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Alcohol expectancy and cerebral responses to cue-elicited craving in adult non-dependent drinkers

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Abstract

Background: Positive alcohol expectancy (AE) contributes to excessive drinking. Many imaging studies have examined cerebral responses to alcohol cues and how these regional processes related to problem drinking. However, it remains unclear how AE relates to cue response and whether AE mediates the relationship between cue response and problem drinking.

Methods: Sixty-one non-dependent drinkers were assessed with the Alcohol Expectancy Questionnaire (AEQ-3) and Alcohol Use Disorder Identification Test (AUDIT) and underwent fMRI while exposed to alcohol and neutral cues. Imaging data were processed and analyzed with published routines and mediation analyses were conducted to examine the inter-relationships between global positive (GP) score of the AEQ-3, AUDIT score, and regional responses to alcohol vs. neutral cues.

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Results: Alcohol as compared to neutral cues engaged the occipital, retrosplenial, and medial orbitofrontal cortex as well as left caudate head and the red nucleus. Bilateral thalamus showed a significant correlation in cue response and in left superior frontal cortical connectivity with GP score in a linear regression. Mediation analyses showed that GP score completely mediated the relationship between thalamic cue activity as well as superior frontal cortical connectivity and AUDIT score. The alternative models that AE contributed to problem drinking and, in turn, thalamic cue activity and connectivity were not supported.

Conclusions: The findings suggest an important role of the thalamic responses to alcohol cues in contributing to AE and at-risk drinking in non-dependent drinkers. Alcohol expectancies may reflect a top-down modulation of the thalamic processing of alcohol cues, influencing the pattern of alcohol use.

Keywords

expectancy; cue; craving; alcohol; fMRI; thalamus

Introduction

Along with an impaired ability to control the urges to drink, craving is a hallmark of alcohol abuse and dependence (1). It is well known that alcohol-related cues evoke craving and expectations of positive outcomes contributed to drinking (2, 3). Alcohol expectancy (AE) represents subjective beliefs about the extent to which drinking will lead to particular outcomes (e.g., positive expectancy would be associated with statements like “drinking makes me feel good; alcohol makes me worry less”) (4). According to the outcome expectancy model of craving, expectancies can be divided into informational and motivational components (5). The former represents specific beliefs or expectancies about alcohol’s effects, whereas the latter reflects the yearning for those effects. For example, seeing one’s friends drink may, along with AE, generate anticipation that alcohol will produce relaxation, pleasure, or relief from withdrawal and lead to the desire to experience those feelings (6). The desire, in turn, triggers urges to drink and precipitates alcohol consumption (5). Thus, AE may interact with environmental cues to contribute to at-risk alcohol use.

AE is an important moderator of problem drinking. For example, AE accounted for a significant proportion of the variance in drinking-related measures (4). AE discriminated between adolescent non-problem drinkers and those subsequently engaged in problem drinking (7). AE related to habitual consumption of alcohol among problem and non-problem adult drinkers (8), with higher expectancies associated with increased levels of consumption. Problem as compared to non-problem drinkers reported significantly higher AE from adolescence through middle adulthood (9). Expectancies about alcohol enhancing social behaviors were particularly relevant to close-friend alcohol use and consequences in college students (10). In an alcohol self-administration study, high-responders reported heavier drinking patterns and lower expectancies for negative consequences (11). In a treatment study lower expectancies of alcohol-produced relaxation were related to abstinence during a one-year period (8).

Numerous studies have examined the effects and neural processes of environmentally triggered craving. Following administration of a non-alcoholic lager, participants reported craving in relation to how much they liked and felt stimulated by the drink (12). In an imaging study of 326 heavy drinkers, alcohol compared to neutral taste cues evoked greater activation in the dorsal striatum, insula, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and ventral tegmental area (VTA), with activation in the dorsal striatum, insula, and precuneus in correlation with alcohol use severity (13). Olfactory alcohol cues elicited craving along with increased activation in the nucleus accumbens and VTA among heavy drinkers, in contrast with control participants (14). In another study, alcohol-related visual cues activated the ventral striatum (VS), OFC and other structures in the medial prefrontal cortex (mPFC) in alcohol dependent individuals, as compared with healthy subjects (15). Across cue modalities, a meta-analysis of 28 functional magnetic resonance imaging (fMRI) studies showed robust activation of limbic prefrontal regions, including the anterior cingulate and ventral mPFC in 679 cases of heavy/dependent drinkers (16). When compared with control participants, case participants exhibited more activation in parietal and temporal regions, including the posterior cingulate, precuneus and superior temporal gyrus. In region-of-interest analyses that interrogated only limbic regions, cue-elicited activation of the VS was most frequently correlated with drinking measures reduced by treatment (16). Taken together, the studies have suggested that cue-elicited craving is associated with activation in brain regions that support reward and incentive salience and individuals with alcohol misuse show more cue-evoked activation in these regions.

