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Neural Correlates of the Addictions Neuroclinical Assessment (ANA) Incentive Salience Factor Among Individuals with Alcohol Use Disorder

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Abstract

The Addictions Neuroclinical Assessment (ANA) is a recently-developed framework offering a more holistic understanding of three neurofunctional and behavioral domains that reflect the neurobiological dysfunction seen in alcohol use disorder (AUD). While the ANA domains have been well-validated across independent laboratories, there is a critical need to identify neural markers that subserve the proposed neurofunctional domains. The current study involves secondary data analysis of a two-week experimental medication trial of ibudilast (50 mg BID). Forty-five non-treatment-seeking participants with AUD (17 F / 28 M) completed a battery of validated behavioral assessments forming the basis of their incentive salience factor score, computed via factor analysis, as well as a functional neuroimaging (fMRI) task assessing their neural reactivity to visual alcohol cues after being on placebo or ibudilast for 7 days. General linear models were conducted to examine the relationship between incentive salience and neural alcohol cue-reactivity in the ventral and dorsal stratum. Whole-brain generalized linear model analyses were conducted to examine associations between neural alcohol cue-reactivity and incentive salience. Age, sex, medication, and smoking status were included as covariates. Incentive salience was not associated with cue-elicited activation in the dorsal or ventral striatum. Incentive salience was significantly positively correlated ($p < 0.05$) with alcohol cue-elicited brain activation in reward-learning and affective regions including the insula and posterior cingulate cortices, bilateral precuneus, and bilateral precentral gyri. The ANA incentive salience factor is reflected in brain circuitry important for reward learning and emotion processing. Identifying a sub-phenotype of AUD characterized by increased incentive salience to alcohol cues allows for precision medicine approaches, i.e. treatments specifically targeting craving and reward from alcohol use. This study serves as a preliminary bio-behavioral validation for the incentive salience factor of the ANA. Further studies validating the neural correlates of other ANA factors, as well as replication in larger samples, appear warranted.

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Keywords

Addictions Neuroclinical Assessment; alcohol use disorder; cue-reactivity; deep phenotyping; neuroimaging

1. Introduction

Alcohol use disorder (AUD) is a complex disorder that incurs substantial individual and societal costs [1]. The heterogeneity of AUD has been long recognized and there have been several attempts to identify alcohol drinking subtypes [2]. Current categorical classifications of AUD, and other addictive disorders, focus on endorsement of symptoms that impair several domains of functioning, but they fail to adequately capture the severity and neurobiological dysfunction of the disorder [3]. Over the last few decades, there have been revolutionary advances in our understanding of the neurobiological underpinnings of addictive disorders; unfortunately, these insights have not been translated into the clinic [4]. In order to advance our understanding of the heterogeneity of AUD and eventually improve the nosology, it is critical to measure process-based impairments using neuroscience-informed approaches rather than relying solely on outcome-based approaches reflected via clinical presentation of symptoms [5].

Incentive-sensitization is one prominent neuroscience-informed theory of addiction [6]. Incentive salience refers to a psychological process that involves changes in the perception of alcohol-related stimuli, such that these stimuli are imbued with salience making them “attractive” over time. Changes in incentive salience are well-documented across addictive disorders and are linked to phasic activation of the mesocorticolimbic dopamine system and to the circuitry of the basal ganglia [7]. Support for this theory of addiction comes primarily from preclinical studies wherein nonhuman primates undergo both repeated presentations of a reward and repeated presentations of stimuli associated with the reward [8]. Positron emission tomography studies have shown sensitization of stimulant-elicited striatal dopamine release in humans [9] [10]. Under these experimental parameters, dopamine neurons fire during an exposure to a novel reward, but repeated exposure to the reward causes the dopamine neurons to stop firing upon consumption. While dopamine signaling is reduced during reward consumption, dopamine signaling is enhanced when animals are exposed to stimuli that were predictive of the reward. In agreement with the prediction of diminished salience of hedonic reward in AUD proposed by the incentive sensitization theory, our laboratory found that stimulation/hedonic reward from alcohol was associated with and preceded craving in participants who drank heavily, but not in participants with AUD [11].

