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Evaluation of the Addictions Neuroclinical Assessment (ANA) Framework through Deep Phenotyping of Problem Drinkers

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Abstract

Background: To advance the development of a neuroscience-informed understanding of alcohol use disorder (AUD) through the Addictions Neuroclinical Assessment (ANA) framework, the present study reports on deep phenotyping of a large sample of problem drinkers.

Methods: Participants (n = 1,679) were primarily heavy drinkers with and without AUD, who completed a phenotypic battery of well-validated scales and behavioral measures of alcohol use and problems, mood, attention, and impulsivity. These scales were subjected to sequential factor analytic work in order to derive a factor solution that explains biobehavioral variation in the sample. To assess the construct validity of the resulting factor solution, scores on each factor were associated with demographic and clinical indicators.

Results: Factor analysis techniques using indicators of alcohol use and problems, mood, attention, and impulsivity implicated four functional domains that compliment and extend the proposed ANA domains: negative alcohol-related consequences, incentive salience, negative emotionality, and executive function. Demographic and clinical variables significantly predicted scores on all ANA domains.

Conclusions: This study provides an independent test of the recently proposed neuroscience-based ANA framework. Results largely support the novel approach in identifying four core constructs in problem drinkers. Future studies can deepen our understanding of how these domains are relevant to AUD by incorporating biomarkers.

Keywords

Addictions Neuroclinical Assessment; Alcohol use disorder; Neuroscience; Phenotyping; Addiction cycle

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1. INTRODUCTION

Alcohol use disorder (AUD) is highly prevalent, costly to individuals and society, and often untreated (Carvalho et al., 2019). AUD is a progressive disorder, with presentations ranging from mild, time-limited, alcohol-related problems to severe, chronic and relapsing, which is often termed addiction. The heterogeneity of AUD has been widely recognized and several efforts to identify patient subtypes have been undertaken, as reviewed by Leggio et al. (2009). More recent efforts have focused on addiction neurobiology, and despite significant advances in our understanding of the neuroscience of addiction (Koob and Volkow, 2016), the translation of that knowledge to clinical practice has been slow and often unsuccessful (Egli, 2018; Heilig et al., 2016). A crucial limitation associated with the translation of addiction neuroscience to clinical samples is the fact that the established diagnostic criteria for AUD are not informative about the underlying clinical neuroscience of the disorder.

To address this issue, the field of psychiatry has moved toward a trans-diagnostic, neuroscience-based research framework approach that focuses on specific domains that can help explain psychiatric disorders as a result of varying degrees of dysfunction in psychology/biological systems (Clark et al., 2017; Insel et al., 2010). In the addiction field, the Addictions Neuroclinical Assessment (ANA) was recently proposed as a novel framework for neuroscience-informed assessment that captures three functional domains-incentive salience, negative emotionality, and executive (dys)function (Kwako et al., 2017; Kwako et al., 2016). This framework aims to understand the heterogeneity in AUD by leveraging deep phenotyping profiles coupled with factor analytic methods (Kwako et al., 2019). While these domains have received initial empirical support (Kwako et al., 2019; Votaw et al., 2020), validation of the ANA framework in independent clinical samples is needed.

The heuristic framework offered in ANA presents new opportunities whereby dysfunctions in these domains may serve as treatment targets. For instance, the ANA can be used to identify novel addiction biomarkers and to refine existing ones (Kwako et al., 2018). To do so would entail filling the translational gaps between behavioral and biological phenotypes, an ongoing challenge in neuroscience and psychiatry. For example, deep behavioral phenotyping derived from clinical, behavioral, and self-report measures, suggest that motor impulsivity, attentional impulsivity, and negative urgency load into the construct of executive (dys)function (Kwako et al., 2019). Moreover, negative emotionality, measured by inventories of depression, anxiety, and items of drinking consequence, appears to be time invariant, indicating that changes in these constructs as treatment outcomes can be measured over time (Votaw et al., 2020). Probing the underlying neurobiology of these constructs may inform the development of AUD biomarkers.