Expectation to have access to alcohol may influence craving and related psychological states. For instance, in social drinkers craving was increased both after receiving alcohol and placebo (though to a less extent) but not after receiving a non-alcoholic drink (17). Importantly, alcohol-approach tendencies were more pronounced after both alcohol and placebo compared to the control beverage, with no difference between alcohol and placebo. In another study of social drinkers alcohol urge and other subjective states were measured before and after an initial drink (alcohol, placebo, or no-alcohol) was consumed (12). Both alcohol and placebo produced increased sedated feelings, and, after placebo, urge was positively related to liking and enjoying the “alcoholic” drinks and feeling more stimulated. A number of studies have specifically examined how expectation to drink or smoke modulated cue-elicited brain responses. For instance, the expectation of receiving an alcoholic drink enhanced activation in the ACC and other prefrontal regions among social drinkers performing a working memory task (18). Healthy individuals with a positive family history of alcoholism showed enhanced striatal dopamine release during expectation of alcohol (19). A study of cigarette smokers demonstrated cue-elicited activations of limbic and prefrontal structures in individuals expecting to smoke immediately after the scan but not in those not allowed to smoke, despite similar levels of craving (20). A stepwise linear regression analysis revealed a correlation between smoking cue-induced craving scores and activation in the prefrontal cortex differentially modulated by the state of expectation. Another study similarly demonstrated cue-evoked ventromedial, ventrolateral, and dorsolateral prefrontal cortical activation that was modulated by the option to smoke (21). Together, the studies suggest cue-elicited activation of the limbic prefrontal striatal circuits depends on the subjective awareness of drug accessibility.

On the other hand, the literature is limited with regards to the interactions between alcohol expectancy (AE) and craving. Although “expectation” and “expectancy” were used interchangeably in some studies, unlike expectation to access alcohol, AE reflects one’s belief and knowledge of positive outcomes of alcohol use and interacts with environmental “primer” to precipitate craving and alcohol consumption. AE was associated with increases in craving following administration of a placebo drink of chilled lemonade served in a vodka-rimmed glass (22). AE has been associated with ACC activation during a vigilance task in adolescents (23). An earlier electro-encephalographic (EEG) study suggested frontal but not parietal EEG power as a predictor of AE, although the prefrontal neuropsychological performance was associated with AE less than consistently across testing batteries (24). A previous structural imaging study showed that AE best predicted problem drinking in women and interacted with impulsivity to predict problem drinking in men, each in association with decreased gray matter volume of the right posterior insula and the left thalamus (25). More recently we demonstrated how thalamic subregional functional connectivities were inter-related with AE and at-risk alcohol use in non-dependent drinkers (26). However, no imaging studies have addressed the potential influence of AE on cue-induced craving or the inter-relationships between AE, cue-elicited brain response and at-risk drinking.

Here, we examined the relationship between AE and cerebral responses in a cue-elicited craving fMRI paradigm in 61 adult non-dependent drinkers. We hypothesized that brain responses to alcohol cues would be modulated by AE and the extent of risky alcohol use and explored the relationships between the brain activity and connectivity, AE, and the severity of at-risk drinking.

Subjects and Methods

Subjects and assessments

Potential candidates were recruited from the greater New Haven, CT area and were screened according to the Structured Clinical Interview for DSM-IV (SCID) (27). Sixty-one non-dependent adult drinkers met eligibility and participated in this study (Table 1). All subjects were physically healthy with no major medical illnesses or current use of prescription medications. None reported having a history of head injury or neurological illness. Other exclusion criteria included current or past dependence on a psychoactive substance (except nicotine) and current or history of Axis I disorders according to the SCID (27). The Human Investigation committee at Yale University School of Medicine approved all study procedures, and all subjects signed an informed consent prior to participation.

