI = 0.94, TLI = 0.90, $\chi^2(14) = 33.32$ ($p = 0.003$), RMSEA = 0.09, SRMR = 0.07. Consistent with our first hypothesis, this model revealed significant associations—in opposing directions—for both Target-P3 ($\beta = -0.29$, $p = 0.008$) and ACR-P3 ($\beta = 0.25$, $p = 0.009$). Moreover, in line with study hypothesis 2, mutual ("cooperative") suppression was observed: The beta coefficients for Target-P3 and ACR-P3 were each weaker when entered as lone predictors of PAI (βs = 0.15 and −0.19 for ACR-P3 and Target-P3, respectively) than when entered together as co-predictors (βs = 0.25 and −0.29, respectively; see Fig. 2).

Distinct mediating role of trait disinhibition in the Target-P3—PAI association

We then tested for indirect effects of Target-P3 and ACR-P3 on PAI through ESI- Disinhibition. Consistent with hypothesis 3a, a significant indirect effect was observed for Target-P3 on PAI through ESI-Disinhibition ($ab = -0.16$, $p = 0.019$), such that a smaller amplitude Target-P3 related to higher scores on the ESI-Disinhibition scale ($a = -0.25$, $p = 0.015$), which in turn related to greater PAI ($\beta = 0.64$, $p < 0.001$; see Fig. 3). However, in line with hypothesis 3b, there was no evidence for an indirect effect of ACR-P3 on PAI through ESI-Disinhibition ($ab = 0.02$, $p = 0.74$; see Fig. 3).[3]

Demonstrating separate components of variance in the ACR-P3

Next, an SEM was fit in which the ACR-P3 was regressed onto two latent factors—one of them a general-P3 factor defined using Target-P3, NNB-P3, and NAB-P3 as indicators, and the other the PAI factor defined by the four drinking measures (see Fig. 4)—exhibited good fit: CFI/TLI = 0.94/0.91, $\chi^2(25) = 53.87$ ($p < 0.001$), RMSEA/SRMR = 0.09/0.09. Consistent with hypothesis 4a, the three nonalcohol-related P3s each loaded strongly onto the general-P3 factor of this model: λs for Target-P3, NNB-P3, and NAB-P3 = 0.54, 0.66, and 0.75, respectively.[4] Further consistent with prediction (hypothesis 4b), ACR-P3 showed a robust positive association with the general P3 factor ($\beta = 0.78$, $p < 0.001$), and in addition (hypothesis 4c), a significant positive association with the PAI factor ($\beta = 0.15$, $p = 0.035$) attributable to unique variance unrelated to general-P3 (see Fig. 3).

[2]A Heywood case emerged in this model, involving the loading of the YAACQ total score onto the latent alcohol problems factor; thus, the model was re-run fixing this loading to 1.0. Model fit statistics and further modeling analyses utilized this revised model.

[3]In response to a helpful anonymous reviewer comment concerning divergent validity, we also tested indirect pathways through alcohol expectancies as assessed by the Comprehensive Effects of Alcohol Questionnaire (Fromme, Stroot, & Kaplan, 1993). None of this measure's 7 subscales (Sociability, Tension Reduction, Liquid Courage, Sexuality, Cognitive and Behavioral Impairment, Risk and Aggression, Self-Perception) emerged as a significant mediator when used in place of ESI-Disinhibition in the current model (all indirect effect p's > 0.12). For completeness, expectancy, and valuation scores were calculated separately for each of the subscales and tested as mediators; again, no significant indirect effects emerged in any of the 14 models for these scores (all indirect effect p's > 0.11).

[4]Magnitude of loadings and prediction of the ACR-P3 from the general factor did not differ appreciably when including mean P3 response to pleasant pictures [47] as a fourth indicator of the general P3 factor. The λs for Target-P3, NNB-P3, NAB-P3, and Pleasant-P3 in this alternative model were 0.51, 0.59, 0.86, and 0.74, respectively, and the β for prediction of ACR-P3 from the four-indicator general P3 factor was 0.72, $p < 0.001$.

