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Appetitive and aversive cue reactivities differentiate neural subtypes of alcohol drinkers

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Abstract

Craving reflects the subjective urge to use drugs and can be triggered by both positive and negative emotional states. No studies have systematically investigated the relative roles of these mechanisms in the pathophysiology of substance misuse. Here, we performed meta-analyses of drug cue-elicited reactivity and win and loss processing in the monetary incentive delay task to identify distinct neural correlates of appetitive and aversive responses to drug cues. We then characterized the appetitive and aversive cue responses in seventy-six alcohol drinkers performing a cue craving task during fMRI. Imaging data were processed according to published routines. The appetitive circuit involved medial cortical regions and the ventral striatum, and the aversive circuit involved the insula, caudate and mid-cingulate cortex. We observed a significant correlation of cue-elicited activity (β estimates) of the appetitive and aversive circuit. However, individuals varied in appetitive and aversive cue responses. From the regression of appetitive (y) vs. aversive (x) β, we identified participants in the top 1/3 each of those with positive and negative residuals as "approach" ($n = 15$) and "avoidance" ($n = 11$) and the others as the "mixed" ($n = 50$) subtype. In clinical characteristics, the avoidance subtype showed higher sensitivity to punishment and, in contrast, the approach subtype showed higher levels of sensation seeking and alcohol expectancy for social and physical pressure. The findings highlighted distinct neural underpinnings of appetitive and aversive components of cue-elicited reactivity and provided evidence for potential subtypes of alcohol drinkers.

Keywords

Alcohol; Drug cue; Individual variation; fMRI; Cue craving task (CCT); Monetary incentive delay task (MIDT)

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Declaration of Competing Interest

The authors declare that they have no competing interests in the current work.

Supplementary materials

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1. Introduction

As one of the diagnostic features of alcohol use disorders (AUDs) in DSM-5 [2], craving represents a psychological state in which individuals experience an intense urge to drink. A recent systematic review and meta-analysis suggested that craving plays significant roles in drug use and relapse outcomes and constitutes an important mechanism underlying substance use disorders (SUDs) [87]. It is of instrumental importance to investigate the psychological and neural processes underlying craving and potential individual differences in these processes [30].

Craving can be triggered by alcohol-related stimuli in the environment, memory of the reinforcing effects of alcohol, withdrawal symptoms, and negative mood. Thus, drinkers may experience craving in response to a wide range of cues. Thoughts of reinforcing effects motivate approach behaviors and engage individuals in alcohol seeking and consumption [44,50,98]. Withdrawal symptoms and anxiety may precipitate alcohol use to alleviate physical and mental distress [27,83]. It is also likely that positive and negative reinforcement both play an instrumental role in motivating alcohol misuse. That is, drinkers may experience a mixed emotional state during craving. Indeed, AUD is known to involve significant individual differences in personality traits, clinical manifestations, and psychiatric comorbidities, and individuals with AUD vary in the psychological, physiological, and neural processes perpetuating alcohol misuse [11,13]. A crucial question is whether craving is primarily an appetitive, aversive, or mixed psychological state and how individuals may experience craving because of these different mechanisms. The conventional phenotypes-based diagnostic classification may involve symptoms and signs of a heterogeneity of mental illness, and it has been argued in research domain criteria (RDoC) research that imaging biomarkers help in distinguishing the mechanisms of psychiatric disorders [16,17,60]. In the case of cue-induced craving, individuals report their craving in response to drug cues, and investigating how appetitive and aversive circuits respond to the cues would provide a venue to distinguishing the psychological mechanisms of craving, in the perspective of RDoC.

Numerous imaging studies have described the neural correlates of cue-induced craving [35,38,81,90,95]. A wide swath of brain regions, including the frontoparietal regions, anterior and posterior cingulate, occipital cortex, insula, striatum, amygdala, and thalamus showed higher responses during exposure to drug as compared to neutral cues in individuals with substance misuse, including AUDs [47,72,80,93,95,96]. Further, these regional activities were correlated with subjective urges to use drugs [5,6,14,42,56,63,67,85,90]. Substantial research has also revealed neural underpinnings of appetitive and aversive emotional states; for instance, studies of the monetary incentive delay task (MIDT) have characterized the neural correlates of win and loss processing [4,19,20]. In a recent study, we performed a comprehensive meta-analysis of imaging studies of MIDT [10] and noted significant overlap of the neural correlates of win and loss processing with those of cue reactivity. The “shared” neural responses may provide an opportunity to distinguishing individual appetitive and aversive drug cue reactivity.

To investigate the neural correlates shared by cue exposure and valenced motivational states, we conducted another meta-analysis of cue reactivity in the cue craving task (CCT). With the meta-analysis findings of MIDT [10] and CCT, we identified the brain regions that respond to both win processing and cue exposure and those to both loss processing and cue exposure, here referred to as appetitive and aversive circuit, respectively. We then characterized appetitive and aversive cue reactivities in an independent group of 76 alcohol drinkers exposed to alcohol and neutral cues during fMRI. Fig. 1 shows a conceptual overview of the analytics. We hypothesized individual variability in appetitive and aversive cue responses and significant differences in clinical characteristics between individuals showing higher appetitive vs. aversive reactivity (approach subtype) and those showing the opposite (avoidance subtype).