All participants were assessed with Alcohol Use Disorders Identification Test (AUDIT) (28), which has been widely used to examine alcohol use behavior and alcohol-related problems. Participants were also assessed with the Alcohol Expectancy Questionnaire or AEQ-3 (29). The AEQ-3 consists of 40 items to address both positive (6 subscales) and negative (2 subscales) alcohol expectancy. Each subscale contains 4 to 6 statements that can be endorsed on a six-point scale, from “disagree strongly (1)” to “agree strongly (6)”. The global positive (GP) subscale contains five items and thus ranges from 5 to 30 in total score, with a greater score indicating higher global positive alcohol expectancy. Although the expectancy

subcomponents are statistically discernible, the high subscale inter-correlations (ranging from $r = 0.42$ to 0.92 , mean = 0.78) suggest that the degree of distinctiveness among the subscales is at best modest (29). Thus, in the current study, we focused on the GP subscore as a variable to quantify individual variation in alcohol expectancy. Participants were also assessed with the Fagerström Test for Nicotine Dependence (FTND) (30) and averaged 0.8 ± 2.0 (mean $\pm$ SD) in FTND score, suggesting low dependence.

Behavioral tasks

We employed a cue-induced alcohol craving task. In alternating blocks participants viewed alcohol-related or neutral pictures and reported alcohol craving. Briefly, a cross appeared on the screen to engage attention at the beginning of each block. After 2 s, six pictures displaying alcohol related cues (alcohol block) or neutral visual scenes (neutral block) were shown for 6 s each. Participants were asked to look at the pictures and think about how they may relate to the scenes. The pictures were collected from the Internet and independently reviewed by two investigators. Alcohol pictures included images of alcoholic drinks, people holding or drinking alcoholic beverages, and bar scenes, whereas neutral pictures comprised natural sceneries. At the end of each block participants were asked to report how much they craved for alcohol on a visual analog scale from 0 (no craving) to 10 (highest craving ever experienced). Each block lasted about 45 s (including time for craving rating) and a total of 6 alcohol and 6 neutral blocks took approximately 9 minutes to complete. Each participant completed two runs of the task.

Imaging protocol and data pre-processing

Imaging protocol was described in detail in the Supplement. Data were analyzed with Statistical Parametric Mapping, following established routines (31, 32), as in the Supplement.

Imaging data modeling

Alcohol and neutral cue blocks were first distinguished. A statistical analytical block design was constructed for each individual subject using a general linear model (GLM), with block onsets convolved with a canonical hemodynamic response (HRF) function and with the temporal derivative of the canonical HRF and entered as regressors in the model. Because each block was associated with a craving rating, we included a column of block onset parametrically modulated by its corresponding craving score as a regressor in the model. Realignment parameters in all six dimensions were also entered in the model. Serial autocorrelation caused by aliased cardiovascular and respiratory effects was corrected by a first-degree autoregressive or AR(1) model. The GLM estimated the component of variance that could be explained by each of the regressors.

In the first-level analysis, we constructed for each individual subject statistical contrasts of “alcohol picture” versus “neutral picture”. These contrasts allowed us to evaluate brain regions that responded differently to viewing of alcohol and neutral pictures. The *con* or contrast (difference in β) images of the first-level analysis were then used for the second-level group statistics (random-effect analysis). Following current reporting standards, all imaging results were evaluated with voxel $p < 0.001$, uncorrected, in combination with cluster

$p < 0.05$, FWE corrected, on the basis of Gaussian random field theory, as implemented in SPM.

In region of interest (ROI) analysis, we used MarsBaR (<http://marsbar.sourceforge.net/>) to derive for each individual subject the effect size of activity difference for the ROIs.

Functional ROIs were defined based on clusters obtained from whole brain analysis. All voxel activations were presented in Montreal Neurological Institute (MNI) coordinates.

General psychophysiological interaction (gPPI)

To explore circuit activities, we examined PPI of the ROIs with differential response to alcohol vs. neutral cues. PPI describes functional connectivity between brain regions contingent on a psychological context. We used a generalized form of context-dependent PPI (gPPI, <http://brainmap.wisc.edu/PPI>) (33). Briefly, in gPPI, the hemodynamic responses of “alcohol picture” and “neutral picture” formed the psychological regressors, whereas in conventional PPI, only “alcohol picture” > “neutral picture” would be included in the GLM. The inclusion of task regressors in gPPI reduces the likelihood that the functional connectivity estimates were driven by simple co-activation. The extracted mean time series of the BOLD signals were temporally filtered, mean corrected, and de-convolved to generate the signal time series of the ROIs for each subject to compose the physiological variable. These time series were then multiplied by the onset times of the “alcohol picture” and “neutral picture” separately, and re-convolved with the canonical HRF to obtain the interaction term or PPI variable. Finally, the psychological regressors of “alcohol picture” and “neutral picture”, the physiological variable of the ROIs, and PPI variables of “alcohol picture” and “neutral picture” were entered as regressors in a whole-brain GLM. GPPI analysis was performed for each individual subject, and the resulting contrast images were used in random-effect group analysis. Likewise, the results were evaluated at voxel $p < 0.001$, uncorrected, in combination with cluster $p < 0.05$, FWE corrected, according to current reporting standards.