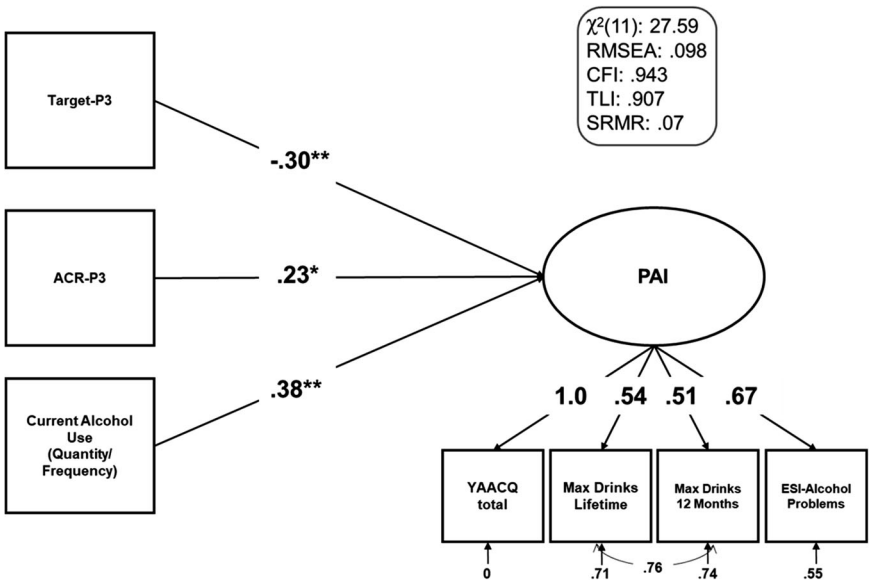

Fig. 2 Opposing associations for Target-P3 and ACR-P3 with problematic alcohol involvement. Target-P3 = amplitude of P3 response to target stimuli in the rotated heads oddball task. ACR-P3 = amplitude of P3 response to alcoholic beverage images in the picture viewing task. PAI problematic alcohol involvement latent factor; loadings of manifest indicators on the latent PAI factor are all significant at $p < 0.01$. Coefficients for Target-P3, ACR-P3, and Current Alcohol Use are regression betas for these measures as concurrent predictors of PAI; sex was included as a covariate in the model, but excluded in the figure for ease of visual presentation; *$p < 0.05$, **$p < 0.01$.

DISCUSSION

Drawing on prior findings establishing two variants of the P3 brain response—Target-P3 and ACR-P3—as indicators of PAI, the present work tested hypotheses arising from the idea that these two P3s index distinct etiologic mechanisms for PAI. Specifically, an extensive body of work indicates that reduced Target-P3 amplitude indexes a general proneness to disinhibitory psychopathology (for reviews, see: [59]). In contrast, the amplitude of the ACR-P3 is reliably enhanced in individuals at risk for or exhibiting alcohol-related problems (e.g., [23–28, 48]). We posited that ACR-P3 reflects a bottom-up affective process elicited specifically by cues for alcohol-inexperienced drinkers, separate from the top-down cognitive process indexed by Target-P3 that relates to general externalizing proneness.

Opposing relations of Target-P3 and ACR-P3 with PAI

One hypothesis suggested by this two-process conceptualization is that these two variants of P3 should exhibit separate associations with PAI. This hypothesis was supported: when included as concurrent predictors, each P3 variant showed significant and opposing associations with scores on a PAI factor. A further hypothesis was that Target-P3 and ACR-P3 would correlate positively with one another—and that this shared variance would operate to dampen (suppress) their distinctive associations with PAI when examined alone. This hypothesis was also supported: the opposing predictive relations for each P3 measure emerged more strongly in a model that included both as predictors of PAI (thereby controlling for their shared variance) than in separate models utilizing one or the other P3 measure as a predictor. This evidence of mutual suppression between Target-P3 and ACR-P3 suggests that heterogeneity is present in each of these predictors, that is, the overlapping variance between Target-P3 and ACR-P3 diminishes their observed relations with PAI, such that when this overlap is accounted for, their unique relationships with PAI become magnified. This finding indicates that the component of variance unique to each P3 indexes a distinct neural process relevant to PAI [60].

Two additional hypotheses focused on examining the constructed network of the two P3 variants. Specifically, we tested whether the variance unique to Target-P3 indexes trait disinhibition, whereas the variance unique to ACR-P3 indexes a separate, PAI-specific process. Supporting the first of these predictions, we found that a measure of trait disinhibition accounted for a significant portion of the observed negative correlation between Target-P3 and PAI. By contrast, no portion of ACR-P3's observed positive correlation with PAI was accounted for by trait disinhibition.

Shared and distinct PAI-related processes indexed by Target-P3 and ACR-P3

A final analysis was performed to test the hypothesis that ACR-P3 taps a separate PAI-specific process, by regressing ACR-P3 onto two latent factors—one of them a general P3 factor defined by Target-P3 along with P3s evoked by nonalcohol-related images, and the other consisting of the PAI factor. This analysis revealed a large positive association for ACR-P3 with the general P3 factor, and separate from this, a small but significant positive association with the PAI factor. This finding indicates that a unique component of variance in ACR-P3, unrelated to variance shared with the general P3 factor, was predictive of some process specific to PAI.