2. Methods

2.1. Meta-analyses of the CCT

Following the guidelines of "Preferred reporting items for systematic reviews and meta-analyses (PRISMA)", we searched the literature on PubMed for imaging studies of cue craving task (CCT) with the key words ((alcohol) OR (ethanol) OR (cannabis) OR (THC) OR (joint) OR (cocaine) OR (crack) OR (amphetamine) OR (methamphetamine) OR (nicotine) OR (smoking) OR (smoke) OR (tobacco) OR (cigarettes) OR (heroin) OR (opiates) OR (drug)) AND ((addiction) OR (dependence) OR (abuse) OR (consumption) OR (craving)) AND ((cue) OR (stimulus) OR (stimuli) OR (reactivity)) AND ((fMRI) OR (functional magnetic resonance imaging) OR (neuroimaging)) NOT (review) NOT (meta-analysis). We identified 1738 studies on February 20, 2022. We also searched on Google Scholar and PsycNet (https://psycnet.apa.org/) using the same key words but found no new studies. A flow-chart for the procedure to arrive at the final sample for meta-analysis is shown in Fig. 2.

Among the 1738 studies, only peer-reviewed original research articles in English language were included (n = 1547). Studies of the contrast of drug > neutral cue in smokers, alcohol drinkers, cocaine users, or individuals using other drugs, were included (n = 281). Medication or behavioral treatment studies were included only if the data of pretreatment scans were available. Studies (n = 44) were removed based on the exclusion criteria, including life-time diagnosis of schizophrenia, major/severe depressive disorder, bipolar or manic disorder, psychotic episodes, obsessive-compulsive disorder, or post-traumatic stress disorder; treatment for mental disorders in the past 12 months, use of psychotropic medications; history of or current neurological disorders/brain trauma, or major medical conditions. Studies employing nonvisual stimuli in the CCT (n = 53) or of participants in treatment only (n = 86) were also excluded. Studies (n = 13) performing solely region of interest (ROI) analyses, which violated the assumption of ALE algorithm that each voxel in the entire brain has equal chance of being activated/showing correlation [66], were also removed. An additional 32 studies were excluded because the coordinates of the contrast (drug > neutral cue) were not reported. A final pool of 53 studies were included in the current meta-analysis. A complete list of the studies is shown in Supplementary Table S1. Notably, in two of these studies, a mixed sample of individuals with different SUDs were

included. We converted all foci that were reported in Talairach to MNI space using the Lancaster transformation [48].

We used the GingerALE software package (version 3.0.2, http://brainmap.org/ale/) to perform ALE meta-analyses on coordinates in MNI space [21,23,86]. The non-additive algorithm was used to reduce the bias of any single experiment [86]. The ALE meta-analysis followed four main steps: computation of ALE scores, establishing a null distribution for statistical testing, thresholding, and cluster statistics, as described in detail in the GingerALE Manual (http://brainmap.org/ale/manual.pdf).

We performed the ALE single dataset analysis of drug > neutral cue using a cluster-forming threshold of voxel-level $p < 0.001$, uncorrected. The resulting supra-threshold clusters were compared to a null distribution of cluster sizes established by 1000 permutations of the data, at an FWE-corrected threshold of $p < 0.05$. We also performed a "Fail-Safe N (FSN)" analysis to evaluate potential publication bias [1]. We used the R program to generate a list of null studies with no statistically significant activation, all with the number of peaks and sample size equal to those of individual studies included in the original meta-analysis. The coordinates of these peaks were randomly drawn from the mask used by the ALE algorithm. We computed the minimum numbers of null studies required for FSN analysis – $5k + 10$ with k denoting the number of studies included in the original meta-analysis [79]. Specifically, at least 275 null studies were required. We combined the original and these null studies and repeated the ALE meta-analyses. If the ALE findings remain significant, the results are sufficiently robust and supported by at least the desired minimal number of contributing studies. If adding a minimum of null studies alters the results of original ALE analyses, a bias due to missing studies (noise) in the meta-analysis is present and the results may not be robust.

2.2. Meta-analysis of the MIDT

In our previous meta-analysis of MIDT [10], we performed ALE analyses on single contrasts of anticipation of win vs. neutral ("win anticipation" hereafter), anticipation of loss vs. neutral ("loss anticipation"), win vs. neutral outcome ("win outcome"), or loss vs. neutral outcome ("loss outcome"). Both anticipation and outcome impact individuals' emotional states. Thus, here, we performed ALE analyses with coordinates of contrasts of both win anticipation and outcome (winAO) and of both loss anticipation and outcome (lossAO) and evaluated the results with a cluster-forming threshold of voxel-level $p < 0.001$, uncorrected. The resulting supra-threshold clusters were compared to a null distribution of cluster sizes established by 1000 permutations of the data, at an FWE-corrected threshold of $p < 0.05$. We then considered the effects of saliency and performed ALE subtraction analyses – winAO > lossAO and lossAO > winAO – each to identify regional activities distinct to win and loss processing, with responses to saliency accounted for. To correct for study sizes [22], GingerALE creates simulated data by pooling the foci datasets and randomly dividing them into two groups of the same size as the original data set. An ALE image is created for each new data set and subtracted from the other, with the result compared to the true data. The ALE values were collated across 5000 permutations to yield an empirical null distribution for statistical inference. A p-value was assigned to each voxel based on how

many times the difference in the null distribution exceeded the actual group difference. We applied a threshold of $p < 0.001$ uncorrected with a minimum cluster size of 100 mm^3 to identify significant differences between any two contrasts. A Z-score indicated the size of the differences at each voxel. The findings are shown in the Supplement.

2.3. Identification of appetitive and aversive cue circuits

To avoid missing any clusters with cue-elicited reactivity in the appetitive and aversive circuits, we used a liberal $p < 0.05$, uncorrected, for the single dataset analyses of drug > neutral, winAO, and lossAO as well as the subtraction analyses of winAO > lossAO and lossAO > winAO. We performed inclusive masking to identify the ROIs of winAO > lossAO and lossAO > winAO as the appetitive and aversive circuit, respectively, for investigation in the empirical study.

