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Abstract:

Objective: Interindividual variation in responses to alcohol is substantial, posing challenges for medical management and for understanding the biological underpinnings of alcohol use disorders (AUD). It is important to understand whether diverse alcohol responses such as sedation, which is predictive of risk and partly heritable, occur concurrently or independently from responses such as blackouts and withdrawal. We hypothesized that latent factors accounting for sources of variance in diverse alcohol response phenotypes could be identified in a large, deeply phenotyped sample of patients with AUD.

Methods We factor analyzed 17 alcohol response related items from the Alcohol Dependence Scale (ADS) in 938 individuals diagnosed with AUD via structured clinical interviews. Demographic, genetic, and clinical characteristics were tested as predictors of the latent factors by MIMIC analysis.

Results: The final factor solution included three alcohol response factors: Physical Symptoms, Perceptual Disturbances, and Neurobiological Effects. Both gender and genetic ancestry were identified as variables influencing alcohol response. Major depressive disorder positively predicted physical symptoms and aggression negatively predicted physical symptoms. Barratt's Impulsivity Scale total score predicted the Physical and Perceptual domains. Family history, average drinks per drinking day, and negative urgency (an impulsivity measure) predicted all three domains.

Conclusions Diverse items from the ADS concurrently load onto three correlated alcohol response factors rather than loading independently. Genetic ancestry and clinical characteristics predicted the severity of items that define the alcohol response factors even after accounting for degree of alcohol consumption. Co-occurring phenotypes point towards an underlying shared physiology of diverse

alcohol responses.

Keywords:

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Main text:

Background:

On a global basis, alcohol misuse and its consequences, including alcohol use disorder (AUD), are leading causes of death and loss of disability-adjusted life-years in both sexes. In 2016, alcohol use was the largest risk factor for deaths in people aged 15-49 (1). While the prevalence of AUD and heavy drinking in US males has changed relatively little in the past several years, both have increased dramatically in women (2). Alcohol use and dependence also account for a vast demand for hospital resources, with over 1 million people hospitalized under diagnoses related to alcohol in 2010 (3).

The psychotropic effects of alcohol encourage its use, and both directly and indirectly lead to morbidity and mortality. Psychotropic effects include euphoria, sedation, anxiolysis, and diminished motor and cognitive performance (4). Clinical manifestations of excessive alcohol use and withdrawal include autonomic dysfunction, perceptual disturbances, blackouts (including both episodic amnesia and lapses in executive cognitive control), self-harm, aggression directed against others, and seizures. These alcohol-related events often necessitate emergency room visits and hospitalizations, with alcohol-related emergency room visits increasing by 61% between 2006 and 2014 (2).

Both in humans and in animal models, interindividual variation in alcohol responses is substantial and is partly heritable (5); inbred rat and mice strains tested under similar conditions of rearing and exposure vary in alcohol responses such as sedation and withdrawal. Heritability of addictions has both substance-specific and substance-nonspecific components exemplified by polymorphisms in drug receptors and enzymes involved in metabolism, as well as shared heritability of addiction vulnerability, variation in reward, stress resiliency, and executive cognitive functioning (6). Heritable variation in alcohol response has stimulated studies to identify genes responsible, as genes influencing alcohol response could also influence vulnerability to other addictions. Alcohol response phenotypes that have been artificially selected in rodent strains include sensitivity to sedation (e.g. the Short Sleep/Long Sleep mice) and withdrawal (e.g. Withdrawal Seizure Resistant/Seizure Prone mice). Additionally, High Response (HR)/Low Response (LR) rat lines have been developed as a model of arousal predictive of alcohol and drug liking (7). The ability to artificially select response phenotypes in animals indicates that some differences in alcohol response are innate, with moderate heritability. In humans, twin studies on subjective response to ethanol indicate that sensitivity to the sedative effects of ethanol is moderately heritable (8).

Pharmacogenomic studies of alcohol response have established that interindividual variation in responses is both pharmacokinetic in origin, as illustrated by *ADH1B* and *ALDH2* variants that cause alcohol-induced flushing (6), and pharmacodynamic, as illustrated by lack of difference in alcohol metabolism to explain variation in alcohol-induced sedation in humans (9) and mice (10). Overall, genetic sources of variability in response remain poorly understood, restricting insights into physiologic mechanisms, the extent to which these response phenotypes are independent or co-determined, and relationships to other heritable phenotypes. Genome wide association studies (GWAS) of AUD have found no loci of large effect beyond single nucleotide polymorphisms (SNPs) at the alcohol dehydrogenases (*ADH)* gene cluster and at the aldehyde dehydrogenase gene *ALDH2*. Potentially, genes of large effect will be identified for other responses. For example, a recent study of novelty response in

the HR rat, a strain selected for a phenotype predictive of addiction liability, found seven genome wide significant loci accounting for a third of the variance in that phenotype, and two thirds of the genetic variance (7).

Both genotypic and phenotypic characterizations of alcohol responses are germane for uncovering predictors of clinical and behavioral outcomes in individuals with AUD or at risk. Previous research relating to clinical alcohol response characterization has focused on the relationship of response to alcohol consumption and AUD. Schuckit found that men around 20 years old who reported a lower response following oral alcohol challenge on subjective measures of alcohol effects, and who differed in objective measures such as body sway and cortisol, were more likely to develop AUD (11), suggesting that a lower response to internal cues during alcohol consumption leads to excessive drinking (low level response theory). Newlin and Thompson (12) added the insight that higher risk drinkers often experience greater stimulant effects along with lower sedation than lighter drinkers. King found that positive and negative effects of alcohol predicted alcohol behaviors and found that in heavy drinkers, peak “liking” and “wanting”, as well as lower sedation, predicted future drinking binges, worse consequences, and higher likelihood of AUD (13).