Functional magnetic resonance imaging (fMRI) cue-reactivity tasks provide a non-invasive opportunity to examine mechanisms underlying clinical AUD phenotypes by investigating brain circuits after exposure to alcohol and control cues [12]. In line with various components of incentive salience, the neural responses of individuals with AUD are altered to both cue and non-cue targets [13–15], with increased alcohol craving after exposure to alcohol-related cues [16, 17], along with dysfunction in reward-based learning [18]. Neural

cue-reactivity paradigms have reliably shown activation in reward-related brain regions such as the ventral striatum, cingulate cortex, and the precuneus [15, 19]. Furthermore, neural cue-reactivity paradigms can be leveraged to capture shifts in striatal signaling that are thought to underlie the transition from casual to habitual and compulsive alcohol use. For example, social drinkers showed higher cue-elicited activation in the ventral striatum relative to heavy drinkers while heavy drinkers showed higher cue-elicited activation in the dorsal striatum compared to social drinkers [20].

The construct of incentive salience has informed novel classification frameworks and deep behavioral phenotyping methods in addiction [21]. Incentive salience is a core domain in both the Alcohol Addiction Research Domain Criteria (AARDoC) framework [3] and the Etiologic, Theory-Based, Ontogenetic Hierarchical Framework for Alcohol Use Disorder (ETOH) [22]. These are complimentary frameworks with the shared goal of improving the construct validity of AUD diagnoses by identifying fundamental mechanisms implicated in AUD. The Addictions Neuroclinical Assessment (ANA) complements the AARDoC and was proposed as a clinical framework to better understand heterogeneity addictive disorders by leveraging neuroscience-informed self-report and behavioral assessments to yield three neurofunctional domains subserving addiction: incentive salience, negative emotionality, and executive dysfunction [23, 24]. The ANA domains have been well-validated across several independent alcohol-focused laboratories [25–29], and have received initial empirical support among other substances, such as methamphetamine [30]. One limitation of the ANA is the lack of strong support for neuroimaging correlates of the proposed domains. The neural substrates mapping to the cognitive processes underlying core addiction theoretical mechanisms of incentive salience, negative emotionality, and transition to compulsive behaviors have been systematically reviewed in the Addictions Neuroclinical Imaging Assessment, in which extensive cortical and subcortical brain structures and networks were found relevant to alcohol misuse [31]. Specifically, the ventral striatum, anterior insula, and ventral medial prefrontal cortex have been linked to incentive salience processes [31]. In order to advance our understanding of the neural mechanisms underlying dysfunction in these domains, there is a critical need to combine deep behavioral phenotyping methods with neuroimaging methodologies.

The purpose of this study was to identify the neural correlates of the incentive salience domain of the ANA during a neural alcohol cue-reactivity task via secondary data analysis of a two-week experimental medication trial of the neuroimmune modulator ibudilast for AUD [32]. Controlling for medication condition and relevant covariates in a sample of patients with AUD, we hypothesized that higher scores on the incentive salience factor would be associated with greater neural alcohol cue-reactivity in the ventral striatum. The incentive salience latent factor would not be associated with cue-elicited activation in the dorsal striatum. An additional goal of the study was to conduct an exploratory whole brain analysis to identify novel brain regions associated with the incentive salience factor during the neural alcohol cue-reactivity paradigm. While the incentive salience domain has been well-validated across several research laboratories, there is a lack of neuroimaging indicators of the domains. This study addresses this critical issue and furthers our understanding of the neural underpinnings of the incentive salience domain among individuals with current AUD.

2. Material and methods

2.1 Participants and Procedures

The current study involved secondary data analysis that was a collected as part of a 2-week human laboratory trial of ibudilast for drinking reduction among non-treatment-seeking individuals with AUD (n = 52) [32]. The Institutional Review Board at the University of California, Los Angeles approved all study procedures. All participants provided written informed consent after discussing the medications with study physicians. In the parent study, participants completed telephone screening, an in-person assessment, medical eligibility screening, a randomization visit where participants received either ibudilast or placebo, a follow-up neuroimaging session one week after randomization, and a final study visit that occurred one week after the neuroimaging session. The data reported in the current study are from a subset (N=45) of individuals with AUD who completed a neuroimaging session one week into the active medication period. The current study's design and hypotheses were not preregistered.

Participants were men and women with AUD who were between 21- and 50-years old. Eligible participants completed a neuroimaging session approximately one week after being randomized to ibudilast (50 mg BID; n = 20) or placebo (n = 25). Participants were recruited through social media and mass transit advertisements. Interested individuals called the laboratory and completed a phone interview for preliminary eligibility.