2.4. The empirical study: cue reactivity in drinkers

2.4.1. Subjects and assessments—Seventy-six alcohol drinkers (37 women; age 21–74 years) participated in the study. All participants were required to be physically healthy with no major medical conditions. Those with current use of psychotropic medications or with a history of head injury or neurological illness were excluded. Other exclusion criteria included current or history of Axis I, including substance (except alcohol and nicotine) use disorders according to the Structured Clinical Interview for DSM-IV [28]. The study was conducted according to a protocol approved by the Institutional Review Board of Yale University. Written informed consent was obtained from all prior to their participation.

All participants were evaluated for alcohol use with the Alcohol Use Disorders Identification Test (AUDIT), with a total score ranging from 0 to 40 [3]. An AUDIT score of 1 to 7, 8 to 14, and 15 or more each suggests low-risk consumption, hazardous or harmful consumption, likelihood of alcohol dependence (moderate-severe alcohol use disorder). Participants were also evaluated for nicotine addiction severity with the Fagerström Test for Nicotine Dependence (FTND) [34]. Ranging from 0 to 10, a higher FTND score indicates more severe nicotine use and dependence. Participants were assessed with the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [99], a self-reported instrument that includes 48 yes/no items, comprising a subscale of sensitivity to punishment (SP, 24 items) and a subscale of sensitivity to reward (SR, 24 items), as well as the UPPS scale to evaluate dimensional impulsivity, including subscales of urgency, lack of premeditation, lack of perseverance, and sensation seeking [92]. In addition, participants were also assessed with the Alcohol Expectancy Questionnaire (AEQ-3) [31], an instrument to evaluate alcohol expectancies, including subscales of Positive Global Changes in Experience (GP), Sexual Enhancement (SEXE), Social and Physical Pleasure (SPP), Increased Social Assertiveness (SOCE), Relaxation and Tension Reduction (TRR), and Arousal and Interpersonal Power (PE).

2.4.2. Cue-induced alcohol craving task—We employed a cue-induced alcohol craving task (CCT) as described in our previous studies [52,91]. Briefly, participants viewed 36 unique alcohol-related or 36 unique neutral pictures and reported alcohol craving in alternating blocks (Supplementary Fig. S1). A cross was used to engage attention at the

beginning of each block. After 2 s, 6 pictures displaying alcohol-related cues (alcohol block) or neutral non-alcoholic drinks/humans in a similar but non-drinking setting (neutral block) were shown for 6 s each. Participants were asked to view and ponder how they might relate to the images. The images were collected from the Internet and independently reviewed by 2 investigators. Alcohol pictures included bar scenes, individuals or a group of people holding or drinking alcoholic beverages, and images of a variety of alcoholic drinks, such as beer, wine, and vodka. Neutral pictures comprised non-alcoholic drinks or of humans in a social but non-drinking setting. Participants were asked at the end of each block to report how much they craved for alcohol with rating from 0 (no craving) to 10 (highest craving ever experienced) on a visual analog scale. Each block lasted about 45 s, including time for craving rating. Paired sample *t* test showed that across subjects craving rating was significantly higher in alcohol vs. neutral blocks (3.17 ± 2.70 vs. 1.95 ± 2.05; $t = 6.78$, $p < 0.001$), indicating that the alcohol images successfully evoked craving. The differences in craving rating between alcohol and neutral blocks were computed for further analyses. A total of 6 alcohol and 6 neutral blocks took approximately 9 mins to complete. Each participant completed one run of the task.

2.4.3. Imaging protocol, data preprocessing and modeling—Conventional T1-weighted spin echo sagittal anatomical images were acquired for slice localization using a 3T scanner (Siemens Trio). Anatomical images of the functional slice locations were next obtained with spin echo imaging in the axial plane parallel to the AC–PC line with repetition time (TR) = 1900 ms, echo time (TE) = 2.52 ms, bandwidth = 170 Hz/pixel, FOV = 250 × 250 mm, matrix = 256 × 256, 176 slices with slice thickness = 1 mm and no gap. Functional blood oxygenation level-dependent (BOLD) signals were acquired using multiband imaging (multiband acceleration factor = 3) with a single-shot gradient echo echoplanar imaging sequence. Fifty-one axial slices parallel to the AC–PC line covering the whole brain were acquired with TR = 1000 ms, TE = 30 ms, bandwidth = 2290 Hz/pixel, flip angle = 62°, field of view = 210 × 210 mm, matrix = 84 × 84, with slice thickness = 2.5 mm and no gap.

Imaging data were preprocessed using SPM8 (Welcome Trust center for Neuroimaging), as in our previous studies [49,91]. No BOLD runs were removed due to significant motion (> 3 mm translation peak-to-peak movement and/or 1.5-degree rotation). Images from the first five TRs at the beginning of each run were discarded to ensure only BOLD signals at steady-state equilibrium between radio frequency pulsing and relaxation were included in analyses. Images of each subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation. The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Images were resampled to 3 mm isotropic voxel size. Finally, the images were smoothed with a Gaussian kernel of 4 mm full width at half maximum.

We employed general linear model (GLM) to identify regional activities of blocks of interest. We distinguished alcohol and neutral image blocks for each subject and included the realignment parameters in all six dimensions in the GLM. The GLM was used to

estimate the component of variance explained by each of the regressors. We constructed for each subject the contrast of alcohol vs. neutral blocks to evaluate regional activities that differentiated viewing of alcohol and neutral cues. The contrast images of individual subjects were used for following region-of-interest (ROI) analyses.