In this study, we sought to identify common factors underlying alcohol responses using a large, deeply phenotyped clinical sample and factor analysis of 17 Alcohol Dependence Scale (ADS) items. The ADS was derived from factor scales described by the Alcohol Use Inventory (14) focusing on alcohol use in the previous 12 months. The items of the ADS were constructed by Skinner and Allen (15) with weight placed on areas related to loss of behavioral control, obsessive drinking style, and psychophysical/psychoperceptual withdrawal symptoms. In a validation of the ADS by Doyle and Donovan (16), a three-factor solution was elucidated representing these same three domains. Outside of the ADS, Mundt et al. described three orthogonal factors corresponding to psychomotor, subjective, and physiological (body temperature, oculomotor) response domains (17). Our study expands upon these findings by seeking to gain a better mechanistic understanding of variation in physical alcohol responses

specifically, rather than behavioral or control differences, and implicating genetic bases in the correlation of response domains.

Alcohol response factors emergent from this approach were used to ask whether diverse alcohol response phenotypes correlate with latent factors, implying concurrent effects and a shared genetic mechanism, or remain independent. Factor scoring on alcohol response factors could have diagnostic and predictive utility, potentially providing a tool to identify genetic and other sources of variability.

Methods: (See Supplementary Methods)

Study Sample: Participants were 938 individuals diagnosed with AUD via structured psychiatric interview (SCID), either meeting DSM-5 criteria for AUD or DSM-IV criteria for alcohol dependence/abuse. All study participants provided written informed consent under a natural history protocol approved by the NIH institutional review board.

Statistical Analyses: Factor analysis was performed using 17 alcohol response related items from the ADS (out of 25 total) as indicator variables. The 17 items chosen were specific alcohol response phenotypes such as hangover, hallucinations, passing out, and convulsions (see Table 2). The other 8 items were excluded because they did not pertain to physical alcohol responses. The data set was randomly split into 2 halves (each with n= 469), one for exploratory factor analysis (Group 1) and a test set for confirmatory factor analysis (Group 2). Exploratory factor analysis in Group 1 (EFA_1) identified latent factors underlying the indicator variables (Table 2). In Factor Analysis, and unlike Principal Component Analysis, factors can be non-orthogonal and intercorrelated. Analyses were conducted in Mplus version 7.4. Weighted least squares was used to estimate the model and the geomin oblique rotation was applied, allowing correlation between factors as recommended when indicators are predicted to load onto more than one factor. Factor selection was guided by examination of fit indices and overall interpretability. The fit indices examined were the root mean square error of approximation

(RMSEA), the comparative fit index (CFI) and the Tucker-Lewis index (TLI). The recommendations of Hu et al. were followed, which suggest CFI and TLI values above 0.95 and RMSEA values below 0.06 to represent good model fit (18). Variables with a loading ≥0.35 were considered to load onto a particular factor. Confirmatory factor analysis (CFA), which fit the indicator items in Group 2 onto the factor structure pre-determined by Group 1, was performed in the test data set to ensure that model fit was still acceptable. In the CFA, variables with loadings <0.35 in EFA_1 were fixed at 0, and modification indices, which reflect improvements in model fit with addition of previously omitted and freely estimated parameters (19), were examined and applied if they improved model fit and were conceptually meaningful. Good model fit was then tested in the full dataset.

In order to assess for stability of item loadings onto the factors, a replication of the factor analysis was carried out using the same model and rotations as described above and further described in Supplementary Methods.

MIMIC Analysis: A multiple indicators, multiple causes (MIMIC) analysis, a model in covariance structure analysis previously described by Joreskog and Goldberger (20), was carried out to identify patient characteristics that predict how individuals score on each latent factor, or "multiple causes" for a latent factor that also has multiple indicators. A variety of social and demographic patient variables were assessed (Table 3) using self-report questionnaires administered under the Natural History Protocol. These questionnaires were part of a set of assessments that were collected over a period of time to characterize a range of phenotypes, including but not limited to alcohol use behaviors, comorbidities (mental health history, substance use measures), and personality and behavioral traits (aggression, impulsivity) that may be associated with alcohol use disorder. Our previous work has examined these measures for group differences in addicted versus nonaddicted individuals as well as alignment with the neurofunctional domains of incentive salience, negative emotionality, and executive function that map onto the phases of the addiction cycle (21, 22, 23). The patient variables chosen in this

study (further described in Supplementary Methods) were used to ask whether physical responses to alcohol identified in this current study are predicted by the same characteristics.

We also tested sociodemographic characteristics including genetic ancestry, environmental factors (childhood adversity), and developmental markers (age at first drink) based on previously described biopsychosocial models for development of SUD (24, 25). Genetic ancestry information was extracted from genotyping on Illumina 850k arrays (data not shown) yielding ancestry informative markers (AIM scores) and analysis of functional variants.

Results: (figures attached separately)

Demographically, the 938 participants in this study were diverse (Table 1a, 1b). 31% were female, and 49% were Caucasian. Mean age at first drink was approximately 15 years, and average standard drinks per drinking day was approximately 13. All had a current diagnosis of AUD. 64% had an additional diagnosis of substance use disorder (SUD) at some point in their lifetime. There was a considerable, but not unexpectedly large, proportion of patients with co-morbid psychopathology, including 24% diagnosed with PTSD, 38.5% diagnosed with an anxiety disorder, and 29% with major depressive disorder. The average score on the ADS was close to 19.

Alcohol Response Factors: EFA_1 resulted in a good model fit for both a two-factor model (RMSEA=. 050, CFI = .976, TLI = .969) and a three-factor model (RMSEA = .036, CFI = .989, TLI = .984). The three-factor model had better fit indices and more distinctly grouped ADS response items, which allowed for more clear recognition of what each domain represented. Table 2 shows the factor loadings for the three-factor solution with each ADS item loading onto at least one of three factor domains described below.

Factor 1 (labeled “Physical”) encompassed physical symptoms related to alcohol use, with

positive loadings for hangovers, “shakes”, vomiting/cramps, delirium tremens, fevers, panic without drink, passing out, convulsions, unclear thinking, and rapid heartbeat. Factor 2 (labeled “Perceptual”) was defined by perceptual disturbances and included positive loadings for “seeing things not really there” and “hearing things not really there”. Factor 3 represents a “Neurobiological” domain, including positive loadings for ataxia, blackouts or loss of memory, and passing out in relation to drinking.