A conceptual interpretation of findings for these two variants of P3 can be advanced based on the broader psychophysiological literature regarding factors contributing to P3 response in different contexts. The P3 is highly ubiquitous, being elicited in any paradigm that requires attention and stimulus discrimination [61], but it is also highly context-dependent, in that its amplitude is influenced by a variety of task parameters [62, 63]. In visual cognitive performance contexts, P3 amplitude has been linked to the engagement of evaluative categorization and/or decision-making processes [50, 64–68]. In such contexts the stimuli themselves are usually abstract (e.g., geometric figures or alphanumeric symbols) and hold no *inherent* significance for research participants; rather, their significance is determined by task demands. By contrast, in picture-viewing tasks, affective visual stimuli are inherently meaningful to participants apart from their task relevance [69, 70]. The common process contributing to P3 amplitude in both types of paradigms is motivational significance

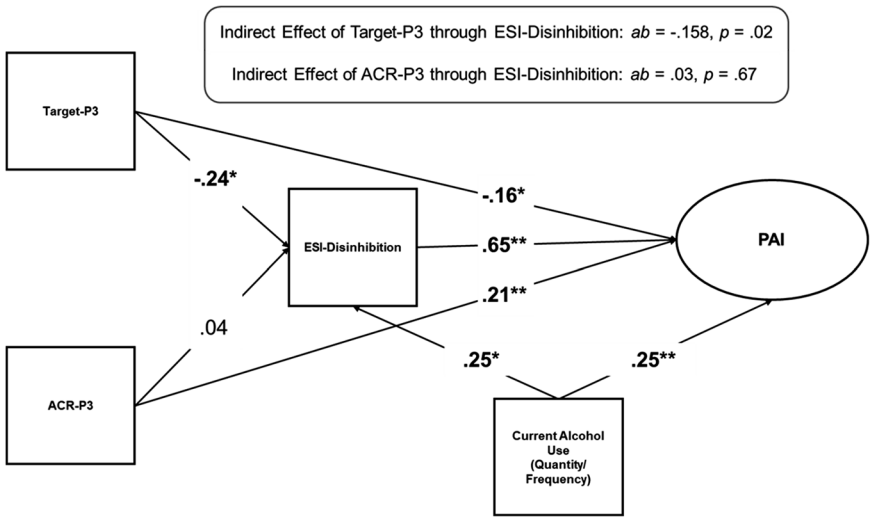

Fig. 3 Indirect effects of P3 variants (Target, ACR) on PAI through trait disinhibition. Target-P3 = amplitude of P3 to target stimuli in the rotated heads oddball task. ACR-P3 = amplitude of P3 to alcoholic beverage images in the picture viewing task. PAI = problematic alcohol involvement latent factor; PAI's manifest indicators are the same as in Fig. 2 but are not depicted to simplify the presentation; sex was also included as covariate predicting PAI but also was not depicted to simply presentation. ESI-Disinhibition = trait disinhibition scale of the externalizing spectrum inventory. Path coefficients for Target-P3 and ACR-P3 as predictors of PAI are derived from models in which the total effect for each predictor was partitioned into direct and indirect effects, with the latter reflecting the predictor's relationship with PAI as a function of its shared association with ESI-Disinhibition. *$p < 0.05$. **$p < 0.01$.

[49, 71], theoretically reflecting phasic responding of the locus coeruleus-norepinephrine system engaging with prefrontal and limbic-associated structures (e.g., anterior insula; [72]) to signal the need to change ongoing action plans [50, 73].

Beyond what they share, several factors distinguishing Target-P3 and ACR-P3 likely contribute to their differential associations with PAI. First, whereas Target-P3 reflects attribution of top-down motivational significance to stimuli requiring a task-relevant response, ACR-P3 reflects attribution of bottom-up motivational significance to stimuli conditioned on alcohol-related reward. The attribution of motivational significance (i.e., salience) is governed by a so-called salience network comprised of anterior insula and anterior cingulate cortices, which function to trigger a switch from default mode to executive control networks when salient stimuli or events are encountered [74–76]. From this perspective, the covariation of Target-P3 amplitude with trait disinhibition likely reflects blunted activation of executive control processes in externalizing-prone individuals by stimuli requiring a top-down, control-related response [42, 43, 59, 77].