2.4.4. ROI analyses and group comparisons between subtypes—We computed for each participant the β estimates of cue-elicited activity (alcohol minus neutral) in the CCT for the mask of the appetitive and aversive cue reactivity circuit identified from meta-analyses. We performed a linear regression on the β estimates with appetitive and aversive cue reactivity each as the dependent and independent variable and used "delta Y" for as an index in subtyping. We identified those participants with largest residuals – top 1/3 each of those with positive ($n = 15$; "approach" subtype) and negative ($n = 11$; "avoidance" subtype) residuals, with the rest designated as "mixed" subtype ($n = 50$). We performed a one-way ANOVA to examine whether the subtypes differed in the clinical measures as well as independent-sample t tests (two-tailed) to compare the approach and avoidance subtypes, specifically.

3. Results

3.1. Meta-analyses of CCT and MIDT

With a cluster-forming threshold of $p < 0.001$ uncorrected and a cluster-level threshold of $p < 0.05$ FWE corrected, cue-elicited neural reactivity was shown in Supplementary Fig. S2A and the clusters are summarized in Supplementary Table S2. A wide array of cortical regions showed higher response to drug vs. neutral cues, including bilateral medial orbitofrontal cortex (mOFC), rostral anterior cingulate cortex (rACC), superior frontal gyri (SFG), precuneus, mid-cingulate cortex (MCC), and posterior cingulate cortex (PCC). The publication bias was evaluated with 275 additional null studies included in the ALE analyses. The ALE maps evaluated at the same threshold showed a cluster of left mOFC (cluster size: 2368 mm^3, MNI coordinates $x = -4$, $y = 50$, $z = -6$, ALE = 0.06; Supplementary Fig. S3), indicating that the main findings of the original meta-analysis were robust. With a more liberal threshold of $p < 0.05$, we identified more clusters for cue-elicited neural reactivity, including bilateral hippocampus, striatum, thalamus, middle temporal gyrus, precentral gyrus, and inferior parietal gyrus and left insula. The clusters are shown in Supplementary Fig. S2B and the clusters are summarized in Supplementary Table S2.

The regional activations for winAO and lossAO were shown in Supplementary Fig. S4 and the clusters are summarized in Supplementary Table S4. Win anticipation and outcome engaged bilateral parahippocampal gyri, ventral and dorsal striatum, amygdala, anterior insula (AI), thalamus, MCC, PCC, supplementary motor area, precentral gyri, and occipital cortex (OC), and right inferior frontal gyrus (IFG) pars orbitalis. Loss anticipation and outcome engaged similar regional activities (except that the OC activation was predominantly in the left hemisphere) and, additionally, the left superior and inferior parietal gyri. The results of ALE subtraction analyses are shown in Supplementary Fig. S5A, and the clusters are summarized in Supplementary Table S5. The contrast "winAO

> lossAO" showed higher likelihood of activation in bilateral PCC, whereas the contrast "lossAO > winAO" showed no significant findings. With a liberal threshold of $p < 0.05$, the subtraction analyses revealed more clusters for both contrasts. The ALE map is shown in Supplementary Fig. S5B, and the clusters are summarized in Supplementary Table S5.

With a $p < 0.05$ to evaluate the findings of both meta-analyses so that we did not miss any clusters, we overlapped the whole-brain maps of cue-elicited reactivity to drug with "winAO > lossAO" and with "lossAO > winAO", respectively (Fig. 3A). Cue-elicited reactivity shared activities with "winAO > lossAO" in bilateral mOFC, rACC, PCC, and OC, as well as right-hemispheric ventral striatum (VS), IFG, and middle frontal gyrus (MFG), and left SFG. Cue-elicited reactivity shared activities with "lossAO > winAO" in the left AI and caudate and right MCC. The scatter plot of beta estimates of cue-elicited reactivity is shown in Fig. 3B, with the three subtypes noted in different colors. We identified those participants with largest residuals – top 1/3 each of those with positive and negative residuals as appetitive and aversive subtype, respectively, with the rest designated as "mixed" subtype.

3.2. Differences in clinical characteristics between drinker subtypes

The means and standard deviations of demographic and clinical measures of drinker subtypes are presented in Table 1. We performed one-way ANOVA to examine the differences in these measures with an additional subtype included – mixed subtype. The subtype effect was significant for SPSRQ punishment ($F = 5.01$, $p = 0.009$), reward ($F = 4.19$, $p = 0.019$) sensitivity, and UPPS sensation seeking ($F = 3.16$, $p = 0.049$), but not for differences in craving rating in response to alcohol vs. neutral stimuli ($F = 0.19$, $p = 0.831$), or for other clinical measures (p's ≥ 0.109). We further performed the post-hoc LSD tests. The avoidance subtype (13.0 ± 5.8) showed significantly higher SPSRQ punishment sensitivity than approach (7.4 ± 4.4; $t = 2.80$, $p = 0.007$) and mixed (8.0 ± 5.1; $t = 3.00$, $p = 0.004$) subtypes, while the latter two showed no significant differences ($t = 0.38$, $p = 0.707$). The mixed subtype (8.8 ± 3.8) showed significantly lower SPSRQ reward sensitivity than approach (12.1 ± 6.0; $t = 2.43$, $p = 0.018$) and avoidance (11.9 ± 5.6; $t = 2.04$, $p = 0.045$) subtypes, while the latter two showed no significant differences ($t = 0.09$, $p = 0.931$). The approach subtype (36.9 ± 5.9) showed significantly higher levels of sensation seeking than mixed (31.5 ± 8.1; $t = 2.36$, $p = 0.021$) and avoidance (30.6 ± 7.1; $t = 2.02$, $p = 0.048$) subtypes, while the latter two showed no significant differences ($t = 0.36$, $p = 0.723$).