CFA performed in the test half of the data set determined that the items assigned to factors by EFA_1 still resulted in good model fit (RMSEA 0.062, CFI 0.963, and TLI 0.957). Final factor analysis of the full data set revealed a strong fit to the three-factor model (RMSEA = 0.057, CFI = 0.967, TLI = 0.961).

Stability of item loadings onto factors: Stability of factors and item loadings onto these factors from EFA_1 tested via second, independent EFA (EFA_2) are shown in Figure 1 (RMSEA= 0.034, CFI =0.991, TLI=0.987). Again, the factors still represented Physical, Perceptual, and Neurobiological categories and fit indices indicated good model fit. However, the items loaded somewhat differently in EFA_2, resulting in less distinct grouping of ADS items (greater cross-loading of items onto two different factors). Factor loadings from the EFA_1 and EFA_2 reveal that while some indicator items loaded strongly onto the same factors each time, others loaded onto different factors or cross-loaded in one group, but not the other. The factor solution and item loadings of EFA_{Total} (RMSEA= 0.034, CFI= 0.991, TLI= 0.986) closely resembled the EFA_1 factor solution. EFA_1 was chosen to be the final factor solution because of better interpretability and was used for the following MIMIC analysis.

The three factors were moderately to highly correlated, as shown in Figure 2 (Factor 1 with Factor 2= 0.762, Factor 1 with Factor 3= 0.735, and Factor 2 with Factor 3= 0.498, $p<0.0001$ for each).

Clinical predictors of alcohol response factors: Results from the MIMIC analysis (Table 3) showed that genetic information and gender predicted domain-specific responses. A history of major depression

predicted more physical symptoms. Aggression negatively predicted physical symptoms and lack of premeditation (planning/deliberation before an act) negatively predicted perceptual symptoms. Barratt's Impulsivity Scale total score predicted the Physical and Perceptual domains. Family history (proportion of 1st and 2nd degree relatives with alcohol-related problems), average drinks per drinking day, and negative urgency (an impulsivity measure) predicted all three domains. MIMIC results are graphically depicted in Figure 3.

Discussion

AUD patients are diverse in age, gender, genetic background, developmental exposures, age at onset, psychiatric comorbidity, level of illness, and more. Despite this diversity, a common underlying structure of responses to alcohol can be detected. We successfully identified three latent factors underlying diverse alcohol response phenotypes: Physical Symptoms, Perceptual Disturbances, and Neurobiological Effects. Furthermore, MIMIC analysis identified a range of patient characteristics as well as genetic ancestry information that predicted how individuals scored on each of these factors. From this we ascertain that genes that have not yet been identified underlie the mechanistic process leading to variation in alcohol response.

Factor scores created from this analysis (Figure 2), synthesizing inputs from multiple items, are potential targets for mechanistic studies, reducing the complexity of data and more robustly measuring latent traits than individual items even within a disease as causally and clinically complex as AUD. Future applications can include genetic studies using individual loci implicated by GWAS, measured ancestry, or polygenic risk scores (PRS) to predict response domains. Future directions can also include studies of prevention and treatment, with response domains being important both as markers of liability and as predictors of adverse consequences that might be ameliorated or exacerbated by treatment.

The concurrent loadings of indicator items onto the Physical factor indicate possible shared genetic liability underlying domain-specific alcohol responses. Rodent models have allowed for

mapping of genes related to alcohol sensitivity and withdrawal. However, genes implicated in these response phenotypes remain largely independent (26). Inbred mouse strains differ significantly in alcohol withdrawal severity, independent of strain differences in alcohol metabolism. Studies by Metten and Crabbe showed that around one-third to one-half of the total variability in withdrawal among animals is influenced by genetic factors. However, commonalities in genetic risk factors for the diverse physical symptoms exhibited by patients have yet to be discovered. Our primary analyses suggest that it may be worthwhile to undertake genomic studies to further investigate a shared genetic basis of responses to alcohol that may exist in humans.

Clinically, it is important that multiple indicators loaded onto the Physical symptom domain. ADS items did not load independently, but instead co-loaded onto the Physical factor, implying concurrent effects of different phenotypes on the overarching domain. Based on these results, clinicians should be aware that patients presenting with one alcohol-related physical problem are at risk of emergence of other physical problems as well. Patients should be surveilled for these and could possibly benefit from prophylactic treatment.

An animal model is lacking to study the genetics or physiology of alcohol induced blackout (AIB). However, the existence of a Neurobiological Effect domain or "blackout domain" implies that specific physiologic and genetic differences influence AIB. AIB are a concern practically unique to AUD as compared to other addictions. Blackouts are significantly associated with a lifetime diagnosis of AUD, with stronger associations seen with higher frequency of blackouts (27). AIB often foreshadow severe AUD symptoms over the course of the disease (27). Blackouts are distinct from passing out because the individual is conscious and capable of carrying out a conversation, but suggestible. They are thought to occur because of alcohol–induced disruption of the hippocampus, a brain region that is vital in the formation of new autobiographical memories (28). Episodic memory fails in blacked out individuals who often awaken the following day with no recollection of events that took place while in a state of diminished self-control. This chain of events dramatically increases risk of hazardous accidents,

physical violence, sexual assault, and other serious harm to themselves and others (29).

The problem of blackouts is compounded by the fact that AUD patients with blackouts are likely to have other problematic responses to alcohol as well. We found that individuals who loaded highly onto the Neurobiological domain were likely to be high scorers in the other domains because each of the three factors were intercorrelated. It has been shown that psychiatric disorders that tend to be comorbid have genetic liability that is partly shared, as seen in the case of schizophrenia and SUD (30). Understanding the genetic basis of these response domains and discovery of shared liability will allow for development of better treatment and prevention strategies for emergent clinical problems.