While there is considerable enthusiasm and potential for an ANA framework, the empirical research on the core constructs of incentive salience, negative emotionality, and executive dysfunction has been limited thus far. To advance the development of a neuroscience-informed understanding of AUD through an ANA framework, the present study employs deep phenotyping of a large sample of problem drinkers. Participants completed a battery of well-validated scales and behavioral tasks that are all conceptually related to the proposed

ANA dimensions. These scales were subjected to sequential factor analytic work in order to derive a factor solution that is both quantitatively and theoretically sound. To validate the resulting factor structure, scores on each factor were associated with demographic and clinical indicators. This study provides an independent evaluation of the ANA framework in a large sample of problem drinkers. We hypothesized that we would identify factors that complement the proposed ANA domains, and that these factors would be distinct from latent factors that are more relevant to AUD phenomenology compared to neuroscience-informed domains. Additionally, we hypothesized that latent factors would be associated with alcohol use severity measures.

2. MATERIALS AND METHODS

2.1. Data source and sample

The current sample is culled from six separate clinical and experimental psychopharmacology studies with similar inclusion criteria and recruitment methods, all conducted in the Addictions Laboratory at the University of California, Los Angeles and carried out in accordance with the Declaration of Helsinki. Specifically, the sample analyzed herein were drawn from studies examining alcohol self-administration, acute subjective responses to alcohol, varenicline and naltrexone combination, naltrexone, and ibudilast as a pharmacotherapy for AUD. Data were also culled from a randomized clinical trial examining combination varenicline and naltrexone for smoking cessation and drinking reduction (NCT02698215). Although some studies involved pharmacological manipulations, *all data analyzed herein were collected at a baseline assessment visit* (i.e., prior to medication randomization or any experimental procedures). All studies recruited community samples of treatment and non-treatment-seeking drinkers from the greater Los Angeles Area. All study procedures were approved by the University of California, Los Angeles Institutional Review Board, and all participants provided written informed consent after receiving a full explanation of the study procedures.

Interested individuals called the laboratory and completed a phone interview for preliminary eligibility. Heavy drinking was verified through one of the following methods: (i) greater than 48 drinks per month; (ii) greater than 4 or 7 drinks per week for females and greater than 6 or 14 drinks per week for males; (iii) an Alcohol Use Disorder Identification Test (AUDIT;(Saunders et al., 1993)) score of 8 of higher; (iv) a score of 2 or higher on the CAGE questionnaire (Ewing, 1984).

All studies had the following exclusion criteria: (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 psychiatric disorders (e.g., 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 (BAC) of greater than 0.000 g/dl as

measured by the Dräger Inc. Alcotest® 6510; and (viii) positive urine toxicology screen for any drug (other than cannabis), as measured by Medimpex United Inc. 10 panel drug test.

2.2. Measures

Across all studies, eligible participants were invited to the laboratory to complete a phenotypic battery consisting of sociodemographic (i.e., age, sex, race) and clinical measures.

Latent factors were derived using measures assessing harmful and hazardous alcohol drinking (AUDIT; (Saunders et al., 1993); Cronbach's α for subscales = 0.71 to 0.78), alcohol use disorder severity (Alcohol Dependence Scale; ADS (Skinner et al., 1984); Cronbach's α for subscales = 0.64 to 0.76), alcohol-related problems (The Drinker Inventory of Consequences; DrInC (Miller et al., 2000); Cronbach's α for subscales = 0.78 to 0.87), alcohol craving (Obsessive-Compulsive Dependence Scale; OCDS; (Anton et al., 1995); Cronbach's α for subscales = 0.77 to 0.88) and Penn Alcohol Craving Scale; PACS; (Flannery et al., 1999); Cronbach's α = 0.91), anxiety symptomatology (Beck Anxiety Inventory; BAI (Beck et al., 1988); Cronbach's α = 0.91) and State-Trait Anxiety Inventory (STAI; (Spielberger, 2010); Cronbach's α = 0.94), depressive symptomology (Beck Depression Inventory; BDI-II (Beck et al., 1961); Cronbach's α = 0.92), attention and working memory (Digit Span; (Wechsler, 2003); Cronbach's α for subscales = 0.68 to 0.75), impulsivity (Barratt Impulsivity Scale; BIS-11; (Patton et al., 1995); Cronbach's α for subscales = 0.43 to 0.60), and delay discounting (Monetary Choice Questionnaire; MCQ; (Kirby et al., 1999); Cronbach's α = 0.93). We included AUDIT subscales and DrInC subscales given that items from these measures were included in previous work examining the ANA framework. Furthermore, DrInC items were previously shown to load onto the negative emotionality domain albeit to a minor extent (i.e., low factor loadings) (Votaw et al., 2020). Thus, it was possible that in our sample these measures that capture aspects of alcohol consumption and problem use might explain unique variance in the factor structures.