In independent-samples t tests approach relative to avoidance subtype showed lower SPSRQ subscore of punishment sensitivity (7.4 ± 4.4 vs. 13.0 ± 5.8; $t = -2.81$, $p = 0.010$), higher UPPS subscore of sensation seeking (36.9 ± 5.9 vs. 30.6 ± 7.1, $t = 2.39$; $p = 0.026$), and higher AEQ subscore of social and physical pressure (24.0 ± 3.5 vs. 19.8 ± 6.7; $t = 2.08$, $p = 0.048$). No other measures showed significant group differences (p's ≥ 0.204).

4. Discussion

To our knowledge, this is the first study to characterize individual differences in the neural mechanisms with respect to appetitive, aversive, or mixed nature of the psychological state during cue-evoked craving. We demonstrated appetitive responses in the mOFC and VS and aversive activity in the AI, caudate and MCC to alcohol cues, consistent with

earlier findings [29,55,77,97]. By distinguishing appetitive and aversive cue reactivity, we provided preliminary evidence for potential subtypes of alcohol drinkers, with the approach and avoidance subtype each showing outsized appetitive and aversive activity, respectively, relative to the regression mean. The approach relative to avoidance subtype showed lower sensitivity to punishment but higher levels of sensation seeking and expectancy of drinking to increase social and physical pleasure. A mixed subtype, comprising most drinkers in the sample, demonstrated a mixed motivational state during cue exposure and intermediate levels of these clinical traits. We discussed the main findings below.

4.1. Shared neural correlates of cue exposure and valenced motivational states

The appetitive circuit involved bilateral mOFC, rACC, PCC, OC as well as right-hemispheric VS and IFG/MFG, and left SFG, brain regions that have been implicated in sensation seeking [12]. Individual variation in sensation seeking trait as evaluated by the UPPS was positively associated with frontostriatal responses to alcohol cues in heavy drinkers [7]. The mOFC shows higher activation during the consummatory phase of win but not loss processing [10]. The mOFC, ACC, and VS encode both the subjective value of drug-related cues and actions to procure the drug [40,62,89]. These regions are also engaged in responses to food and money [18,54] as well as social interaction and reward [33,37], consistent with the findings of higher expectancy to increase social and physical pleasure in the approach subtype of drinkers. The brain regions are anatomically inter-connected to support appetitive cue responses [61,73,74]. In support, patients with AUD relative to healthy individuals showed altered functional connectivity between the VS and medial prefrontal cortex (mPFC) in response to wins vs. losses, and stronger VS-mPFC connectivity was associated with more frequent drinking and alcohol craving [26,76].

The aversive circuit involved the AI, caudate and MCC, consistent with earlier reports of these regional activities in negative emotions and avoidance learning [8,45,78,82]. The involvement of AI in aversive responses is compatible with the insula in processing salient stimuli and interoceptive signals [64,68]. The interoceptive circuit integrates multiple sources of information to support the experience of craving as well as behavioral control and emotion regulation [15]. A human brain lesion study implicated the AI in the learning of loss cues and the dorsal striatum in associative and motor aspects of decision-making to avoid negative outcomes [75]. Moreover, in neurotypical populations, higher Behavioral Inhibition System scores were associated with insula and dorsal striatal activation during anticipation of avoidance [43]. In a recent study of the Human Connectome Project, stronger caudate responses to punishment were associated with more severe alcohol use severity [55]. As a node in the cingulo-fronto-parietal network, the MCC is involved in fear, pain processing, and behavioral avoidance [78]. We recently reported that midcingulate cortical activations interrelated chronic craving and physiological responses to negative emotions in individuals with cocaine use disorder [97]. Together, these earlier findings are consistent with aversive cue reactivity of the AI, caudate, and MCC.

4.2. Clinical characteristics of the subtypes

The avoidance relative to approach subtype of drinkers showed markedly higher levels of punishment sensitivity, suggesting heightened tendency in avoidance behaviors and negative

reinforcement – drinking to alleviate emotional distress – as a dominant mechanism of alcohol misuse. Previous studies demonstrated mixed results in the relationship between punishment sensitivity and alcohol misuse, with studies showing a positive [41,51], negative [39,84] or no [57,88] correlations. Other studies highlighted the specific roles of alexithymia on coping motives for drinking, suggesting that sensitivity to punishment alone may not be a driver of alcohol misuse [58]. Thus, the relationship amongst individual traits, coping strategy, and alcohol use may be complex [25] and require a larger sample and more thorough clinical evaluation to fully elucidate.

In contrast, drinkers of the approach vs. avoidance subtype showed higher levels of sensation seeking and expectancy for social and physical pleasure, suggesting a drinking motive in enhancing positive emotional state. The finding is consistent with many reports of sensation seeking [32,36,59] and positive alcohol expectancies [94], including expectancy of social and physical pleasure [65], as a risk factor of alcohol use and misuse. An earlier study demonstrated that craving ratings during cue exposure were positively correlated with AEQ social and physical pleasure [9]. Thus, in contrast with the roles of punishment sensitivity or avoidance traits, our findings support a literature associating approach behavior with higher and/or maladaptive alcohol consumption.

Notably, the great majority of drinkers demonstrated a mixed psychological state during cue exposure and, as a group, showed intermediate levels of punishment sensitivity and sensation seeking relative to the approach and avoidance subtypes. A primary consideration is that although the MIDT involves win and loss trials, at stake is money that can be won or not lost. Participants may expect to respond quickly so they will not lose, effectively winning, during the “loss trials” and the psychological processes involved may not be truly distinct from those of win trials. Thus, as encouraging as the results are, it is likely that to truly differentiate appetitive and aversive circuit activities, one would have to employ stimuli/outcomes of categorical differences, for instance, by replacing monetary loss with the delivery of an electric shock. A second consideration is that the meta-analyses identified ROIs across participants. Individuals vary in the appetitive and aversive processes and analyses of within-subject incentive and cue reactivity would reveal more robust findings. This would require experiments querying both cue and valenced motivational reactivity within the same participants.