Mediation analysis

Due to space limitation, mediation analyses were presented in the Supplement.

Results

Cue-induced craving and regional activations to alcohol cue exposure

Alcohol as compared to neutral cue elicited higher craving rating (3.1 ± 2.5 vs. 1.9 ± 2.1 , $p < 0.0001$, paired t test). Alcohol but not neutral cue elicited craving was also correlated positively with global positive (GP) score across subjects ($r = 0.43$, $p < 0.0006$; and $r = 0.16$, $p = 0.2141$, respectively).

In examining regional responses to alcohol vs. neutral cues, we first conducted a two-sample t test to compare men and women. Even at a relaxed threshold at voxel $p < 0.005$, uncorrected, no clusters showed a significant sex difference. Thus, men and women were combined in the analysis. Exposure to alcohol as compared to neutral cues engaged higher activation of cortical and subcortical structures, including the occipital cortex, medial

orbitofrontal cortex, retrosplenial cortex/parieto-occipital sulcus, left caudate head, and a cluster in the midbrain predominantly in the area of the red nucleus. Conversely, neutral as compared to alcohol cues involved higher activation in the superior parietal gyrus/cuneus, supramarginal gyrus, and the posterior cingulate gyrus (Figure 1). These clusters are summarized in Table 2. We extracted the beta contrast of alcohol vs. neutral cue response for each of these clusters and none showed a significant correlation with craving rating during the alcohol block (all p 's > 0.24) or with difference in craving rating between the alcohol and neutral blocks (all p 's > 0.13).

Cue reactivity in relation to alcohol expectancy and problem drinking

As with the analyses of regional responses to alcohol vs. neutral cues, we compared men and women in voxelwise regression against GP score and observed no sex differences at voxel $p < 0.005$, uncorrected. With men and women combined and in a whole-brain linear regression of "alcohol vs. neutral" cue exposure against GP score for all subjects with age as a covariate, bilateral thalamus ($x = 12, y = -13, z = 13, 1,971 \text{ mm}^3, z = 3.43$; $x = -15, y = -19, z = 10, 1,458 \text{ mm}^3, z = 3.29$), in the area of pulvinar and medial dorsal nucleus, showed activation in positive correlation with GP score (Figure 2A). The analyses with sex as an additional covariate identified essentially the same clusters: $x = 12, y = -13, z = 13, Z = 3.37$, volume = $1,944 \text{ mm}^3$; $x = -15, y = -19, z = 10, Z = 3.34$, volume = $1,404 \text{ mm}^3$. We extracted the beta contrast of thalamic activation to alcohol vs. neutral cue for individual subjects. Figure 2B and 2C show the linear regression of GP and AUDIT score against cue-elicited thalamic activity for men and women separately. In a slope test we observed that the correlation between thalamic cue activation with GP or with AUDIT score did not differ between men and women ($p = 0.95$ and $p = 0.44$, respectively) (34).

Psychophysiological interaction

We used bilateral thalamus clusters as a seed region in gPPI analysis. The results showed a number of cortical and subcortical regions with higher interaction with the thalamus during alcohol vs. neutral cue blocks (Figure 3; Table 3). Of these 9 clusters, we examined whether any of these regional interactions correlated with the GP and AUDIT score. As GP and AUDIT scores were highly correlated, we corrected for the number of clusters with a $p = 0.05/9 = 0.0056$ in examining the results. The gPPI magnitude of the cluster located at the left superior frontal gyrus/sulcus showed a positive correlation both with the GP ($r = 0.38$, $p = 0.0023$) and AUDIT ($r = 0.39$, $p = 0.0022$) score (Figure 4A). A slope test showed no difference between men and women in the regression of the gPPI against GP ($p = 0.79$) or AUDIT ($p = 0.27$) score (Figure 4B and 4C).