The construct validity of the latent factors was assessed by an interview-based assessment of alcohol use over the previous 30 days (total number of drinking days and drinks per drinking day [DPDD], using the Timeline Followback; (Sobell and Sobell, 1992) and family history of alcohol problems (FH+; assessed by the Family Tree Questionnaire; (Mann et al., 1985). The Structured Clinical Interview of DSM-IV (SCID) or DSM-5 was administered by a master's level clinician to determine age at first drink and assess for current AUD symptoms. In order to streamline the merging of data across multiple studies using both DSM-IV and DSM-5 criteria, participants who were diagnosed with alcohol dependence using DSM-IV terminology are considered to have an AUD. We selected to include these measures of consumption and AUD severity as construct validity measures for two reasons: (1) these measures were never proposed for the ANA and no studies examining ANA factors have included them in their factor analyses, and (2) the inclusion of these factors would have resulted in high correlations between consumption and problem measures, which can impact the discriminative validity of the identified factors.

2.3. Statistical Analysis

2.3.1. Exploratory Factor Analysis (EFA).—A covariance matrix was constructed from individual level data in order to follow the pairwise deletion of missing data rule (O'Rourke and Hatcher, 2013) (Table S1). Pairwise deletion allows participants to contribute to the model if they had data on at least one indicator variable. This approach is ideal for handling missing data in large samples such as ours considering that not all measures were administered to all participants. EFA was used to identify latent factors underlying the above measures. Analyses were conducted using PROC FACTOR in SAS 9.4 using an orthogonal varimax rotation. Variables with a loading ≥ 0.40 were considered to load on particular factor (O'Rourke and Hatcher, 2013). Factors that had eigenvalues greater than 1, in combination with scree tests, suggested that factors were meaningful. An EFA solution was considered unsatisfactory if it included a factor that was composed of less than three measures. If this was the case, an EFA was computed extracting the number of factors that had three or more significant loadings on each factor (O'Rourke and Hatcher, 2013). Weighted factor scores were then computed for each participant from the acceptable EFA to indicate their standing on each latent factor. Factor scores were then used as criterion variables in subsequent analyses. Importantly, EFA/confirmatory factor analysis cross-validation could not be reliably performed because splitting the sample would have reduced the number of participants on these measures below the recommended minimum per measure in factor analysis (Floyd and Widaman, 1995; O'Rourke and Hatcher, 2013).

2.3.2. Regression Analyses.—Demographic and clinical predictors were used to examine the construct validity of the derived latent factors. Specifically, we examined the association between the latent factors and the following predictor variables: sex, age, race/ethnicity, age at first drink, family history of alcohol problems (FH+), number of drinking days, drinks per drinking day (DPDD), and AUD diagnosis. The regression analyses were used to examine the validity of the extracted factor scores as they relate to a host of demographic and alcohol-related variables. Data available on request from the authors.

3. RESULTS

3.1. Sample

The sample included a total of 1,679 individuals. Approximately 67% of the sample were male, and 25% were Non-Hispanic White. The mean age of participants was 35 (SD = 11.78). The mean number of drinking days was 18.22 (SD = 8.61) and the mean number of drinks per drinking day was 5.97 (SD = 3.56). Participants had a mean AUDIT score of 14.99 (SD = 7.90) indicating harmful or hazardous drinking. Descriptive statistics for participants' sociodemographic and clinical characteristics are presented in Table 1.

3.2. Exploratory Factor Analyses

An initial EFA was conducted using all of the variables available in the deep phenotyping battery described above. The scree plot from the first EFA revealed variance discontinuities that suggested five latent factors (Figure S1). The pattern matrix providing the factor loadings and reflecting the correlation coefficients between each variable and each rotated factor is provided in Table 2. The first factor accounted for 66.65% of the variance, with an

Eigenvalue of 35.66, and was primarily composed of the ADS Loss of Control and Withdrawal subscales, AUDIT Dependence and Problems subscales, and all five DrInC subscales. The second factor accounted for 12.44% of the variance, with an Eigenvalue of 6.65, and was primarily composed of the ADS Obsessive subscale, all three AUDIT subscales, both OCDS subscales, the PACS total score, and the DrInC Physical subscale. The third factor accounted for 8.53% of the variance, with an Eigenvalue of 4.56, and was primarily composed of the BAI, BDI, and STAI-Trait scores. The fourth factor accounted for 6.81% of the variance, with an Eigenvalue of 3.64, and was primarily composed of the both Digit Span subscales and delay discounting. The fifth factor accounted 5.57% of the variance, with an Eigenvalue of 2.98, and was primarily composed of the BIS Motor and Attentional subscales. Descriptive statistics on the indicator variables appear in the online supplement in Table S2.