4.3. Limitations of the study, other considerations, and conclusions

A few limitations should be considered. Firstly, only 20% of the drinkers in the current study reported an AUDIT score > 14, suggesting that the sample comprised largely non-dependent drinkers. Thus, the findings should be considered as specific to this population of social drinkers and drinkers with mild to moderate alcohol use severity. Secondly, we employed “delta Y” or deviation from the regression mean as an index in subtyping. A larger sample size would provide the opportunity to perform cluster analyses of appetitive and aversive cue reactivities for more robust grouping. Thirdly, although the paradigm successfully evoked craving, we did not explicitly match the physical features (e.g., spatial frequency or color) of alcohol-related and neutral stimuli. In addition, the masks of appetitive and aversive circuits were identified with a liberal threshold of $p < 0.05$ uncorrected, raising the issue

of Type 1 error in the analyses of individual differences with a small sample. Furthermore, the MIDT may not fully separate appetitive and aversive responses. A task that employs stimuli of categorical differences (e.g., monetary reward vs. electronic shock) may help in addressing this issue. In future research, investigators may expose a larger sample of individuals to drug cues in a cue craving task as well as to anticipation of monetary reward and electric shocks in an incentive delay task to examine how cue-evoked neural processes associate with those of appetitive and aversive states within subjects. More broadly, although fMRI measures show promise in detecting neuropathology [46], studies have underscored the poor test-retest reliability of univariate fMRI [24,69]. Growing evidence demonstrates that multivariate approaches improve both reliability and validity of fMRI [70] and that the accuracy of classifying mental disorders would improve with multiple dimensions of observable behaviors and neurobiological measures [53]. Finally, we did not examine sex differences because of the small sample size. Prior evidence showed that males drink more often in anticipation of positive emotions [71], whereas females are more likely motivated to drink to avoid aversive emotional states [65]. Indeed, although the sex composition was not significantly different, more drinkers in the approach subtype were males, relative to the avoidance subtype. It would be of tremendous interest to investigate how sex influences subtyping of drinkers.

To conclude, we characterized individual differences in the neural mechanisms of alcohol cue reactivity with respect to appetitive, aversive, and mixed nature of the psychological state. By subtyping drinkers according to these neural markers, we identified individual differences in the clinical characteristics and potentially the etiological processes of alcohol misuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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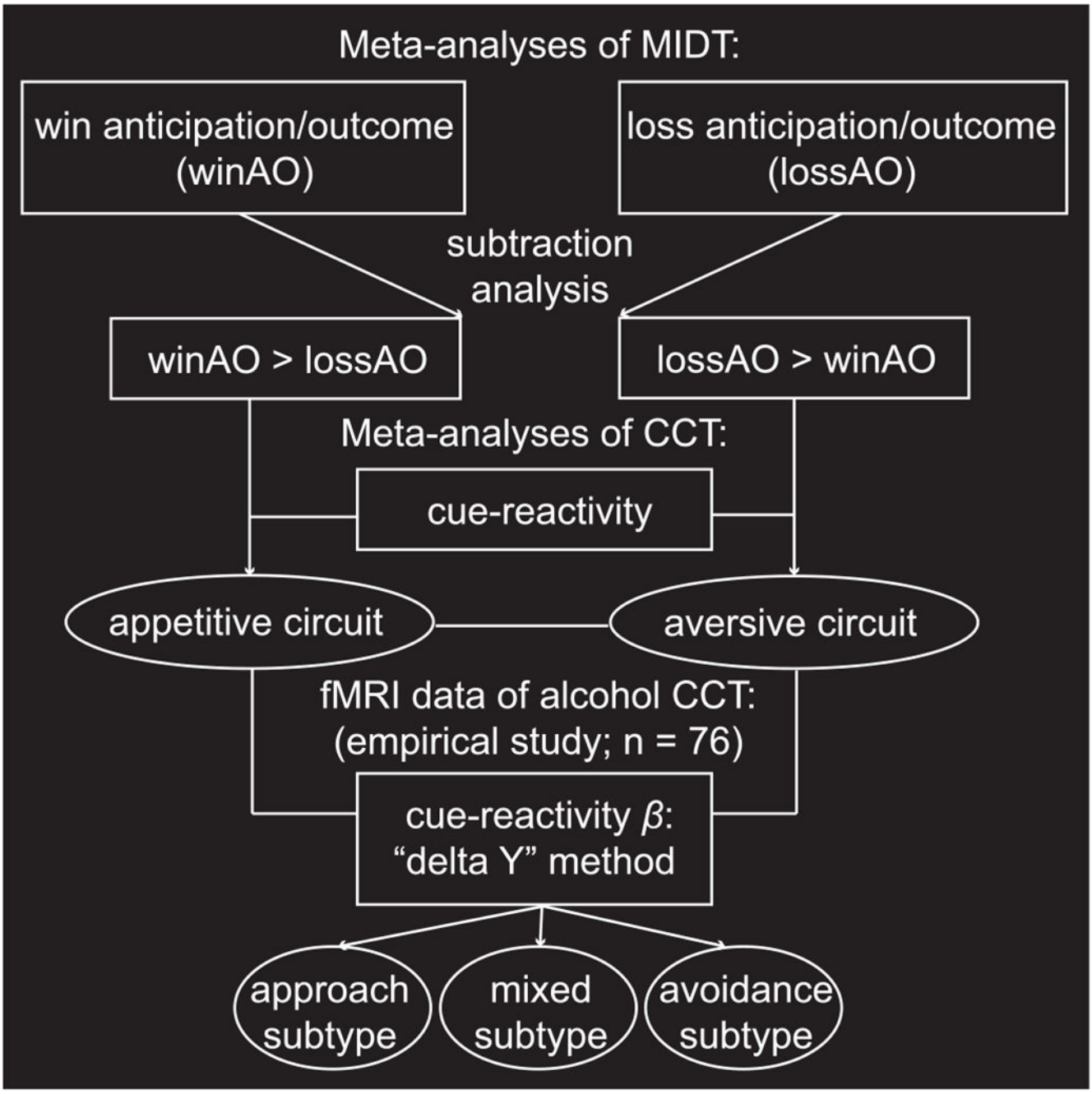

Fig. 1.