Likelihood of heavy drinking was initially screened over the phone by a score of 2 or higher on the CAGE questionnaire [33], a mnemonic for questions focused on Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers. In addition, participants who were eligible to come in for the screening visit also had to meet DSM-5 criteria for current AUD and report drinking at or above heavy drinking criteria (14+ drinks/week for men and 7+ drinks/week for women) over the last 30 days. Exclusion criteria included: (i) current involvement in treatment programs for alcohol use or have received treatment in the prior 30 days to study participation; (ii) use of non-prescription psychoactive drugs or use of prescription medications for recreational purposes; (iii) self-reported history of major mental illness (i.e., bipolar disorder or psychotic disorders); (iv) current use of antidepressants, mood stabilizers, sedatives, anti-anxiety medications, seizure medications, or prescription painkillers; (v) self-reported history of contraindicated medical conditions (e.g., chronic liver disease, cardiac disease); (vi) if female, pregnant (as verified by a urine sample), nursing, or planning to get pregnant in the next 6 months or refusal to use a reliable method of birth control; (vii) breath alcohol concentration greater than 0.000 g/dl as measured by the Dräger Inc. Alcotest® 6510; (viii) positive urine toxicology screen for any drug (other than cannabis), as measured by Medimpex United Inc. 10 panel drug test; (ix) non-removable ferromagnetic objects in body; (x) claustrophobia; and (xi) serious head injury or prolonged period of unconsciousness (>30 minutes).

Eligible participants were invited to the laboratory to complete an in-person testing battery that included sociodemographic variables, self-report questionnaires, and interview-based assessments (described below). Smoking status (categorical; Smoker vs Non-Smoker) was

determined using the first question on The Fagerström Test for Nicotine Dependence [34], which asks participants if they currently smoke cigarettes.

2.2 Measures

Participants who were eligible for the 2-week ibudliast clinical trial were invited to the laboratory to complete a phenotypic battery consisting of sociodemographic (i.e., age, sex, race) and clinical measures. Clinical measures to capture alcohol/substance use and motivations include: The Timeline Followback [35] to measure cigarette, cannabis, and alcohol frequency and amount over the previous 30 days, the Structured Clinical Interview of DSM-5 was administered by a master's level clinician to assess for (i.e., past 12 months) AUD symptoms [36], the Alcohol Use Disorder Identification Test (AUDIT) to measure harmful or hazardous alcohol drinking [37], and the Reasons for Heavy Drinking Questionnaire (RHDQ), which is comprised of heavy drinking for normalizing and heavy drinking for reinforcement subscales [38].

The incentive salience latent factor was derived using measures that have been previously used to capture the incentive salience latent factor of the ANA. These items consist of questions 18 *("Do you almost constantly think about drinking and alcohol?")* and 25 *("After taking one or two drinks, can you usually stop?")* from the Alcohol Dependence Scale (ADS)[39]; questions 1 *("How much of your time when you're not drinking is occupied by ideas, thoughts, impulses or images related to drinking")*, 11 *("If you were prevented from drinking alcohol when you desired a drink, how anxious or upset would you become")*, and 13 ("*How strong is the drive to consume alcoholic beverages?*") from the Obsessive Compulsive Drinking Scale (OCDS)[40]; and all 5 items from the Penn Alcohol Craving Scale (PACS)[41]. These individual items have been used in previous ANA studies among alcohol drinking samples to derive the incentive salience latent factor [27–29]. The rationale for selecting these measures was that the latent factor should be derived using items that have been vetted and confirmed in the literature while also examining the weights of the individual PACS items. The Impaired Control Scale and the Marlatt Relapse Interview were not included in the main trial and were not available for the factor analysis. In summary, ADS items 18 and 25, OCDS items 1, 11, and 13, and PACS items 1–5 were included in the factor analysis.