Based on the results of this first EFA, it was determined that a five-factor solution was not appropriate given that the fifth latent factor is comprised of only two significant loadings (BIS Motor and Attentional subscales), thus, not meeting the minimum acceptable requirement in factor analysis of at least three significant loadings on each retained latent factor (O'Rourke and Hatcher, 2013). A subsequent EFA was conducted extracting a four-factor solution. The pattern matrix providing the factor loadings and reflecting the correlation coefficients between each variable and each rotated factor is provided in Table 3. The first factor accounted for 72.79% of the variance, with an Eigenvalue of 34.68, and was primarily composed of the ADS Control and Withdrawal subscales, AUDIT Dependence and Problems subscales, and all five DrInC subscales. We interpret this first factor as an alcohol-related consequences domain. The second factor accounted for 11.93% of the variance, with an Eigenvalue of 5.69, and was primarily composed of the ADS Obsessive subscale, all three AUDIT subscales, both OCDS subscales, and PACS Total. We interpret this second factor to very closely parallel the incentive salience domain proposed in the ANA. The third factor accounted for 8.77% of the variance, with an Eigenvalue of 4.18, and was primarily composed of the BAI Total, BDI Total, and STAI Trait. This third factor is highly indicative of the negative emotionality domain in the ANA. The fourth factor was interpreted as representing the executive function domain proposed in the ANA. The fourth factor accounted for 6.51% of the variance, with an Eigenvalue 3.10, and was primarily composed of both Digit Span subscales and Delay Discounting. Subsequent factors accounted for small proportions of variance with negligible Eigenvalues.

3.3. Regression Analyses

The results of the regression analyses seeking to elucidate demographic and clinical correlates of the factor scores are presented in Table 4. Significant predictors of higher scores on the consequences factor included being male, older age, younger age at first drink, family history of alcohol problems, more drinking days, more DPDD, and AUD diagnosis. Significant predictors of higher score on the incentive salience factor included being male, older age, younger age at first drink, family history of alcohol problems, more drinking days, more DPDD, and AUD diagnosis. Significant predictors of higher scores on the negative emotionality factor included older age, more drinking days, and AUD diagnosis. Higher

scores on the executive function factor were significantly associated with younger age, White race, and no family history of alcohol problems.

4. DISCUSSION

The current study used a large deeply phenotyped clinical sample to evaluate neurofunctional domains relevant to AUD. Using a host of well-validated indicators that reflect AUD phenomenology and are conceptually related to the proposed ANA approach, factor analysis techniques implicate functional domains that map onto and extend the stages of the addiction cycle and the proposed ANA domains: incentive salience, negative emotionality, and executive function. In support of our hypothesis, these functional domains explained biobehavioral variation in this clinical sample. Critically, the ANA domains are distinct from latent factors that reflect AUD phenomenology (i.e., alcohol-related consequences). Using the largest deeply phenotyped clinical sample to date, this study provides an independent test of the recently proposed neuroscience-based ANA framework and largely supports the novel approach in identifying core constructs in problem drinkers.

Three of the four latent factors extracted in this independent sample support the ANA domains and reflect neurobiological mechanisms that are putatively related to the development and maintenance of addiction (Koob and Le Moal, 1997). The alcohol-related consequences factor explained the most variability and primarily reflects adverse results of heavy drinking in physical, interpersonal, intrapersonal, impulse control, and social responsibility domains (DrInC subscales). Additionally, weaker loadings on this factor included measures that represent loss of behavioral control, and psychoperceptual and psychosocial withdrawal. While the rationale for developing the DrInC was to measure alcohol problems as a distinct construct from DSM-IV alcohol dependence (Miller et al., 2000), the experience of alcohol-related consequences reflects multiple DSM-5 AUD domains. The magnitude and duration of negative consequences of alcohol use likely contributes to clinical severity of AUD. For example, individuals with AUD who are treatment seeking report greater alcohol-related consequences compared to non-treatment seekers (Ray et al., 2017). Thus, the alcohol consequences latent factor better reflects AUD phenomenology rather than a neurofunctional domain. However, the negative consequences factor is likely related to the ANA factors considering that disruption in the neurocircuits mediating their respective behaviors may be due to chronic and heavy alcohol consumption. In a similar vein, heavy drinking is associated with a host of negative social, occupational, and health problems (Stahre et al., 2014). As such, the consequences factor may be a useful predictor of AUD severity. It is also important to note that this domain accounted for the greatest percentage of common variance, which is likely related to characteristics of the sample who were primarily problem drinkers. Nonetheless, the other factors representing neuroscience-based (i.e., ANA) domains still explained a nontrivial amount of variability in the dataset and their inclusion in the final model was supported by robust eigenvalues.