To the extent that attributions of top-down versus bottom-up motivational significance are dissociable, variants of P3 reflecting these processes should differentially correlate with trait disinhibition. In support of this view, Patrick and Bernat [77] reported a dissociation in the effects of externalizing proneness on P3 reactivity in a three-stimulus variant of the oddball task used here, in which affective and neutral pictures were presented as rare nontargets along with rare targets (heads) and frequent nontargets (ovals). As is frequently observed [49], affective pictures elicited an enhanced P3 response relative to all other stimuli. High externalizing was associated with reduced P3 response to novel picture stimuli *as a set*, and to target head stimuli as well, but the degree of P3 amplitude enhancement for affective pictures compared to neutral pictures was unrelated to externalizing. The implication is that externalizing-prone individuals were deficient in processing picture stimuli in terms of their relevance to the instructed task (i.e., respond behaviorally or not), but not with respect to their inherent motivational significance (see also [78]).

Another factor distinguishing Target-P3 from ACR-P3 is their respective statuses as liability versus consequence indicators. Considerable research points to reduced Target-P3 as a heritable marker of liability for rather than exposure to substance use problems. For example, Hicks et al. [20] reported that genes alone (i.e., no significant role for environmental factors) accounted for the association between Target-P3 amplitude and externalizing problems in a large sample of adolescent twins, and Yancey et al. [22] likewise reported a genetic basis for the ESI-DIS scale's association with Target-P3. In other work, Joyner et al. [21] used a co-twin control design to demonstrate that Target-P3 amplitude relates to substance use disorder symptoms as a function of liability influences, rather than exposure history. In contrast, ACR-P3 is believed to index individual differences in the incentive salience of alcohol-related cues acquired through direct experiences with alcohol use [29, 32, 33]. This is not to say, however, that liability factors play no role in the acquisition of incentive salience to alcohol cues. Indeed, there are important individual differences in the tendency to attribute incentive salience to reward-predictive cues, which likely have a heritable basis [31, 79].

Finally, whereas Target-P3 amplitude reduction indexes liability for a broad spectrum of externalizing-related problems (of which substance involvement comprises one of many expressions), ACR-P3 is posited to reflect a substance use-specific risk factor. In support of this idea, recent evidence points to a dissociation in the P3 response to substance-related and other reward-related cues [46, 48], indicating that ACR-P3 does not index general sensitivity to reward.

Interestingly, however, Piasecki et al. [80] reported that low sensitivity to alcohol's subjective effects, a known correlate of ACR-P3 [25–30], moderated P3 amplitude elicited by smoking cues in a sample of smokers, suggesting that susceptibility to drug-cue incentive salience attribution may generalize across drugs of abuse.

Findings from the current study have important implications for conceptualizing PAI-related neuropsychological processes and biological indicators of those processes. In a recent theoretical review, Perkins et al. [81] advanced an *ontogenetic* model for understanding the role of neurobiological systems and processes in psychopathology—one that considers the dynamic progression from genotypic propensity (latent liability) to phenotypic expression (manifest symptomatology) across time and periods of development [82–85]. From the viewpoint of this model, neural