2.3 Neuroimaging Procedures

Neuroimaging took place at the UCLA Center for Cognitive Neuroscience (CCN) on a 3.0T Siemens Prisma Scanner (Siemens Medical Solutions USA, Inc., Malvern, PA). A T2-weighted, high-resolution matched-bandwidth (MBW) anatomical scan (time to repetition (TR) = 5,000 ms, time to echo (TE) = 34 ms, flip angle = 90°, voxel size: 1.5 mm × 1.5 × 4 mm, field of view (FOV) = 192 mm2, 34 slices, ~1.5 minutes) and a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR = 2,530 ms, TE = 1.74 ms, time to inversion = 1,260 ms, flip angle = 7°, voxel size: 1 mm3, FOV = 256 mm2, ~6.2 minutes) were acquired for co-registration to the functional data. A T2*-weighted echo planar imaging (EPI) scan (TR = 2,200 ms, TE = 35ms, flip angle = 90°, FOV = 192 mm, slices = 36, 3.0 mm, ~12 minutes) was acquired to examine the blood oxygen-level dependent (BOLD) signal during the visual alcohol cue reactivity task.

Alcohol Cue-Reactivity Task—Participants completed a 720s-long visual alcohol cue-reactivity task (Schacht et al., 2013), in which they were presented with 24 pseudo-randomly interspersed blocks of alcoholic beverage images (ALC), non-alcoholic beverage images (BEV), blurred images to serve as visual controls, and a fixation cross. Each block was composed of 5 individual pictures of the same type, each presented for 4.8 seconds, for a total of 24-seconds. Each block was followed by a 6-second washout period during which participants reported on a 1–4 Likert scale their current urge to drink. Alcoholic beverage blocks were distributed between images of beer, wine, and liquor (2 of each).

2.4 Neuroimaging Preprocessing

Preprocessing of neuroimaging data followed conventional procedures as implemented in FMRIB Software (FSL v6.0.1 http://www.fmrib.ox.ac.uk/fsl), including motion correction (Jenkinson et al., 2002), high-pass temporal filtering (100-second cut-off), and smoothing with a 5-mm full-width, half-maximum Gaussian kernel. Functional and structural data were skull-stripped to remove non-brain tissue. Each subject's functional images were registered to their MBW, followed by their MPRAGE using affine linear transformations, and then were normalized to the Montreal Neurological Institute (MNI) 152-brain-average template through non-linear registration (Andersson et al., 2007).

As an important manipulation check, we previously conducted a whole-brain analysis across groups to confirm that the alcohol cue-reactivity paradigm activated the expected mesocorticolimbic reward circuitry (i.e., ventral striatum/nucleus accumbens) in the ALC vs. BEV contrast (See Supplemental materials in [32]).

2.5 Statistical Analyses

2.5.1 Factor Analysis—

A covariance matrix was constructed from individual level data in order to follow the pairwise deletion of missing data rule [42]. Pairwise deletion allows participants to contribute to the model if they had data on at least one indicator variable. The factor analysis was used to identify the incentive salience latent factor underlying the above measures. Analyses were conducted using PROC FACTOR in SAS 9.4. Variables with a loading ≥ 0.40 were considered to load on particular factor [42]. Latent factors that had eigenvalues greater than 1, in combination with scree tests, suggested that factors were meaningful. A factor analysis solution was considered unsatisfactory if it included a factor that was composed of less than three measures. Weighted factor scores were then computed for each participant from the factor analysis to indicate their standing on the incentive salience latent factor. Factor scores were then used as continuous predictor variables in subsequent analyses.

2.5.2 Sample Demographics and Clinical Characteristics Analyses—

Group differences on demographic and clinical variables between the low and high incentive salience groups (via median split of the incentive salience latent factor) were tested using *t*-tests for continuous outcomes and chi-square (χ^2) tests for categorical outcomes.

2.5.3 A priori region of interest analyses—

The primary contrast of interest, ALC>BEV, was defined in first-level models. FSL's Featquery tool was used to extract

mean percent signal change for all subjects from *a priori* striatal regions of interest (ROIs). The first ROI, bilateral ventral striatum (VS), was defined anatomically as the nucleus accumbens using the Harvard-Oxford subcortical structure probability atlas and binarized at a 0.5 probability threshold (Kaag et al., 2019; Ray et al., 2014). The bilateral dorsal striatum (DS) ROI was defined anatomically as the caudate and putamen from the Harvard-Oxford atlas used above, also binarized at a 0.5 probability threshold. Overlap between the VS and DS regions were subtracted from the DS mask to distinguish between dorsal and ventral striatal areas (Kaag et al., 2019; Liu et al., 2017). Pearson correlation coefficients were calculated to examine zero-order associations between incentive salience, cue-induced craving, and neural activation to alcohol cues. Multiple linear regression analyses were used to examine the relationship between incentive salience latent factor scores (derived from ADS 18 and 25, OCDS 1, 11, and 13, and PACS 1–5) and alcohol cue-reactivity in the ventral and dorsal striatum. In these analyses, demographic variables, smoking status, and medication were used as statistical controls. Student's *t*-tests, Pearson correlations, and general linear model regression analyses were conducted using SAS 9.4. Statistical significance was set at $p < 0.05$. The data and analysis code that support the findings of this study are available from the corresponding author upon reasonable request.