Clinical Correlates of Alcohol Response Factors: A genetic basis underlying scoring on alcohol response factors is further evidenced by ancestry-informed prediction of individual factor scoring in the response domains. Participants with alleles highly differentiated in ancestral African populations were less likely to indicate physical symptoms as well as blackout symptoms after controlling for amount of alcohol used. Along the same lines, gender was a predictor of scoring on the Physical domain.

Interestingly, social and demographic variables predict the severity of alcohol response factors in individuals, outside of the influence of simply drinking more alcohol. Suggestive of the multidimensionality of AUD, indicator items for response factors are tied to other aspects of the clinical picture. Such environmental predictors likely interact with genetic liability in a gene-environment interplay leading to level and diversity of alcohol responses. Indicator items for the Physical factor encompass many of the symptoms of alcohol withdrawal (AW) including delirium tremens and seizure and are predicted by major depressive disorder (MDD). These results point towards the possibility that dysphoria and negative emotionality contribute to more severe physical symptoms in patients with AUD. Shared neural mechanisms may underly negative emotional state, stress, and physiologic withdrawal. In fact, the pathophysiology of withdrawal, familiar to clinicians as irritability, tremors, hallucination, and seizure, is thought to involve the effects of stress hormones on neurotrophic factor

signaling (31). Furthermore, addictive substances induce adaptive changes in brain function that are the bases for tolerance, craving, withdrawal and affective disturbance. The ability of addictive drugs to adaptively shift the brain to an allostatic state leads to long-lasting negative emotionality and predisposes to relapse triggered by either stress or drug-related cues (32). Considerable interindividual variation exists in sensitivity and resilience and is partly heritable due to the influence of functional variants of genes mediating stress or stress response. Examples of the former are the *NPY* (33) and *FKBP5* (34) genes and an example of the latter is the *SLC6A4* polymorphism altering serotonin transporter expression in the amygdala, changing response to emotional stimuli (shown by fMRI) and contributing to dysphoria and drug consumption after exposure to stress (35). The close relationship between affective disturbance, alcohol use, and withdrawal should be monitored by clinicians, who may be able to prevent lapse and relapse by targeting motivation enhancement therapy towards negative emotionality traits.

Negative urgency is shown to underlie all three domains of alcohol response. Negative urgency involves acting rashly when in extreme distress. It has been proposed to derive from stress related to negative emotional states during withdrawal/negative affect stage of the addiction cycle (36). Strong individual differences in impulsivity precede addiction and impulsivity is a liability factor that has been tied to several genes, including a stop codon of the HTR2B receptor (37). The frontal cortex mediates executive cognitive function and moderates impulsivity, as evidenced by lesions of the frontal cortex that disinhibit behavior, the effects of drugs (e.g. methylphenidate), functional genetic variants (e.g. COMT Val158Met) that modulate dopamine levels, and fMRI response of this region (38). Impulsive behavior is thus the product of both urgency and moderation of impulse and can be tied to different, interacting regions of the brain. The imbalance between the two is accentuated by alcohol intoxication. Liability to partake in uncontrolled drinking may be associated either with negative urgency or impulsivity with other origins, in either case leading to blackouts, which are thought to arise from dramatic and rapid increases in BAC (29).

Average drinks per drinking day predicted all three domains. Alcohol consumption measures were included in the analysis to control for amount of alcohol used when identifying predictors of the response domains.

Limitations: Because our clinical sample consisted of AUD patients with high levels of alcohol consumption, responses such as blackout, passing out, and seizure, which rely on heavy alcohol exposure for recognition, were more detectable in our sample. Our findings support the existence of three alcohol response domains; however, these results are also limited by the items chosen in the ADS. Another limitation of this study was that we did not differentiate patients in our population sample that had moderate versus severe alcohol use disorder. A future study with this differentiation may give better insight into what predicts future alcohol use behaviors and which predictors may be relevant for moderate drinkers versus severe drinkers.

Few of the patients we studied carried functional polymorphisms of *ADH1B* and *ALDH2* that trigger alcohol-induced flushing and might alter other alcohol responses, as well (see Supplementary Methods). Our sample was predominantly European and African American and contained few individuals of East Asian descent. None of our subjects carried protective Arg48 and ALDH2 Lys487 alleles. Therefore, we had limited ability to relate flushing to other alcohol response items.

Conclusions: We identify three factors relevant for diverse alcohol response phenotypes, Physical Symptoms, Perceptual Disturbances, and Neurobiological Effects. Diverse items from the ADS concurrently load onto the same factors rather than loading independently. Gender, ancestry, personality traits, and degree of alcohol consumption predict the severity of items that define the alcohol response factors. Patients presenting with one problem, for example delirium tremens or blackouts, are likely to experience several problems in clinical settings, either acutely or sometime in the future. These co-occurring phenotypes point towards an underlying shared physiology of diverse alcohol responses.

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Figure Legends

Table 1a and 1b. Demographic and clinical characteristics of participants with alcohol use disorder in factor analysis (n = 938)*.

[a] Based on the Structured Clinical Interview for DSM-IV Disorders and DSM-5 Disorders (SCID-IV, SCID-5)

[b] Alcohol Dependence Scale (ADS)
25 items with Likert Scale scoring
0: No evidence of alcohol dependence
1-13: Low level of alcohol dependence
14-21: Intermediate level of alcohol dependence
22-30: Substantial level of alcohol dependence, physical dependence likely
31-47: Severe level of alcohol dependence

[c] Timeline Follow-back (events recounted over past 90 days- average number of drinks per drinking day.)

[d] Alcohol Use Disorders Identification Test (AUDIT)
A total score of more than 8 indicates harmful or hazardous drinking

[e] Lifetime Drinking History (LDH) Questionnaire
LDH Questionnaire asks patients to note their age at first drink separately from questions about ages of regular drinking and drinking frequency. The question does not delineate between self administration of first drink or administration by someone else.