Mediation analysis

With mediation analysis we further examined the inter-relationship between thalamic activation to alcohol (vs. neutral) cue exposure, alcohol expectancy (GP score) and problem drinking (AUDIT score). AUDIT score was highly correlated with GP score in men and women combined ($r = 0.5934$, $p = 4.66 \times 10^{-7}$) and thalamic activity during alcohol vs. neutral cue exposure was correlated with GP score ($r = 0.4218$, $p = 0.0007$) and with AUDIT score ($r = 0.2708$, $p = 0.03476$). However, the inter-relationships between these neural and clinical measures remained open. We performed mediation analyses to test two specific hypotheses:

1) thalamic activity contributed to higher alcohol expectancy and, in turn, problem drinking; and 2) higher alcohol expectancy led to problem drinking and, in turn, altered thalamic activity during cue exposure. The results showed that GP score completely mediated the correlation between the thalamic response to alcohol vs. neutral cue and AUDIT score in men and women combined (Figure 5A). The alternative models where AUDIT score mediated the correlation between GP score and thalamic activity were not supported (Figure 5B). Likewise, we conducted mediation analyses on thalamic connectivity with the superior frontal gyrus (SFG), GP score and AUDIT score. The results showed that GP score completely mediated the correlation between the gPPI strength and AUDIT score in men and women combined (Figure 5C). The alternative models where AUDIT score mediated the correlation between GP score and connectivity strength were not supported (Figure 5D).

Discussion

We identified regional activations in response to alcohol vs. neutral cues in the occipital, retrosplenial, and medial orbitofrontal cortex as well as the left caudate head and the red nucleus, in accord with earlier imaging studies of cue (35) and reward-related responses (36)-(37). Although not showing higher responses to alcohol vs. neutral cues, bilateral thalamus demonstrated a positive correlation in cue response with GP score and with AUDIT score in a linear regression across participants. Psychophysiological interaction analyses showed higher thalamic connectivity with a number of cortical and subcortical structures, including the left superior frontal gyrus (SFG) during cue exposures. Thalamic SFG connectivity was also correlated with both GP and AUDIT scores. Further, mediation analyses showed that GP score completely mediated the relationship between thalamic cue activity as well as thalamic SFG connectivity and AUDIT score. These findings suggested that alcohol expectancy was reflected in thalamic cue responses and a potentially unique role of cue-elicited thalamic responses in supporting the influence of the expectancy of positive alcohol effects on drinking behavior.

Comprising subnuclei with distinct anatomical connections that relay and integrate information between cortical and subcortical structures, the thalamus is instrumental in supporting multiple cognitive and affective processes (38, 39). For example, the medial dorsal nucleus responds to reward anticipation (40, 41) and mediates working memory and executive control, which are often compromised following excessive alcohol consumption (42, 43). The anterior thalamic nucleus is part of the Papez circuit and supports episodic memory and emotional expression. Deficits in episodic and emotional memory are key manifestations of the Wernicke-Korsakoff syndrome in alcohol addicted individuals (43, 44). The pulvinar supports attention and cross-modal integration of information (45). There is a substantial literature of thalamic dysfunction in alcohol misuse, with studies reporting both increased (46, 47) and decreased (40, 44, 48) thalamic activity and connectivity in drinkers relative to non-drinkers.

Drug cue reactivity is known to be a psychologically complex process and would likely engage the thalamus. On the other hand, imaging studies of cue reactivity did not typically implicate the thalamus (49). As shown in a meta-analytic review, alcohol cue exposure most consistently engaged the ventromedial prefrontal cortex, posterior cingulate cortex and the

striatum, although ventral striatal activations were reported largely in studies that interrogated only the limbic circuits with region of interest analysis (16). There was substantial intra- and inter- study variability in brain responses to drug cues, suggesting that cue reactivity is amenable to modulation by a variety of experimental variables. In an earlier study of over 300 participants, authors reported robust thalamic response to alcohol vs. litchi juice drinks (13), suggesting that gustatory rather than visual stimulation may have more powerful effects on the thalamus. Further, of the clinical variables that influenced cue-elicited brain responses, length of use and addiction severity appeared to influence activities of the thalamus, amygdala, dorsal anterior cingulate cortex among other regions of the mesolimbic circuit (49).