2.5.4 Exploratory Whole-brain Analysis—An exploratory whole-brain general linear model was conducted to assess the relationship between the incentive salience latent factor (derived in same manner as ROI analyses) and neural alcohol cue reactivity across all subjects. Medication group (ibudilast or placebo), age, sex, and cigarette smoking status (smoker vs non-smoker) were entered as covariates. Z-statistic images were thresholded using a cluster-forming threshold of $Z > 2.3$ and a (corrected) cluster significance threshold of $p < 0.05$ (Worsley, 2001).

3.0 Results

3.1 Factor Analysis and Sample Demographics

The factor analysis, which included data from all participants in the neuroimaging sample (N=45), yielded a one-factor solution. The scree plot and pattern matrix providing the factor loadings and reflecting the correlation coefficients between each variable and each factor is provided in the Supplemental Materials. Briefly, this single factor accounted for 65.25% of the variance, with an Eigenvalue of 6.15, and items 18 and 25 from the ADS, items 1, 11, and 15 of the OCDS, and all PACS items loaded onto this single factor. Similar to other ANA studies, we interpret this single factor as the incentive salience domain. Subsequent factors accounted for small proportions of variance with negligible Eigenvalues.

Full sample demographics and clinical characteristics for the neuroimaging sample have been previously reported in [43]. Table 1 includes sample characteristics for individuals with "Low" and "High" incentive salience based on a median split on the incentive salience latent factor. Compared to individuals in the Low Incentive Salience group, individuals in the High Incentive Salience group were more likely to be a cigarette smoker, report more drinks per week, have more severe AUD, and engage in heavy drinking to feel "normal".

Correlation and a priori ROI regression analyses—Zero-order correlations between the incentive salience latent factor, ventral and dorsal striatum cue-elicited activation, and in-scanner alcohol craving scores are shown in Table 2. The incentive salience latent factor was not significantly related to cue-elicited activation in the ventral ($p = 0.97$) or dorsal striatum ($p = 0.29$). There was a statistically significant positive relationship between the incentive salience factor and self-reported cue-elicited alcohol craving in the scanner ($p = 0.007$).

A priori multiple linear regression analyses showed that incentive salience factor scores did not predict alcohol cue-elicited activation in the ventral striatum controlling for medication and other variables in the model ($b = 0.005$; $SE = 0.04$; $t = 0.13$; $p = 0.90$). No other variables (age, sex, smoking status, and medication) in the model were significantly associated with alcohol cue-elicited ventral striatal activity (p's > 0.05). The incentive salience factor scores were not significantly associated with alcohol cue-elicited dorsal striatal activation controlling for other variables in the model ($b = 0.04$; $SE = 0.02$; $t = 1.57$; $p = 0.12$). No other variables (age, sex, smoking status, and medication) in the model were significantly associated with alcohol cue-elicited dorsal striatal activity (p's > 0.05).

3.2 Whole-brain analyses

The incentive salience factor score was positively associated with neural activation to alcohol cues in regions including the bilateral precuneus, bilateral precentral gyrus, insula and posterior cingulate cortex (see Figure 1 and Table 3), controlling for age, sex, smoking status, and medication. No regions showed a significant negative association between activation and incentive salience factor scores.

3.3 Sensitivity Analyses

Sensitivity analyses by medication group were conducted for both the ROI and whole-brain statistical models. Conducting the analyses within each medication group, instead of using medication as a covariate, did not substantively change the relationship between the incentive salience factor and neural cue-elicited activation (see Supplemental Tables 2–4 and Supplemental Figure 2).