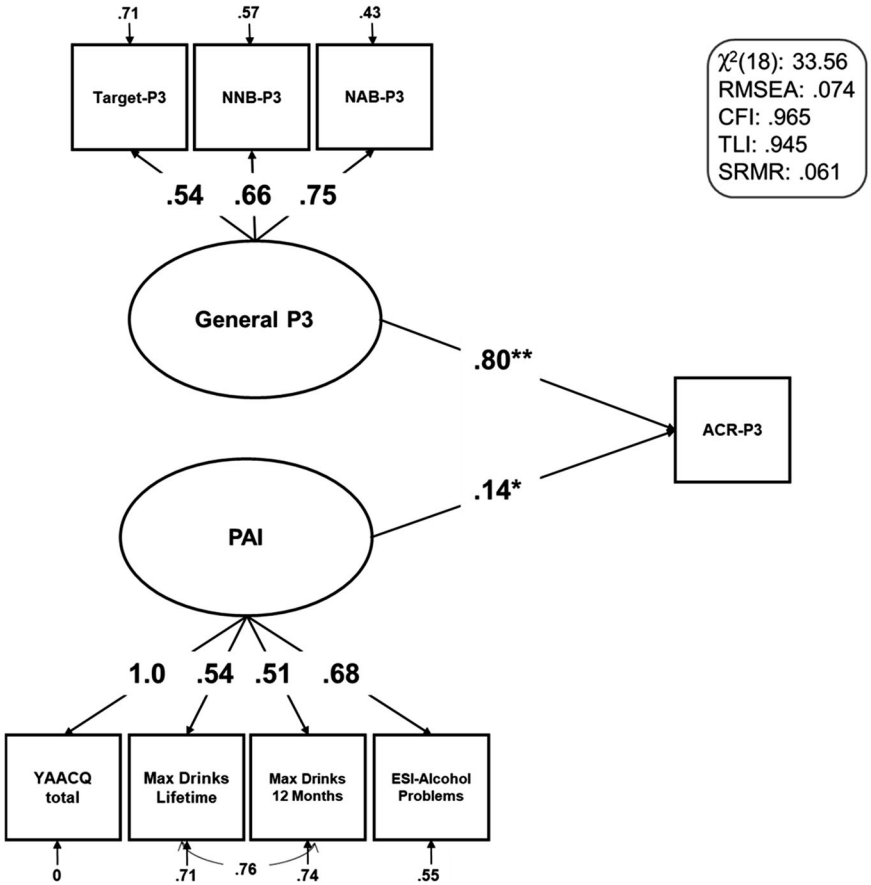

Fig. 4 Model demonstrating a unique association for ACR-P3 with PAI, distinct from its association with a general P3 factor. Target-P3 = amplitude of P3 to targets in the rotated heads oddball task. ACR-P3, NNB-P3, and NAB-P3 = amplitude of P3 to alcoholic beverage images, neutral non-beverage, and nonalcoholic beverage images in the picture-viewing task, respectively. General P3 and PAI = latent factors reflecting variance shared among P3s to nonalcohol images of different types, and among different indicators of problematic alcohol involvement, respectively; loadings of manifest indicators on each latent factor are all significant at $p < 0.01$. Coefficients for General P3 and PAI are regression betas for these latent factors as concurrent predictors of ACR-P3; sex was included as a covariate in the model, but excluded in the figure for ease of visual presentation; $*p < 0.05$, $**p < 0.01$.

and other biological measures can be informative in different ways—as indicators of broad risk (e.g., for impulse control disorders, or phobic-fear disorders), of antecedents to clinical symptomatology (e.g., neural sensitization to reward or punishment cues), of features of active psychopathology (e.g., tolerance or withdrawal symptoms of substance addiction), or of consequences of psychopathology (e.g., alterations in functioning that persist after cessation of heavy drinking or other drug use). The two P3 variants examined here exemplify these nuanced etiological processes: Target-P3 operates as an indicator of broad disinhibitory liability, which in turn confers risk for various types of externalizing disorders [22], whereas ACR-P3 is much more closely tied to the clinical expression of symptomatology in problematic alcohol use.

Limitations and future directions

Despite its many strengths, the current work contained weaknesses that should be addressed in future research. First, while a community sample has advantages in terms of broad applicability and potential generalizability of results, it provides limited representation of the most severe expressions of problematic alcohol use, particularly in terms of physical dependence features such as active withdrawal symptoms and AUD treatment-seeking (which served as exclusion criteria in the current work). Follow-up research is needed to test the reported effects in clinical samples and to examine how alcohol- and nonalcohol-related P3s might change as a function of treatment and recovery. Similarly, the cross-sectional design of the current work precluded characterizing the degree to which associations between Target-P3 and ACR-P3 might change as consumption increases. Presumably, increased consumption would not change any overlap in their heritability but would contribute uniquely to variability in ACR-P3, resulting in a decrease in their covariation overall. Future work using longitudinal designs is needed to examine this possibility. Conversely, refinement of ERP tasks that make alcohol images more "target-" or "oddball-like" would likely increase the proportion of variance in the ACR-P3 related to general externalizing proneness, and correspondingly reduce the proportion related to alcohol-cue incentive salience attribution. Thus, different versions of tasks should be developed to best capture distinct variance components of interest for particular investigative purposes. Lastly, it will be important in future research to extend current study findings to other substance classes. Specifically, current results suggest that P3 responses to cannabis-, cocaine-, or opioid-related images should contain variance unique to each problematic substance class, separate from the more general P3 that relates to these outcomes via general externalizing proneness.

CONCLUSION

Notwithstanding these limitations, the present work provides important new evidence for heterogeneity in P3 brain response to

different types of stimuli in relation to PAI. Our findings support a two-process theory of substance addiction involving concurrent elements of weak general top-down control and strong specific bottom-up incentive salience attribution to drug-related cues.

Current results also serve to illustrate how multiple distinct sources of variance can exist within a single brain response measure [86], and they highlight the importance of an ontogenetic process-based understanding of how psychophysiological measures relate to clinical problems and affiliated traits [81].

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AUTHOR CONTRIBUTIONS

KJJ leads conceptualization, analysis, and results interpretation, and co-leads initial drafting and edits. CJP co-leads initial drafting and edits. DHM led data collection and management and contributed edits. DMM contributed edits. BDB co-led conceptualization, initial drafting, and edits, supervised data collection and management, and secured funding for primary data collection.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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