Here, as with the majority of imaging studies, we did not observe increased thalamic activation during exposure to pictorial alcohol vs. neutral cues. However, bilateral thalamus clusters exhibited higher response to alcohol vs. neutral cues in association with alcohol expectancy. These clusters comprised primarily the dorsomedial nucleus and pulvinar, in the area of frontal and parietal association thalamus, according to a tractography study (38), which integrate multiple modalities of sensory inputs to support cognition. Interestingly, although the thalamus did not show higher response to alcohol vs. neutral cues, thalamic responses appeared to play an important role in distinguishing relapsors from non-relapsors in treatment studies and to predict individual vulnerability to relapse (50–53), as recently reviewed (54). As alcohol expectancy conduces to alcohol use, along with these earlier studies the current results support thalamic cue response as a useful biomarker of problem drinking and alcohol addiction.

The thalamus interacted with the left superior frontal gyrus (SFG) during cue exposure and the magnitude of psychophysiological connectivity was also positively correlated both with the GP and AUDIT scores. As part of the prefrontal task network, the SFG has been widely implicated in inhibitory control and other executive functions. However, it is important to distinguish the roles of right- and left- hemispheric prefrontal cortices and the exact locale of cortical regions in these executive processes. Whereas the right-hemispheric frontal cortex is involved in action control (55), the roles of the left prefrontal cortical regions appear to be more complex and in many instances antithetical to those of right-hemispheric counterparts. For instance, in studies of the stop signal task, we showed that response speeding as compared to slowing, as a behavioral index of risk taking, engaged predominantly left prefrontal and subcortical structures, whereas post-error slowing involved right-hemispheric ventrolateral prefrontal cortex (56, 57).

Studies of electrical stimulation provided additional evidence in support of hemispheric differences in prefrontal cortical control of impulsive behavior. High-definition transcranial anodal direct current stimulation (tDCS, which increased neuronal activity, as compared to cathodal stimulation) of the left dorsolateral prefrontal cortex (DLPFC) at a location near the SFG (F3) increased risky choices in the Balloon Analog Risk Task (58). This finding was consistent with other reports that left anodal/right cathodal and right anodal/left cathodal tDCS of the DLPFC each increased (59, 60) and diminished (60–62) risk-taking behavior. In a recent work, reward expectancy was associated with higher left ventrolateral PFC activity in a decision making task (63). Together, these studies spoke to distinct roles of the left- and

right- hemispheric prefrontal cortex in facilitating approach and avoidance behavior. The current findings of increased thalamic – left SFG connectivity in association with higher alcohol expectancy may provide a new circuit marker of at-risk drinking.

In relation to alcohol misuse, young adults who used alcohol on a regular basis showed significantly higher activation than those who do not use alcohol regularly in the left SFG, despite similar behavioral performance, in an imaging study of the go/nogo task (64). Although interpreted as a compensatory process by the authors, the latter findings may reflect a distinct role of the left SFG in impulsive response, as discussed earlier. In addicted individuals, alcohol dependence severity was negatively associated with activation in the right SFG during impulsive relative to delayed decisions in a delayed discounting task (65), again suggesting contrasting roles of the left and right SFG in cognitive control. It would be of interest to further explore the role of thalamus, left SFG and thalamic-prefrontal cortical connectivity in cue-elicited responses and whether these responses translate into alcohol seeking behavior in a laboratory or real-life setting.

More broadly, the effects of expectancy on subjective experience of environmental stimuli have been most thoroughly investigated for placebo analgesia – expectations that a treatment will produce pain relief cause pain reduction even when the treatment itself is inert (66). In behavioral terms, individuals learn to expect a certain outcome and harness physiological resources to support such expectations (67). Indeed, as the current results showed, alcohol expectancy was highly correlated with cue-elicited craving during the alcohol but not neutral blocks. Notably, imaging studies showed that placebo effects involved reduced activation of the anterior cingulate cortex and thalamus to pain stimulation (66). In contrast, nocebo effect – negative expectation of the manipulation or treatment – was associated with increased activation of the thalamus, amygdala, and the hippocampus (68). These results suggested flexible thalamic response to expectancy that associated individual variation in expectancy, acquired via conditioning or instrumental learning, to physiological effects.