4.0 Discussion

The purpose of the current study was to identify neural correlates of the incentive salience domain of the ANA during a neural alcohol cue-reactivity task among individuals with AUD. The incentive salience factor is a prominent domain in mechanism-based classification frameworks for AUD [3, 22]. We found that the incentive salience latent factor was not associated with cue-elicited activation in the ventral or dorsal striatum. A whole-brain analysis showed that the incentive salience latent factor was associated with cue-elicited activation in the bilateral precuneus and precentral gyrus, as well as the insula and posterior areas of the cingulate cortex. While the ANA has been well validated across alcohol-focused laboratories, deep behavioral phenotyping methods have not been combined with neuroimaging technologies to fully understand the pathophysiology of these neurofunctional domains. The data from the current study provide a critical step forward in

identifying neuroimaging correlates that are associated with the incentive salience domain of the ANA among individuals with AUD.

In contrast to our primary hypothesis, the incentive salience latent factor was not associated with alcohol cue-elicited activation in the ventral striatum. There was also no relationship between cue-induced alcohol craving in the scanner and cue-induced activation in the ventral striatum. This was relatively surprising to us given the robust evidence that alcohol cues are associated with increased neural activity in the ventral striatum and that increased activity is related to self-reported alcohol craving [15, 44–48]. However, the drinking status of the sample (i.e., heavy drinkers with AUD) may have influenced neural cue reactivity because higher cue-elicited activation has been seen in the ventral striatum of social drinkers relative to heavy drinkers. Given that the current study did not include a sample of social drinkers, drinking status and duration of drinking problems may be important to monitor/account for in future work. Several human neuroimaging alcohol cue-reactivity studies also show no relationship between cue-induced neural activity in the ventral striatum and self-reported alcohol cue-induced intensity of craving or desire suggesting that cue-elicited activation of the ventral striatum is not necessary for the subjective experience of craving and/or desire for alcohol [49–51]. In this study, incentive salience score and self-reported alcohol craving in-scanner, were positively associated, indicating a convergence of the two constructs. So, this leads to an interesting question of the mechanism by which the incentive salience factor can be associated with self-reported alcohol craving independent of cue-elicited activation in the ventral striatum.

Alcohol cues can trigger alcohol craving via both implicit and explicit mechanisms (see [52] for a thorough review of incentive salience sensitization in AUD). The implicit mechanisms involve a cue affecting alcohol craving through bottom-up cognitive processes that operate below conscious awareness. The ventral striatum, which includes the nucleus accumbens, plays a key role in the manifestation of incentive salience in this process by engaging approach and action response systems via the basal ganglia [53–55]. In parallel to implicit associations, alcohol-related cues may activate explicit associations, which immediately enter working memory, and directly bring into conscious awareness cue- and alcohol-related attitudes, expectancies, and goals [52]. Attribution of incentive salience to the alcohol cues in working memory can increase the likelihood that cue-elicited thoughts capture attention in a conscious manner. In the current study, it may be the case that alcohol cues activate explicit associations that drive subjective craving for alcohol. For example, after briefly viewing exteroceptive alcohol cues in the scanner, participants may have thought about their typical alcoholic beverage, alcohol use, and positive alcohol use outcomes which collectively influences their subjective craving for alcohol. Further empirical work is needed to confirm this “direct” pathway from cue detection and incentive salience attribution to the subjective experience of craving and desire.

A whole-brain analysis showed that the incentive salience factor was associated with cue-elicited activation in the precuneus, right cingulate cortex, and precentral gyrus. These findings are in line with fMRI studies that have reliably shown activation in regions including the ventral striatum, prefrontal cortex, cingulate, insula, and precuneus [15, 19]. In particular, the precuneus may be sensitive to changes in cue-reactivity and possibly to

changes in addiction severity [56], and has been shown to be a predictor of subsequent drinking in the real world [57], which suggests that this region may serve as an intervention target, particularly with regard to the salience of alcohol cues [57, 58]. The insular cortex and posterior cingulate have been implicated in addiction and relapse [19]. The insula is associated with the salience network, emotional processes, and interacts with the ventral striatum during reward delivery [59]. The posterior cingulate is implicated in internally directed attention. As alcohol cues are known to engage these regions and behaviors in individuals with AUD [15], it is notable that the incentive salience latent factor was associated with cue-elicited activation in the insula and posterior cingulate.

The current study and previous ANA research have validated the incentive salience latent construct using self-report indicators. Future research should assess the trade-off between using convenient self-report measures and task-based behavioral assessments for cue reactivity and incentive salience. Behavioral tasks can detect sensitized incentive salience even below conscious awareness, while functional MRI studies confirm these behavioral tasks are activating the relevant incentive salience neurocircuitry. Investigating the use of self-report versus behavioral or neurobiological indicators in measuring incentive salience within an assessment battery for AUD is essential. While the use of fMRI tasks may enhance our understanding of AUD phenotypes and predictive validity, a simpler self-report approach may be easier to implement in various research and clinical settings.