Incentive salience can be defined as a psychological process where drug cue stimuli are transformed and imbued with salience, making them attractive (or salient). This process then leads to compulsive drug seeking due to the increased salience of the drug-cue, resulting in a pathological wanting, or craving, for a drug. This process has been linked to phasic

dopaminergic activity in mesocorticolimbic circuitry in response to reward-related cues, while also engaging habit formation and compulsive-like responding for drugs and alcohol via activation of cortical-striatal-pallidal-thalamic loops (Koob and Volkow, 2016). Individuals with substance use disorder show altered neural activity (Jasinska et al., 2014) and increased self-reported craving (Gilman et al., 2012) in response to drug-related cues. Our factor analytic work is in line with these preclinical and clinical studies. We found that indicators measuring aspects of drinking frequency and problems, obsessive and compulsive alcohol drinking, and craving loaded on to an incentive salience latent factor. This factor may represent a spectrum of the incentive salience process, where in the end-stages craving, compulsive and potentially habitual responding are the main drivers for alcohol seeking. Kwako et al. (2019) demonstrated that *single-item categorical* indicators from the ADS and OCDS, as well as depression and trait anxiety measures loaded onto a single factor. Our results suggest that *continuous* scores on the ADS Obsessive subscale, AUDIT subscales, both OCDS subscales, and PACS total score load onto the incentive salience factor. Notably, we did not observe high loadings for anxiety and depressive symptomology on this factor. In addition to differences in sample characteristics, discrepancies in factor loadings between our study and Kwako et al. (2019) may be due to how the ADS and OCDS indicator variables (categorical vs continuous) were used in factor analytic models. In this case, it is possible that continuous indicator scores better distinguished these traditional alcohol craving measures from mood-related dimensions. Future work is needed to examine whether single-item categorical responses or continuous scores on a given indicator are more useful indicators of the ANA domains. Furthermore, a validated, yet simplified, version of the assessment would have a host of benefits to dissemination. Although the self-report measures of incentive salience used in the current study dovetail the proposed ANA indicators (Kwako et al., 2016), behavioral measures of incentive salience, in combination with self-report measures, would provide a deeper understanding of dysfunction within this domain.

Negative emotionality refers to the increases in negative affective states, including dysphoria, anxiety, and anhedonia, that occur in individuals with AUD, particularly during alcohol withdrawal and craving (Heilig et al., 2010; Sinha et al., 2009). In individuals with AUD exposure to stress and alcohol cues induces a persistent negative emotional craving state which is associated with dysregulated physiological responses (Sinha et al., 2009). The neural mechanisms that contribute to this domain involve heightened activity in brain stress systems and dysregulation of antistress systems (Koob et al., 2014). The neural circuitry underlying negative emotionality includes the extended amygdala, lateral habenula, and ventral striatum (Heilig et al., 2016). Our results show that indicators of anxiety and depression symptomology reflect a negative emotionality domain, with highest factor loadings for the STAI Trait and BDI-II. Similarly, Votaw et al. (2020) showed the highest factor loadings for the BDI-II and BAI, with the lowest factor loadings for the DrInC items and trait anger scale. In contrast, Kwako et al. (2019) had the highest factor loadings for trait aggression and agreeableness. However, it is worth noting that the current study and previous work in clinical samples (Kwako et al., 2019; Votaw et al., 2020) suggests that anxiety measures represent significant indicators of negative emotionality.