Overview of the analytic procedures. Meta-analyses were performed of the monetary incentive delay task (MIDT) and cue craving task (CCT) to identify appetitive and aversive circuits that may respond differentially to drug cues. The circuit activities were queried in an empirical study and used to distinguish approach, mixed, and avoidance neural subtypes of 76 drinkers.

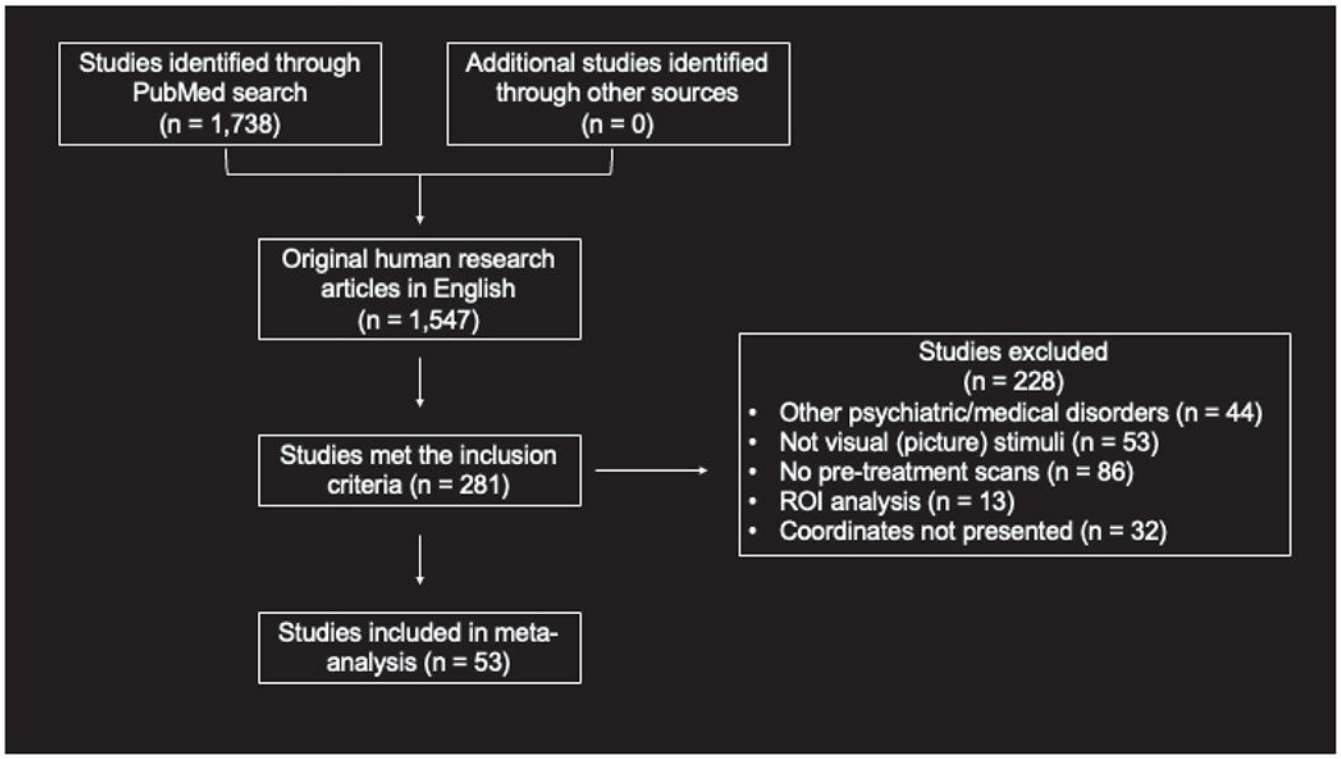

Fig. 2.

A flow-chart for the procedure to arrive at the final sample for meta-analysis of cue-elicited reactivity, following 'Preferred reporting items for systematic reviews and meta-analyses (PRISMA)'.