This study has a host of strengths and limitations to be considered. The moderate sample size than typically used in factor analyses, the pharmacotherapy component (unable to rule out effects associated with being willing to and/or taking study medication), the potential impact of the smoothing kernel impacting the VS/DS separation represent notable limitations. The well-characterized visual cue exposure task and the control for medication condition in all analyses, partially mitigates these concerns. Larger studies that can phenotype all three ANA dimensions, examine the relationships among the domains, and subject them to comprehensive neuroimaging profiling, including additional tasks and resting-state functional connectivity, may be necessary to fully capture the neurobiological underpinnings proposed by the model. Functional connectivity approaches can provide a more intricate and comprehensive view of the circuits at play, as opposed to focusing solely on a single region of interest. For example, a functional connectivity approach can be used to evaluate regions in which neural activation in response to alcohol cues is temporally correlated with cue-elicited activation in the precuneus and/or insula. More work is needed to examine whether the incentive salience factor, in addition to negative emotionality and executive dysfunction, are stable across time (i.e., time invariant) using longitudinal research designs. Another important future direction is the need for a uniform phenotyping assessment to improve replicability of ANA findings. Once there is a validated uniform phenotyping assessment the field can work towards developing an abbreviated version of the battery and examine its predictive utility in precision medicine. Although we did not replicate previous work with identical indicators, we still modeled a comparable single-factor incentive salience construct with items assessing the perceived intensity of urges and the ability to resist urges from self-report measures. Replicating this incentive salience factor in a different sample with a similar set of indicators highlights the robustness of this latent construct within an AUD non-treatment-seeking population.

In closing, this study provides insights as to brain regions that may serve as neural correlates of the incentive salience domain of the ANA. That the brain regions identified in the whole brain analysis (i.e., precuneus and cingulate) are well-studied in addiction and relapse offer further support of the construct validity of the incentive salience domain of the ANA. The association with activation in learning and memory brain structures suggests that alcohol cues activate explicit associations that drive subjective craving for alcohol. Future work is needed confirm the findings from the current study using larger neuroimaging samples and to expand the search for neural correlates underlying other ANA domains, namely executive dysfunction and negative emotionality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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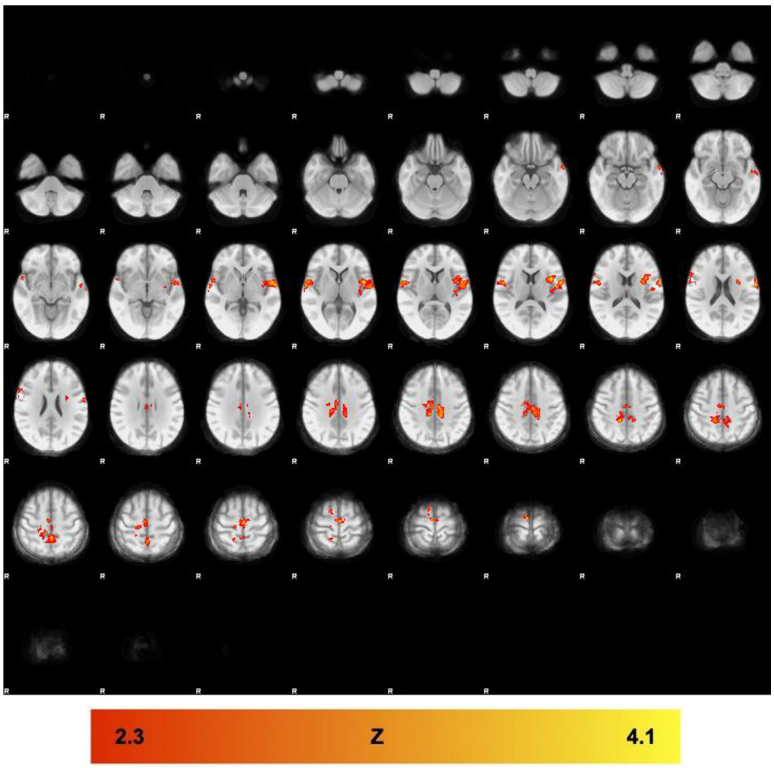

Figure 1.