A number of limitations need to be considered. First, it is worth noting that, although a substantial number of participants reported an AUDIT score greater than eight, it remains to be seen whether the current findings would generalize to heavier drinking populations, including those with an alcohol use disorder. Second, cue-related regional activations did not appear to relate to acute craving rating. This may have reflected the nature of the experimental design; the alternating presentation of alcohol and neutral cue blocks may have masked the differences in craving elicited by alcohol and neutral cues. Further, the alcohol cue pictures have not been validated independently and some of the alcohol cue stimuli involved human faces known to elicit emotions that may complicate the measures of alcohol cue response. In particular, human faces elicited activation of occipital and temporal areas, including the fusiform gyrus (69), which may be conflated with cue-elicited activation. Third, it is important to note that, although the thalamic effect size of cue response, GP score, and AUDIT score were correlated pairwise, their inter-relationship remained to be clarified. Mediation analyses delineated how alcohol expectancy mediated the contribution of thalamic effect size to at-risk drinking, but the causal link between thalamic cue response, alcohol expectancy and problem alcohol use needs to be confirmed in a longitudinal setting.

In conclusion, the current study demonstrated the cue-elicited thalamic activity and connectivity in association with alcohol expectancy. To our knowledge these findings are the first to relate alcohol expectancy to cue elicited brain responses and provide new markers of alcohol misuse. The etiologies of alcohol misuse are multi-faceted. The current findings of altered thalamic activation and connectivity in relation to alcohol expectancy may complement work of other psychological processes and neural circuits to more fully capture the biological markers of at-risk alcohol consumption (70). Identifying these regional markers of at-risk alcohol use may also facilitate research of effective treatment, such as non-invasive brain stimulation, of individuals with alcohol use disorders (71, 72).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Regional activations to alcohol (A) vs. neutral (N) cues at $p < 0.001$ uncorrected. All clusters with cluster $p < 0.05$ FWE corrected are shown in Table 2. mOFC: medial orbitofrontal cortex; RN: red nucleus; OC: occipital cortex; CN: caudate nucleus; RSC/POS: retrosplenial cortex/parieto-occipital sulcus; SMG: supramarginal gyrus; SPG/Cu: superior parietal gyrus/cuneus; PCG: posterior cingulate gyrus.

Figure 2.

(A) Bilateral thalamus showed regional activations to alcohol > neutral cues in correlation with global positive alcohol expectancy (AE) score in all subjects at voxel $p < 0.001$, uncorrected, in combination with cluster $p < 0.05$ FWE corrected. (B) Regression of thalamic activity (beta contrast: alcohol > neutral cue) against AE score separately for men ($p = 0.05$, $r = 0.37$) and women ($p = 0.007$, $r = 0.46$), and for all subjects ($p = 0.0007$, $r = 0.42$). A slope test showed no difference between men and women ($p = 0.95$). (C) Regression of thalamic activity (alcohol > neutral cue) against AUDIT score separately for men ($p = 0.05$, $r = 0.34$) and women ($p = 0.43$, $r = 0.15$), and for all subjects ($p = 0.03$, $r = 0.27$). A slope test showed no difference between men and women ($p = 0.44$).

Figure 3.

Brain regions showing a higher psychophysiological interaction with bilateral thalamus during alcohol vs. neutral cue blocks (warm color) and during neutral vs. alcohol cue blocks (cool color) at $p < 0.001$ uncorrected. Clusters meeting cluster $p < 0.05$, FWE corrected are summarized in Table 3. AG: angular gyrus; CB: cerebellum; HG: hippocampal gyrus; MTG: middle temporal gyrus; OC: occipital cortex; PCL/PMC: paracentral lobule/premotor cortex; PCu: precuneus; SFS: superior frontal sulcus; Th/CN/Pa: thalamus/caudate nucleus/pallidum.

Figure 4.

(A) Left superior frontal sulcus/gyrus showed a higher psychophysiological interaction with bilateral thalamus during alcohol vs. neutral cue blocks at voxel $p < 0.001$, uncorrected, in combination with cluster $p < 0.05$ FWE corrected. (B) Regression of the gPPI magnitude against global positive alcohol expectancy (AE) score separately for men ($p = 0.01$, $r = 0.42$) and women ($p = 0.11$, $r = 0.30$), and for all subjects ($p = 0.0023$, $r = 0.38$). A slope test showed no difference between men and women ($p = 0.79$). (C) Regression of the gPPI magnitude against AUDIT score separately for men ($p = 0.0034$, $r = 0.50$) and women ($p = 0.18$, $r = 0.26$), and for all subjects ($p = 0.0022$, $r = 0.39$). A slope test showed no difference between men and women ($p = 0.27$).

Figure 5.