Dysfunction in executive processes is well documented among individuals with substance and alcohol use disorders. Indeed, evidence shows that individuals with substance use disorders have deficits in attention, response inhibition, planning, working memory, behavioral flexibility, and valuation of future events (Goldstein and Volkow, 2011). Loss of top-down control in the frontal cortex is paralleled by aberrant glutamatergic signaling to the basal ganglia and extended amygdala, perpetuating compulsive drug and alcohol use. Our results demonstrate that items measuring attention (Digit Span Forward), working memory (Digit Span Backwards), and valuation of future rewards (delay discounting) correspond to an executive function latent factor, with the Digit Span Forward and Backwards scores having the highest factor loadings. These measures partially capture executive functions that organize behavior across time and enhance consideration of, and planning for future situations. Importantly, a subset of executive functions (i.e., valuation of future rewards) share more definitional and neurobiological overlap with state impulsivities (i.e., choice impulsivity) relative to trait impulsivity (Bickel et al., 2012). In contrast to Kwako et al. (2019), we were not able to retain a trait impulsivity latent factor using the BIS subscales. Given that trait impulsivity can be conceptualized as a stable personality trait relevant to AUD, it is possible that the differences between studies can be attributed to variation in racial/ethnic makeup of the study sample, range of drinking behaviors, and the presence of comorbid substance use disorders. Thus, these findings should be replicated in a large sample across racial and ethnic groups that better reflect the U.S. general population.

Since we did not employ a control sample for the present study, we cannot directly speak to how these domains would apply to a population without hazardous alcohol use. However, in a population with hazardous alcohol use, the ANA domains could inform alcohol-specific outcomes and treatments (Heilig et al., 2010). In the incentive salience domain, those with high incentive salience are likely to have greater craving for alcohol and thus may benefit from treatment specifically targeting craving and reward from alcohol. Pharmacological treatment options that have been shown to reduce craving include naltrexone and acamprosate (Blanco-Gandía and Rodríguez-Arias, 2018). Individuals with a large degree of negative emotionality may benefit from treatments that address mood dysphoria and substance use concurrently considering the increase in negative affective states that is likely to occur during alcohol withdrawal and craving. A recent review of pharmacotherapy options for comorbid depression and alcohol dependence found some support for the use of pharmacological treatment in individuals with co-occurring depression and AUD, as well as positive effects for the use of antidepressants on various outcomes related to major depression and AUD (Hillemacher and Frieling, 2019). In the domain of executive (dys)function, cognitive rehabilitation with tasks that involve memory, attention, or executive function may be helpful in restoring impairments in this domain caused by excess alcohol use (Bates et al., 2002). Lastly, in the domain of alcohol-related consequences, we note that high levels of negative consequences related to alcohol use are generally associated with severity of problems and motivation for treatment-seeking (Moallem et al., 2013).

The observed associations between ANA domains and demographic and clinical variables provided a consistent theme, whereby high scores on incentive salience and negative emotionality domains were significantly and positively associated with drinking variables and AUD. The association between the executive function domain and alcohol use variables

was less robust, although a family history of alcohol problems contributed to lower executive function scores. Additional measures should be utilized to assess the construct validity of ANA domains. For example, individuals seeking treatment for AUD differ from non-treatment-seeking participants on a host of demographic and clinical measures including greater alcohol consumption, alcohol craving, and AUD symptom counts (Ray et al., 2017). Thus, determining the relationship between treatment seeking status and ANA domains is an important area for future research. While the results of the current study complement the ANA framework, it is unclear how the proposed ANA domains might change over the course of AUD development. Votaw et al. (2020) showed that the negative emotionality domain was relatively stable among AUD treatment-seekers over 12-months; however, whether incentive salience and executive functions are time invariant is unknown. To help address these and other questions, the NIH-funded Adolescent Brain Cognitive Development (ABCD) Study provides a unique opportunity to track ANA domains and examine their relationship with alcohol and substance use across development.

The results of this study must be interpreted in light of its strengths and limitations. Strengths include the large, well-characterized clinical sample, the use of well-validated measures, and the inclusion of individuals across a range of drinking phenotypes. Limitations include the considerable degree of missing data because not all individuals completed every assessment, the use of measures requiring retrospective recall, and the relative lack of behavioral measures. In addition, the exclusion criteria used across studies (i.e., psychiatric disorders, psychiatric medications, etc.) may limit generalizability.

On balance, this study used a deeply phenotyped clinical sample to provide an independent evaluation of the proposed ANA framework in a large independent sample. Results were largely consistent with the proposed factor structure comprised of incentive salience, negative emotionality and executive (dys)function. Future studies can deepen our understanding of how these domains are relevant to AUD by utilizing neuroimaging, genetic, and other levels of analyses. In conclusion, the ANA framework shows promise for capturing the heterogeneity of AUD through neuroscience-informed assessments that can be replicated and extended in independent samples.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Sample demographics and clinical measures across studies.