Incentive salience whole-brain analysis clusters. Regions in which the incentive salience latent factor was significantly correlated with neural cue-reactivity in the ALC>BEV contrast (see Table 3 for list of clusters). Color bar represents z-values. Whole-brain results are thresholded at $z > 2.3$, cluster-forming threshold of $p<0.05$. Brain maps are displayed in radiological convention (right = left), and all coordinates are in MNI space.

Table 1.

Demographic and clinical variables for the neuroimaging sample by Low and High Incentive Salience (via median split of incentive salience latent factor)

Variable	Low Incentive Salience (N=23)	High Incentive Salience (N=22)	Test Statistic
Age	32.52 (8.76)	32.68 (8.89)	$t(43) = -0.06$; $p = 0.95$
Sex (Male)	13 (56.52%)	15 (68.18%)	$\chi^2(1) = 0.65$; $p = 0.42$
Cigarette Smoker	**8 (24.78%)**	**16 (72.72%)**	**$\chi^2(1) = 6.51$; $p = 0.01$**
Marijuana Use Days	4.13 (8.31)	5.81 (8.85)	$t(43) = -0.65$; $p = 0.51$
Timeline Followback- Drinking days	18.96 (7.10)	22.18 (5.67)	$t(43) = -1.67$; $p = 0.10$
Timeline Followback-Drinks per drinking day	4.82 (2.16)	6.52 (4.15)	$t(43) = -1.73$ $p = 0.09$
Timeline Followback-Drinks per week	**20.04 (9.22)**	**35.23 (8.26)**	**$t(43) = -2.44$; $p = 0.02$**
DSM-5 AUD Symptom Count	**3.78 (1.16)**	**6.09 (2.50)**	**$t(43) = -3.99$; $p < 0.001$**
Alcohol Use Disorder Identification Test Total Score	**12.91 (3.79)**	**20.32 (6.02)**	**$t(43) = -4.95$; $p < 0.001$**
Alcohol Dependence Scale Total Score	**8.61 (4.59)**	**15.95 (6.28)**	**$t(43) = -4.49$; $p < 0.001$**
Obsessive Compulsive Drinking Scale Total Score	**9.13 (3.98)**	**18.77 (6.39)**	**$t(43) = -6.09$; $p < 0.001$**
Penn Alcohol Craving Scale Total Score	**7.57 (3.56)**	**16.64 (5.10)**	**$t(43) = -6.93$; $p < 0.001$**
Reasons for Heavy Drinking – Normalizing	**5.52 (6.22)**	**11.23 (6.65)**	**$t(43) = -2.97$; $p = 0.005$**
Reasons for Heavy Drinking - Reinforcing	**21.52 (4.38)**	**24.09 (4.08)**	**$t(43) = -2.03$; $p = 0.048$**

Table 2.

Pearson correlations between incentive salience, ventral and dorsal striatum cue-elicited activation, and in-scanner alcohol craving score.

	1	2	3	4
1. Incentive salience factor score[a]	1.00			
2. Ventral striatum cue-elicited activation	−0.01	1.00		
3. Dorsal striatum cue-elicited activation	0.16	0.24	1.00	
4. In-scanner alcohol craving score	**0.27****	−0.12	**−0.35***	1.00
Mean	0.00	0.03	0.04	2.13
Standard Deviation	1.00	0.25	0.14	1.13

[a]The incentive salience latent factor score is a standardized distribution where mean = 0 and standard deviation = 1.

*indicates a significant association at $p < 0.05$.

**indicates a significant association at $p < 0.01$.

Table 3.

Clusters with significant association between the incentive salience latent factor and the ALC>BEV contrast, across groups. Z-statistic maps were thresholded using cluster-corrected statistics with a height-threshold of $Z > 2.3$ and cluster-forming threshold of $p < 0.05$. Coordinates are listed in MNI space.

Brain Region	Cluster Voxels	Max Z-statistic	x	y	z
Positive Correlation with incentive salience factor during Alc>Bev contrast					
R Cingulate Cortex (posterior)	1993	3.8	10	−30	40
Bilateral Precuneus		3.63	0	−50	58
L Precentral Gyrus	1341	4.04	−62	−2	20
L Insula		2.93	−39	2	2
R Precentral Gyrus	485	3.68	62	−6	2
R Insula		2.48	50	−4	2