[f] UPPS-P Impulsive Behavior Scale
The scale uses a 4 point Likert response format, with calculation of a mean for groups of items corresponding to the 5 scales: Negative Urgency, Lack of Premeditation (lack of planning/deliberation before an act), Lack of Perseverance, Sensation Seeking, and Positive Urgency. Higher scores indicate more impulsive behavior.

[g] Barratt's Impulsivity Scale (BIS)
Each item is scored on a 4 point Likert scale, producing scores for three subscales: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness.

[h] Buss-Perry Aggression Questionnaire (BPAQ)
29 items on a 5 point Likert Scale

[i] Childhood Trauma Questionnaire (CTQ)
Items corresponding to Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, and Physical Neglect scored on a 5 point Likert scale. Scores from each of the 5 scales (range 5 to 25) are summed to produce the Scale Total Score (range 25 to 125), used here.

[l] Perceived Stress Scale (PSS)
4 point Likert scale with 40 as maximum score. Higher scores indicate patients feel more unpredictable, uncontrollable, and overloaded in their lives.

[n] Self Reported Race

[p] Self- Identified Gender

*****Some questionnaires were not administered to all 938 participants. Two tailed tests were used.

Table 2. Final three-factor solution from factor analysis in participants with alcohol use disorder. Solution from Exploratory Factor Analysis (EFA_1) and Confirmatory Factor Analysis (CFA). Seventeen ADS items were used as indicator variables. "Passing Out" was the only item to cross-load onto two factors, Physical and Neurobiological.

*Indicates factor loadings >.350

+Indicates item did not meet criteria for factor loading (>.350), but conceptually fits into the domain.

Figure 1. Stability of item loadings on factors seen in alcohol use disorder.

Exploratory factor analysis performed in two groups (EFA_1, EFA_2) and then the full dataset (EFA_{Total}) show similar factor structures can be elicited from Alcohol Dependence Scale items. Factor loadings shown in parentheses.

*Indicates cross-loading of indicator item onto two different factors within the same analysis group

+Indicates item did not meet criteria for factor loading (>.350), but conceptually fits into the domain.

Figure 2. Individual participant scores on factors seen in alcohol use disorder.

The three factors were: Physical Symptoms, Perceptual Disturbances, and Neurobiological Effects. Factor scores are indicative of how each participant scored on each factor and scores produced have a mean of 0. Each factor correlated with the others and scoring onto each of the three factors was similar for each participant, i.e. high scorers in the Neurobiological domain were generally also high scorers on Physical and Perceptual domains. MIMIC (multiple indicators, multiple cases) analysis determined that males and females significantly differed in physical symptoms, but no other category.

Table 3. MIMIC model results in a study of alcohol use responses. MIMIC= multiple indicators, multiple causes. Estimates are standardized coefficients. Bolded items represent significant predicators of latent factors determined by exploratory factor analysis of Alcohol Dependence Scale items. (See Supplemental Methods for descriptions of the clinical assessments)

A preliminary MIMIC analysis was performed testing several variables that are not shown here because they were not shown to be significant. They are:

Lifetime diagnosis of PTSD[a]

Lifetime diagnosis of SUD[a]

Age at first drink[e]

Lack of Perseverance[f]

Sensation Seeking[f]

Positive Urgency[f]

Smoking status[k]

[a] Structured Clinical Interview for DSM-IV Disorders and DSM-5 Disorders (SCID-IV, SCID-5)

0= No history of disorder 1= History of disorder

[c] Timeline Follow-back (events recounted over past 90 days)

[f] UPPS-P Impulsive Behavior Scale

[g] Barratt's Impulsivity Scale (BIS)

[h] Buss-Perry Aggression Questionnaire (BPAQ)

[i] Childhood Trauma Questionnaire (CTQ)

[k] Smoking History Questionnaire (SHQ)

0= Non-smoker 1= Smoker

[m] Family Tree Questionnaire (FTQ)

Outcome measure is a Family History Density score, which is the proportion of first- and second-degree relatives with history of alcohol-related problems.

[n] Self Reported Race

0= Non-white/unknown 1 =White/Caucasian

[o] Ancestry Informative Marker Score

Proportion of ancestry of an individual relating to each population

[p] Self- Identified Gender

0= Male 1= Female

Figure 3. Plot of significant predictors of the three latent factors from the MIMIC analysis, using standardized coefficients.

Table 1a.

	Score Range	N		Minimum		Maximum		Median		Mean		Std. Deviation		p value
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	
ADS Score[b]	0-47	644	294	0	0	47	46	18	21	18.12	20.68	8.82	9.33	<0.001*
Avg Drinks Per Drinking Day[c]	-	644	294	0	1.74	73.07	80	12.55	9.27	13.75	11.44	8.46	8.38	<0.001*
Age First Drink (years)[e]	-	287	132	4	4	37	45	15	15	14.61	15.92	3.58	5.54	0.004*
Total Audit Score[d]	0-40	317	145	3	3	40	40	24	26	23.18	24.77	8.92	9.62	0.084
Negative Urgency[f]	1-4	541	256	1	1	4	4	2.5	2.75	2.49	2.69	0.68	0.71	<0.001*
BIS Total Score[g]	30-120	630	286	38	41	106	113	67	69	67.31	69.5	12.21	13.7	0.016*
Aggression Score[h]	29-145	630	286	29	30	135	131	69	67	71.35	70.48	21.06	22.28	0.567
Childhood Trauma Score[i]	25-125	624	287	25	25	110	125	36	43	41.46	47.86	16.8	20.35	<.0001*
Perceived Stress Score[l]	0-40	314	145	0	0	39	40	19	21	18.92	20.99	7.77	8.34	0.01*

Table 1b.