Measure	Total Sample (N=1,679)		
	N	Mean / %	SD
Sex			
Male	1,120	66.71%	
Female	512	30.49%	
Missing	47		
Age (Years)	1631	35.23	11.78
Missing	48		
Race/Ethnicity			
White (Non-Hispanic)	416	24.78 %	
Black/Other	1263	75.22%	
Family History of Alcohol Problems [a]			
Yes (FH+)	683	40.68%	
No (FH−)	677	40.32%	
Not Assessed	45		
Missing	12		
Age at First Drink [b]	902	16.16	3.83
Not assessed	777		
Drinking Days [c]	1641	18.22	8.61
Missing	38		
DPDD [c]	1641	5.97	3.56
Missing	38		
AUDIT Total [d]	917	14.99	7.90
Not assessed	762		
Current AUD [b]			
Yes	348	20.73%	
No	798	47.53%	
Not assessed	533		

[a] Family history of alcohol problems based on self-reports of at least one parent having alcohol-related problems (FH+; binary outcome: 0=No; 1=Yes); Derived from the Family Tree Questionnaire.

[b] Alcohol Use Disorder (AUD; binary outcome: 0=No; 1=Yes) and Age at First Drink based on the Structured Clinical Interview for DSM-IV (SCID-IV) or DSM-5 (SCID-5).

[c] Drinking Days and Drinks per Drinking Day (DPDD) based on the Timeline Followback conducted via interview.

[d] Alcohol Use Disorder Identification Test (AUDIT).

Table 2.

Pattern matrix for the exploratory factor analysis using measures from several domains.[a]

	Latent Factors (Eigenvalues / % Variance Explained)				
	Factor 1 35.66 / 66.65%	**Factor 2 6.65 / 12.44%**	**Factor 3 4.56 / 8.53%**	**Factor 4 3.64 / 6.81%**	**Factor 5 2.98 / 5.57%**
ADS Loss of Control	**0.440**	0.385	0.196	0.245	0.115
ADS Obsessive	0.381	**0.685**	0.240	−0.147	0.055
ADS Withdrawal	**0.427**	0.337	0.357	−0.112	0.079
AUDIT Consumption	0.273	**0.544**	0.049	0.066	0.022
AUDIT Dependence	**0.508**	**0.630**	0.156	−0.177	0.031
AUDIT Problems	**0.578**	**0.419**	0.201	−0.022	0.054
BAI Total	0.303	0.286	**0.599**	−0.020	0.200
BDI Total	0.226	0.185	**0.738**	−0.180	0.025
STAI Trait	0.249	0.201	**0.882**	−0.033	0.050
OCDS Obsessive	0.390	**0.686**	0.247	−0.158	0.043
OCDS Compulsive	0.355	**0.753**	0.212	0.036	0.095
PACS Total	0.218	**0.812**	0.207	−0.036	0.048
Digit Span Forward	0.012	0.058	−0.125	**0.725**	0.042
Digit Span Backward	−0.048	0.037	−0.106	**0.770**	0.048
BIS Motor	0.125	0.145	0.181	0.025	**0.635**
BIS Nonplanning	−0.096	−0.095	−0.165	0.087	0.356
BIS Attentional	0.090	0.125	0.179	−0.007	**0.847**
Delay Discounting (k)	0.096	0.214	−0.044	**−0.407**	−0.018
DrInC Physical	**0.705**	**0.404**	0.269	0.008	0.045
DrInC Interpersonal	**0.865**	0.286	0.145	−0.150	0.005
DrInC Intrapersonal	**0.777**	0.224	0.267	−0.068	0.006
DrInC Impulse Control	**0.740**	0.326	0.123	−0.049	0.045
DrInC Social Responsibility	**0.829**	0.272	0.170	−0.035	0.017

[a]Boldface indicates factor loadings ≥ 0.40. ADS = Alcohol Dependence Scale; AUDIT, Alcohol Use Disorder Identification Test; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; OCDS = Obsessive-Compulsive Drinking Scale; PACS = Penn Alcohol Craving Scale; BIS = Barratt Impulsiveness Scale; DrInC = The Drinker Inventory of Consequences.

Table 3.