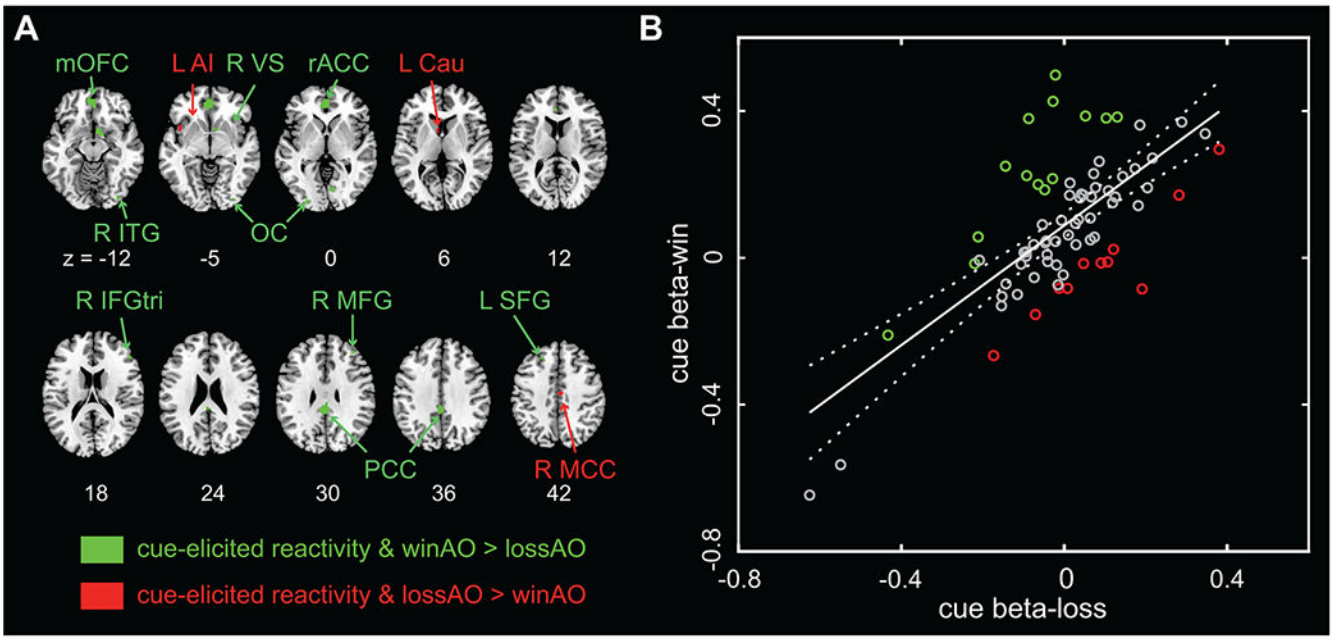

Fig. 3.

(A) Cue-elicited reactivity of the appetitive and aversive circuits. The former involved bilateral medial orbitofrontal cortex (mOFC), rostral anterior cingulate cortex (rACC), posterior cingulate cortex (PCC), and occipital cortex (OC) as well as right-hemispheric ventral striatum (VS), inferior/middle frontal gyrus (IFG/MFG) and left superior frontal gyrus (SFG). The aversive circuit involved the right mid-cingulate cortex (MCC) and left anterior insula (AI) and caudate (Cau). **(B)** Scatter plot of beta estimates of cue-elicited reactivity for approach (green), mixed (gray), and avoidance (red) subtypes. One data point was out of range and not shown.

Table 1

Demographic and clinical measures of drinker subtypes.

Measures		Approach (n = 15)	Mixed (n = 50)	Avoidance (n = 11)	F test		T test	
					F/χ^2	p	t/χ^2	p
Age (years)		29.4 ± 10.3	37.9 ± 13.7	36.8 ± 16.3	2.28	0.11	−1.33	0.20
Sex (M/F)		10/5	24/26	5/6	1.79 *	0.41	1.17 *	0.28
AUDIT		10.5 ± 6.6	9.7 ± 10.8	9.9 ± 9.1	0.04	0.97	0.18	0.86
FTND		0.1 ± 0.3	0.8 ± 2.0	0.6 ± 2.1	1.03	0.36	−0.89	0.40
Craving Diff.		1.4 ± 0.7	1.2 ± 1.6	1.2 ± 2.1	0.19	0.83	0.44	0.67
SPSRQ	SP	7.4 ± 4.4	8.0 ± 5.1	13.0 ± 5.8	5.01	**0.01**	−2.81	**0.01**
	SR	12.1 ± 6.0	8.8 ± 3.8	11.9 ± 5.6	4.19	**0.02**	0.07	0.95
UPPS	Urg.	25.9 ± 6.1	24.4 ± 6.3	26.7 ± 6.0	0.71	0.49	−0.34	0.74
	Pre.	22.6 ± 5.8	21.0 ± 6.2	19.8 ± 5.4	0.70	0.50	1.22	0.24
	Per.	18.8 ± 4.2	18.8 ± 4.6	17.0 ± 4.2	0.69	0.50	1.05	0.31
	SS	36.9 ± 5.9	31.5 ± 8.1	30.6 ± 7.1	3.16	**0.049**	2.39	**0.03**
AEQ	GP	14.8 ± 5.1	13.3 ± 6.5	13.9 ± 6.8	0.34	0.72	0.38	0.71
	SEXE	17.4 ± 6.1	15.8 ± 7.7	15.7 ± 6.3	0.30	0.74	0.68	0.50
	SPP	24.0 ± 3.5	20.6 ± 6.3	19.8 ± 6.7	2.28	0.11	2.08	**0.046**
	SOCE	21.9 ± 5.5	18.7 ± 7.7	19.6 ± 7.7	1.10	0.34	0.89	0.38
	TRR	17.9 ± 4.9	17.6 ± 6.1	18.5 ± 5.4	0.10	0.91	−0.29	0.77
	PE	18.9 ± 5.8	16.7 ± 6.6	18.2 ± 7.6	0.78	0.46	0.29	0.78

Note: Values are mean ± SD; M: male; F: female; AUDIT: Alcohol Use Disorders Identification Test; FTND: Fagerström Test for Nicotine Dependence; Craving Diff: differences in craving rating for alcohol vs. neutral stimuli; SPSRQ: Sensitivity to Punishment (SP) and Sensitivity to Reward (SR) Questionnaire; UPPS: Urgency (Urg), Lack of Premeditation (Pre), Lack of Perseverance (Per), Sensation Seeking (SS) Questionnaire; AEQ: Alcohol Expectancy Questionnaire; GP: global positive experience; SEXE: sexual enhancement; SOCE: increased social assertiveness; SPP: social and physical pleasure; TRR: relaxation and tension reduction; PE: arousal/interpersonal power; F and p values reflect one-way ANOVA; t and p values reflect independent-samples t tests (two-tailed) of Approach vs. Avoidance;

* Chi-square test of sex ratio.