`	Frequency	Percent
Race[n]		
Non-white/unknown	478	51
White	460	49
Total	938	100
Gender[p]		
Male	644	68.7
Female	294	31.3
Total	938	100
Treatment Category		
Treatment-Seeking	174	18.6
Non Treatment-Seeking	764	81.4
Total	938	100
Lifetime Diagnosis of MDD[a]		
No	666	71
Yes	271	28.9
Missing	1	0.1
Total	938	100
Lifetime Diagnosis of PTSD[a]		
No	709	75.6
Yes	223	23.8
Missing	6	0.6
Total	938	100
Lifetime Diagnosis of Any SUD[a]		
No	334	35.6
Yes	604	64.4
Total	938	100
Lifetime Diagnosis of Any Anxiety Disorder[a]		
No	577	61.5
Yes	361	38.5
Total	938	100

Table 2

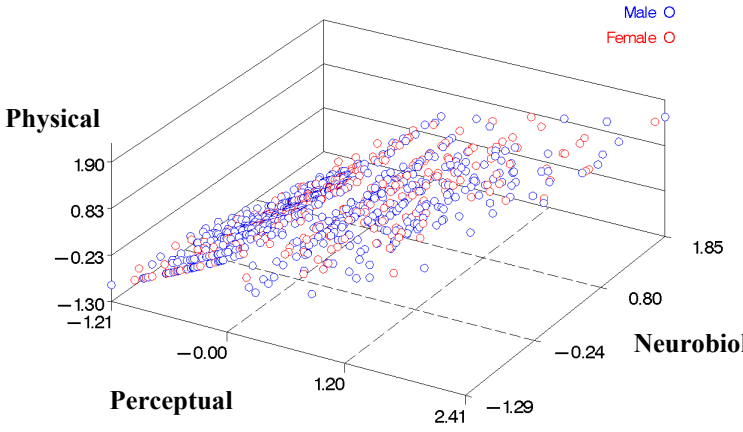
Alcohol Dependence Scale Items	Physical	Perceptual	Neurobiological
Do you often have hangovers on Sundays or Monday mornings?	**0.62***	-0.22	0.15
Have you had the "shakes" when sobering up (hands tremble, shake inside)?	**0.64***	0.02	0.03
Do you get physically sick (e.g., vomit, stomach cramps) as a result of drinking?	**0.65***	-0.02	0.04
Have you had the "DTs" (Delirium Tremens), that is, seen felt or heard things not really there; felt very anxious, restless, or overexcited?	**0.61***	0.25	-0.04
When you drink do you stumble about, stagger, and weave?	0.27	0.07	**0.48***
As a result of drinking, have you felt overly hot and sweaty (feverish)?	**0.59***	0.19	0.01
As a result of drinking, have you seen things that were not really there?	0.01	**0.84***	0.04
Do you panic because you fear you may not have a drink when you need it?	**0.53***	0.22	0.02
Have you had blackouts ("loss of memory" without passing out) as a result of drinking?	0.02	0.02	**0.92***
In the past 12 months, have you passed out as a result of drinking?	**0.35***	-0.07	**0.60***
Have you had a convulsion (fit) following a period of drinking?	**0.34**+	0.28	-0.05
After drinking heavily, has your thinking been fuzzy or unclear?	**0.52***	0.09	0.21
As a result of drinking, have you felt your heart beating rapidly?	**0.59***	0.18	-0.04
As a result of drinking, have you heard "things" that were not really there?	0.04	**0.92***	-0.02
Have you had weird and frightening sensations when drinking?	0.26	**0.50***	0.15
As a result of drinking have you "felt things" crawling on you that were not really there (e.g., bugs, spiders)?	-0.07	**0.78***	0.04
How long do your blackouts last? (<1 hour, several hours, or ≥1 day)	-0.02	0.03	**0.86***