Pattern matrix for the exploratory factor analysis using measures from several domains.[a]

	Latent Factors (Eigenvalues / % Variance Explained)			
	Factor 1 34.68 / 72.79%	**Factor 2 5.69 / 11.93%**	**Factor 3 4.18 / 8.77%**	**Factor 4 3.10 / 6.51%**
ADS Loss of Control	**0.431**	0.380	0.264	0.236
ADS Obsessive	0.371	**0.670**	0.287	−0.172
ADS Withdrawal	**0.414**	0.317	0.391	−0.135
AUDIT Consumption	0.269	**0.541**	0.099	0.055
AUDIT Dependence	**0.501**	**0.621**	0.194	−0.199
AUDIT Problems	**0.570**	**0.410**	0.245	−0.040
BAI Total	0.284	0.255	**0.645**	−0.048
BDI Total	0.207	0.127	**0.741**	−0.247
STAI Trait	0.231	0.140	**0.879**	−0.111
OCDS Obsessive	0.380	**0.666**	0.293	−0.186
OCDS Compulsive	0.346	**0.740**	0.283	0.017
PACS Total	0.211	**0.792**	0.267	−0.063
Digit Span Forward	0.018	0.068	−0.061	**0.729**
Digit Span Backward	−0.042	0.046	−0.042	**0.766**
BIS Motor	0.105	0.185	0.270	0.091
BIS Nonplanning	−0.101	−0.048	−0.119	0.154
BIS Attentional	0.071	0.180	0.279	0.083
Delay Discounting (k)	0.093	0.215	−0.057	**−0.404**
DRINC Physical	**0.695**	0.386	0.319	−0.019
DRINC Interpersonal	**0.861**	0.277	0.170	−0.170
DRINC Intrapersonal	**0.770**	0.203	0.295	−0.098
DRINC Impulse Control	**0.733**	0.323	0.162	−0.060
DRINC Social Responsibility	**0.824**	0.262	0.204	−0.056

[a]Boldface indicates factor loadings ≥ 0.40. ADS = Alcohol Dependence Scale; AUDIT, Alcohol Use Disorder Identification Test; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory; OCDS = Obsessive-Compulsive Drinking Scale; PACS = Penn Alcohol Craving Scale; BIS = Barratt Impulsiveness Scale; DRINC = The Drinker Inventory of Consequences.

Table 4.

Relationship between ANA domains and demographic and clinical variables.[a]

	Consequences			Incentive Salience			Negative emotionality			Executive Function		
	β	**SE**	**p-value**	**β**	**SE**	**p-value**	**β**	**SE**	**p-value**	**β**	**SE**	**p-value**
Sex[b]	**0.083**	**0.040**	**0.038**	**0.179**	**0.070**	**0.012**	0.016	0.028	0.843	0.077	0.058	0.1903
Age	**0.154**	**0.039**	**<0.001**	**0.196**	**0.069**	**0.005**	**0.201**	**0.083**	**0.018**	**−0.387**	**0.054**	**<0.001**
Race[c]	−0.042	0.040	0.289	−0.020	0.025	0.443	−0.078	0.084	0.354	**−0.340**	**0.055**	**<0.001**
Age at first drink	**−0.157**	**0.054**	**0.004**	**−0.168**	**0.070**	**0.018**	−0.102	0.085	0.233	−0.003	0.038	0.712
FH+[d]	**0.215**	**0.043**	**<0.001**	**0.328**	**0.087**	**<0.001**	−0.049	0.090	0.589	**−0.278**	**0.057**	**<0.001**
Drinking Days	**0.369**	**0.048**	**<0.001**	**0.562**	**0.058**	**<0.001**	**0.265**	**0.081**	**0.002**	−0.048	0.148	0.768
DPDD[e]	**0.424**	**0.047**	**<0.001**	**0.411**	**0.064**	**<0.001**	0.097	0.084	0.250	0.112	0.160	0.491
AUD[f]	**0.501**	**0.036**	**<0.001**	**0.567**	**0.058**	**<0.001**	**0.218**	**0.083**	**0.010**	−0.015	0.065	0.816

[a] Estimates are standardized coefficients. Values in boldface indicate significant predictors on each domain.

[b] Sex (0=Female, 1=Male)

[c] Race (0 = Non-Hispanic White, 1 = Black/Other)

[d] FH+, Family History of Alcohol Problems (0=No, 1=Yes)

[e] DPDD, Drinks per Drinking Day

[f] AUD, Alcohol Use Disorder (0=No, 1=Yes)