Mediation analysis. (A) Global positive alcohol expectancy score (GP) completely mediated the correlation between the thalamic (Thal.) response to alcohol vs. neutral cue and AUDIT score in men and women combined. (B) The alternative model where AUDIT score mediated the correlation between GP score and thalamic response were not supported. (C) Likewise, GP score completely mediated the correlation between the strength of thalamic SFG connectivity and AUDIT score. (D) The alternative model where AUDIT score mediated the correlation between GP score and connectivity strength was not supported. The p values associated with mediation are for the path “a*b” (see Methods).

Table 1:

Demographics and drinking measures of male and female participants

Subject characteristic	Men (n=33)	Women (n=28)	P value *
Age (years)	30.8 ± 8.1	30.4 ± 8.9	0.82
AUDIT score	11.3 ± 11.3	9.6 ± 9.1	0.53
Duration of alcohol use (years)	12.6 ± 8.0	12.9 ± 9.6	0.91
# of drinking days/month, prior year	8.2 ± 6.0	10.9 ± 5.0	0.07
# of drinks/per occasion	3.8 ± 2.6	3.4 ± 2.3	0.50
# of drinks/month, prior year	38 ± 45.4	41.2 ± 40.9	0.78
Alcohol expectancy GP score	13.3 ± 6.0	14.8 ± 6.1	0.33
FTND score	0.42 ± 1.4	1.25 ± 2.6	0.12
Current smoker (yes/no)	6/27	9/19	0.21

Note: values are mean ± S.D.;

* two-tailed two-sample t test, except for smoker status which used Chi- square test; AUDIT: Alcohol Use Disorder Identification Test; GP: global positive subscore of the Alcohol Expectancy Questionnaire-3; FTND: Fagerström Test for Nicotine Dependence.

Table 2:

Regional activations to alcohol vs. neutral cue exposure.

Volume (mm ³)	peak voxel (Z)	MNI coordinates (mm)			side	identified brain region
		x	y	z		
<i>Alcohol > Neutral cues</i>						
*19,494	6.66	21	-91	4	R	Superior/Middle occipital gyrus/Cuneus
*20,412	6.48	-24	-85	-5	L	Superior/Middle occipital gyrus/Cuneus
*7,263	5.42	-12	-43	13	L/R	Retrosplenial cortex/parieto-occipital sulcus
*5,481	4.77	-9	44	-11	L/R	Medial orbitofrontal cortex
3,699	4.08	-6	59	31	L/R	Dorsomedial prefrontal cortex
3,807	4.01	-3	-16	-8	L/R	Red nucleus
3,402	4.00	-12	20	7	L	Caudate nucleus
<i>Neutral > Alcohol cues</i>						
*7,857	4.69	9	-79	31	L/R	Superior parietal gyrus/cuneus
4,617	4.33	-60	-28	13	L	Superior temporal gyrus
5,643	4.14	57	-40	37	R	Supramarginal gyrus
3,780	4.05	15	-34	46	L/R	Posterior cingulate gyrus

Note: voxel $p < 0.001$ uncorrected and cluster-level $p < 0.05$, FWE corrected; R: right; L: left.* clusters with voxel peak meeting $p < 0.05$, FWE.

Table 3:

Brain regions showing psychophysiological interaction with bilateral thalamus during exposure to alcohol vs. neutral cue.

Volume (mm ³)	peak voxel (Z)	MNI coordinates (mm)			side	identified brain region
		x	y	z		
<i>Positive</i>						
*32,184	5.79	24	-88	-11	R	Occipital cortex/Cerebellum
	5.42	-24	-88	-11	L	Occipital cortex/Cerebellum
*2,511	4.87	33	-16	-20	R	Hippocampus
*1,593	4.85	-54	-52	-11	L	Middle temporal gyrus
*8,154	4.82	-6	-31	55	L/R	Paracentral lobule/PMC
*1,620	4.81	-3	-61	19	L/R	Precuneus
*7,398	4.75	-6	-7	10	L/R	Thalamus/Caudate/Pallidum
*1,782	4.75	-27	11	55	L	Superior frontal sulcus
*2,457	4.68	-9	-46	-14	L/R	Cerebellum
*3,672	4.59	-36	-70	37	L	Occipital cortex
<i>Negative</i>						
None						

Note: voxel $p < 0.001$ uncorrected and cluster-level $p < 0.05$, FWE corrected;

* clusters with voxel peak $p < 0.05$, FEW; R: right; L: left; PMC: premotor cortex.