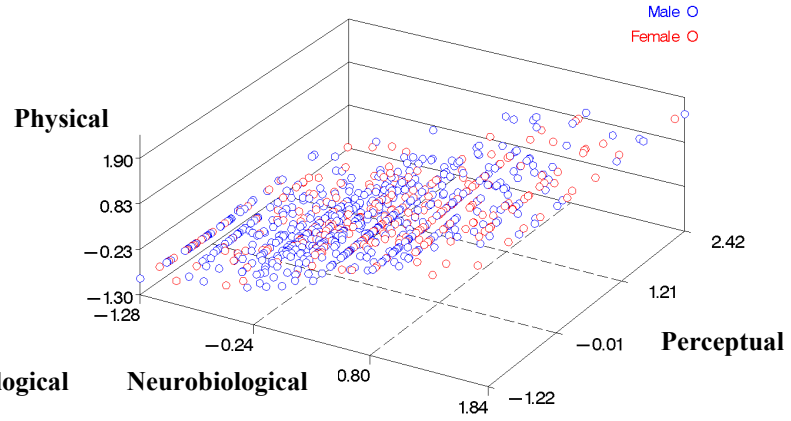
Table 3

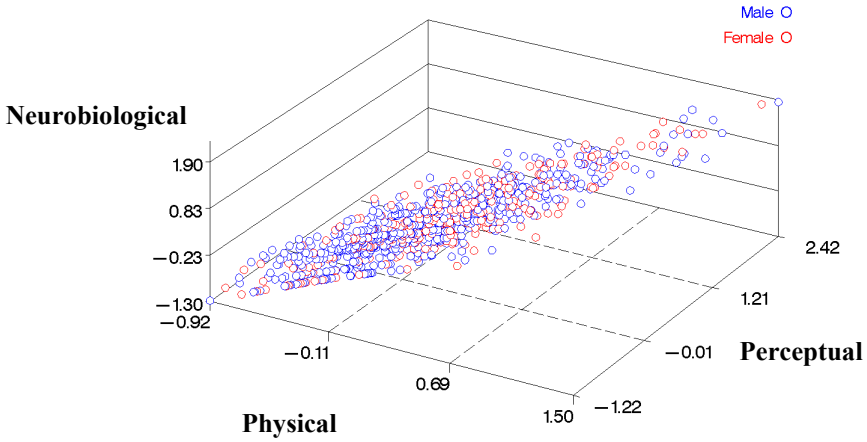
	Physical n=702			Perceptual n=702			Neurobiological n=702		
	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value
Lifetime history of MDD[a]	**0.095**	**0.036**	**0.009***	Lifetime history of MDD[a]	-0.006	0.048	0.900	Lifetime history of MDD[a]	0.068	0.038	0.075
Lifetime anxiety diagnosis[a]	0.069	0.037	0.062	Lifetime anxiety diagnosis[a]	0.092	0.050	0.067	Lifetime anxiety diagnosis[a]	0.036	0.040	0.369
Gender[p]	**0.099**	**0.036**	**0.006***	Gender[p]	0.010	0.049	0.830	Gender[p]	0.030	0.038	0.424
Africa[o]	**-0.194**	**0.099**	**0.050***	Africa[o]	-0.399	0.385	0.299	**Africa[o]**	**-0.466**	**0.204**	**0.022***
Europe[o]	-0.101	0.097	0.297	Europe	-0.695	0.393	0.077	Europe	-0.123	0.204	0.546
Asia[o]	-0.274	0.305	0.368	Asia	-1.778	1.273	0.162	Asia	-0.462	0.643	0.472
Negative Urgency[f]	**0.227**	**0.046**	**<0.0001***	**Negative Urgency[f]**	**0.331**	**0.104**	**0.001***	**Negative Urgency[f]**	**0.329**	**0.057**	**<0.0001***
Lack of Premeditation[f]	-0.023	0.031	0.448	**Lack of Premeditation[f]**	**-0.205**	**0.102**	**0.044***	Lack of Premeditation[f]	0.088	0.061	0.151
BIS Total Score[g]	**0.004**	**0.002**	**0.013***	**BIS Total Score[g]**	**0.014**	**0.005**	**0.011***	BIS Total Score[g]	0.001	0.003	0.813
Aggression[h]	**-0.003**	**0.001**	**0.002***	Aggression[h]	0.001	0.003	0.674	Aggression[h]	-0.001	0.002	0.484
CTQ Total Score[i]	0.001	0.001	0.315	CTQ Total Score[i]	0.003	0.003	0.184	CTQ Total Score[i]	0.001	0.002	0.754
Family History[m]	**0.223**	**0.092**	**0.016***	**Family History[m]**	**0.680**	**0.270**	**0.012***	**Family History[m]**	**0.756**	**0.175**	**<0.0001***
Avg Drinks Per Drink Day[c]	**0.014**	**0.003**	**<0.0001***	**Avg Drinks Per Drink Day[c]**	**0.016**	**0.005**	**0.003***	**Avg Drinks Per Drink Day[c]**	**0.014**	**0.003**	**<0.0001***

	Physical n=793			Perceptual n=793			Neurobiological n=793		
	Coefficient	SE	p-value	Coefficient	SE	p-value	Coefficient	SE	p-value
Lifetime history of MDD[a]	**0.205**	**0.072**	**0.005***	Lifetime history of MDD[a]	-0.031	0.096	0.747	Lifetime history of MDD[a]	0.144	0.078	0.066
Lifetime anxiety diagnosis[a]	0.102	0.071	0.151	Lifetime anxiety diagnosis[a]	0.155	0.095	0.103	Lifetime anxiety diagnosis[a]	0.049	0.079	0.535
Gender[p]	**0.215**	**0.073**	**0.003***	Gender[p]	-0.020	0.099	0.843	Gender[p]	0.085	0.077	0.275
Race[n]	**0.219**	**0.068**	**0.001***	Race[n]	-0.140	0.093	0.132	**Race[n]**	**0.284**	**0.073**	**<0.0001***
Negative Urgency[f]	**0.403**	**0.047**	**<0.0001***	**Negative Urgency[f]**	**0.230**	**0.065**	**<0.0001***	**Negative Urgency[f]**	**0.339**	**0.048**	**<0.0001***
Lack of Premeditation[f]	-0.051	0.041	0.218	**Lack of Premeditation[f]**	**-0.141**	**0.055**	**0.010***	Lack of Premeditation[f]	0.068	0.045	0.127
BIS Total Score[g]	**0.160**	**0.048**	**0.001***	**BIS Total Score[g]**	**0.197**	**0.063**	**0.002***	BIS Total Score[g]	0.021	0.052	0.681
Aggression[h]	**-0.171**	**0.042**	**<0.0001***	Aggression[h]	0.034	0.062	0.586	Aggression[h]	-0.063	0.045	0.163
CTQ Total Score[i]	0.050	0.035	0.161	**CTQ Total Score[i]**	**0.096**	**0.045**	**0.032***	CTQ Total Score[i]	0.020	0.037	0.588
Family History[m]	**0.080**	**0.034**	**0.020***	**Family History[m]**	**0.105**	**0.044**	**0.017***	**Family History[m]**	**0.149**	**0.038**	**<0.0001***
Avg Drinks Per Drink Day[c]	**0.292**	**0.034**	**<0.0001***	**Avg Drinks Per Drink Day[c]**	**0.125**	**0.044**	**0.004***	**Avg Drinks Per Drink Day[c]**	**0.141**	**0.034**	**<0.0001***

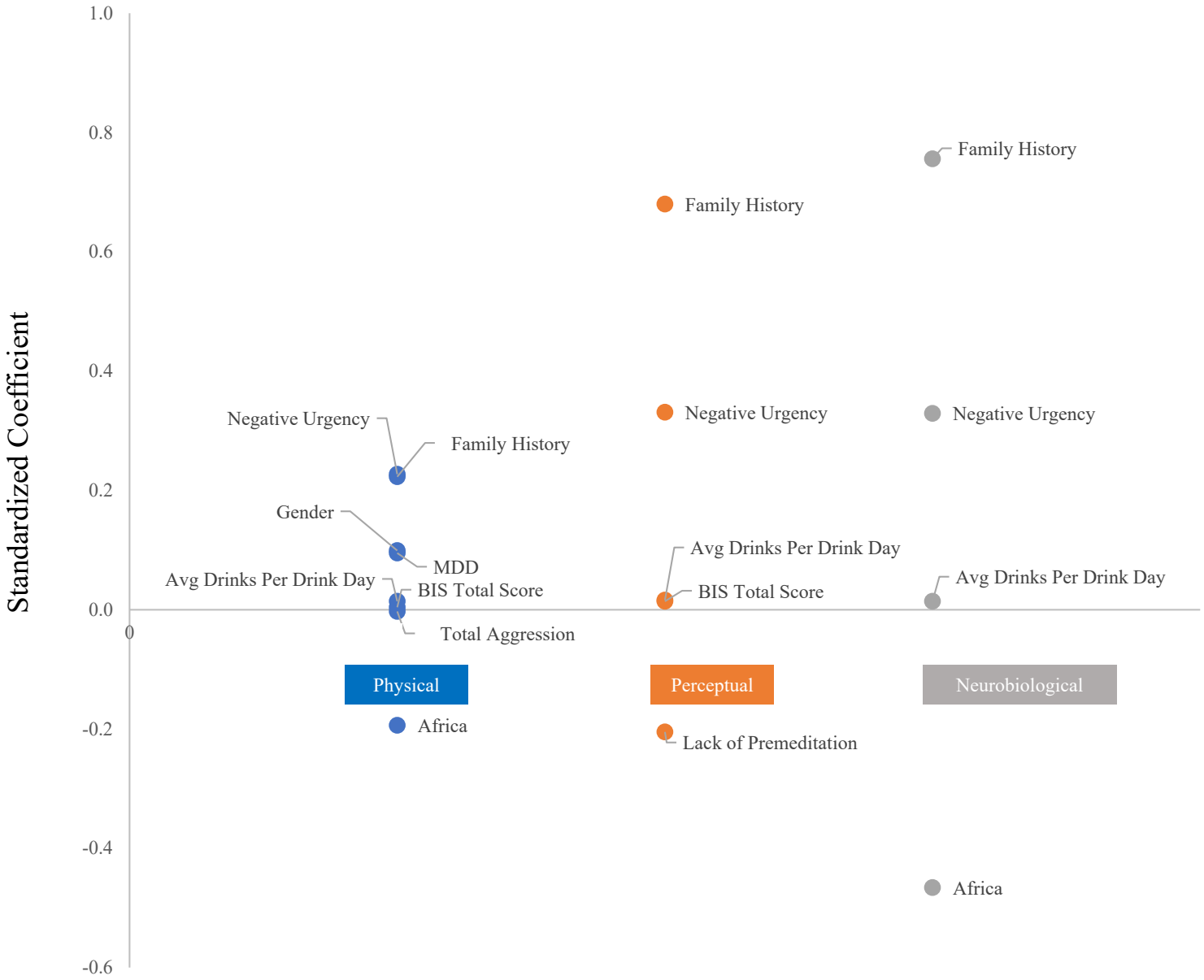
EFA_1	EFA_{Total}		EFA_2
Hangover (0.62)	Hangover (0.48)		"Shakes" when Sober (0.75)
"Shakes" when Sober (0.64)	"Shakes" when Sober (0.59)		Sick (vomit) (0.60)
Sick (vomit) (0.65)	Sick (vomit) (0.64)		Delirium Tremens (0.83)
Delirium Tremens (0.61)	Delirium Tremens (0.53)*	Physical	Feverish (0.79)
Feverish (0.59)	Feverish (0.65)		"Seen Things" not there (0.69)*
Panic without drink (0.53)	Panic without drink (0.58)		Panic without drink (0.79)
Passed out (0.35)*	Convulsions (0.34)+		Convulsions (0.48)
Convulsions (0.34)+	Fuzzy/Unclear thinking (0.43)		Fuzzy/Unclear thinking (0.47)*
Fuzzy/Unclear thinking (0.52)	Rapid Heart Beat (0.53)		Rapid Heart Beat (0.62)
Rapid Heart Beat (0.59)			"Heard Things" not there (0.57)*
			Weird/Fright Sensation (0.62)
			"Felt Things" not there (0.78)
"Seen Things" not there (0.84)	"Seen Things" not there (0.87)		
"Heard Things" not there (0.92)	"Heard Things" not there (0.92)	Perceptual	"Seen Things" not there (0.46)*
Weird/Fright Sensation (0.50)	Weird/Fright Sensation (0.56)		"Heard Things" not there (0.59)*
"Felt Things" not there (0.78)	"Felt Things" not there (0.73)		
	Delirium Tremens (0.37)*		
			Hangover (0.58)
Ataxia (0.48)	Ataxia (0.46)		Ataxia (0.55)
Amnesia (Blackout) (0.92)	Amnesia (Blackout) (0.84)	Neurobiological	Amnesia (Blackout) (0.84)
Passed out (0.60)*	Passed out (0.64)		Passed out (0.77)
Duration of Amnesia (0.86)	Duration of Amnesia (0.84)		Fuzzy/Unclear thinking (0.38)*
			Duration of Amnesia (0.85)







Correlations between factors (p<.0001):	
F1 with F2	0.762
F1 with F3	0.735
F2 with F3	0.498


Standardized Coefficient
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
0
Negative Urgency
Family History
Gender
MDD
Avg Drinks Per Drink Day
BIS Total Score
Total Aggression
Physical
Africa
Family History
Negative Urgency
Avg Drinks Per Drink Day
BIS Total Score
Perceptual
Lack of Premeditation
Family History
Negative Urgency
Avg Drinks Per Drink Day
Neurobiological
Africa

Highlights:

-Three common factors relevant for diverse alcohol responses are identified: Physical Symptoms, Perceptual Disturbances, and Neurobiological Effects

-Alcohol response items from the Alcohol Dependence Scale concurrently load onto these 3 factors rather than loading independently

-The 3 factors are correlated; patients presenting to clinicals settings with a problem such as delirium tremens are likely to experience several other problems either acutely or in the future