Archival Report

Biological Psychiatry: CNNI

Alcohol Expectancy and Cerebral Responses to Cue-Elicited Craving in Adult Nondependent 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: A total of 61 nondependent drinkers were assessed with the Alcohol Expectancy Questionnaire and Alcohol Use Disorder Identification Test and underwent functional magnetic resonance imaging while exposed to alcohol and neutral cues. Imaging data were processed and analyzed with published routines, and mediation analyses were conducted to examine the interrelationships among global positive score of the Alcohol Expectancy Questionnaire, Alcohol Use Disorder Identification Test score, and regional responses to alcohol versus neutral cues.

RESULTS: Alcohol as compared with neutral cues engaged the occipital, retrosplenial, and medial orbitofrontal cortex as well as the left caudate head and red nucleus. The bilateral thalamus showed a significant correlation in cue response and in left superior frontal cortical connectivity with global positive score in a linear regression. Mediation analyses showed that global positive score completely mediated the relationship between thalamic cue activity as well as superior frontal cortical connectivity and Alcohol Use Disorder Identification Test 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 nondependent drinkers. AEs may reflect a top-down modulation of the thalamic processing of alcohol cues, influencing the pattern of alcohol use.

Keywords: Alcohol, Craving, Cue, Expectancy, fMRI, Thalamus

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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 such as "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 drinkers as compared with 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

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expectancies of alcohol-produced relaxation were related to abstinence during a 1-year period (8).

Numerous studies have examined the effects and neural processes of environmentally triggered craving. Following administration of a nonalcoholic 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 with neutral taste cues evoked greater activation in the dorsal striatum, insula, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and ventral tegmental area, 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 ventral tegmental area among heavy drinkers, in contrast to control participants (14). In another study, alcohol-related visual cues activated the ventral striatum, OFC, and other structures in the medial prefrontal cortex (PFC) in alcohol-dependent individuals as compared with healthy subjects (15). Across cue modalities, a meta-analysis of 28 functional magnetic resonance imaging studies showed robust activation of limbic prefrontal regions, including the ACC and ventromedial PFC, in 679 cases of heavy/dependent drinkers (16). When compared with control participants, case participants exhibited more activation in the parietal and temporal regions, including the posterior cingulate, precuneus, and superior temporal gyrus. In region of interest (ROI) analyses that interrogated only limbic regions, cue-elicited activation of the ventral striatum 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 that 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 after receiving placebo (albeit to a lesser extent) but not after receiving a nonalcoholic drink (17). Importantly, alcohol approach tendencies were more pronounced after both alcohol and placebo compared with 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 nonalcohol) 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 PFC 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 that 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 regard to the interactions between 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 electroencephalographic study suggested frontal but not parietal electroencephalographic 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 interrelated with AE and at-risk alcohol use in nondependent drinkers (26). However, no imaging studies have addressed the potential influence of AE on cue-induced craving or the interrelationships among AE, cue-elicited brain response, and at-risk drinking.

Here, we examined the relationship between AE and cerebral responses in a cue-elicited craving functional magnetic resonance imaging paradigm in 61 adult nondependent 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.

METHODS AND MATERIALS

Subjects and Assessments

Potential candidates were recruited from the greater New Haven, Connecticut, area and were screened according to the Structured Clinical Interview for DSM-IV (27). A total of 61 nondependent adult drinkers met eligibility requirements 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 Structured Clinical Interview for DSM-IV (27). The Human Investigation Committee at the Yale University School of Medicine approved all study procedures, and all subjects signed an informed consent form prior to participation.

Table 1. Demographics and Drinking Measures of Male and Female Participants

Subject Characteristic	Men (n = 33)	Women (n = 28)	p Value[a]
Age, Years	30.8 ± 8.1	30.4 ± 8.9	.82
AUDIT Score	11.3 ± 11.3	9.6 ± 9.1	.53
Duration of Alcohol Use, Years	12.6 ± 8.0	12.9 ± 9.6	.91
Number of Drinking Days per Month, Prior Year	8.2 ± 6.0	10.9 ± 5.0	.07
Number of Drinks per Occasion	3.8 ± 2.6	3.4 ± 2.3	.50
Number of Drinks per Month, Prior Year	38 ± 45.4	41.2 ± 40.9	.78
Alcohol Expectancy GP Score	13.3 ± 6.0	14.8 ± 6.1	.33
FTND Score	0.42 ± 1.4	1.25 ± 2.6	.12
Current Smoker, Yes/No	6/27	9/19	.21

Values are mean ± SD or n.

AUDIT, Alcohol Use Disorder Identification Test; FTND, Fagerström Test for Nicotine Dependence; GP, global positive subscore of the Alcohol Expectancy Questionnaire.

[a]Two-tailed two-sample t test except for smoker status, which used chi-square test.

All participants were assessed with the 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 (29). The Alcohol Expectancy Questionnaire consists of 40 items to address both positive AE (six subscales) and negative AE (two subscales). Each subscale contains four to six statements that can be endorsed on a 6-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 GP AE. Although the expectancy subcomponents are statistically discernible, the high subscale intercorrelations (ranging from r = .42 to r = .92, mean = .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 AE. Participants were also assessed with the Fagerström Test for Nicotine Dependence (30) and averaged 0.8 ± 2.0 (mean ± SD) in Fagerström Test for Nicotine Dependence score, suggesting low dependence.

Behavioral Task

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 seconds, six pictures displaying alcohol-related cues (alcohol block) or neutral visual scenes (neutral block) were shown for 6 seconds 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 alcohol on a visual analog scale from 0 (no craving) to 10 (highest craving ever experienced). Each block lasted about 45 seconds (including time for craving rating), and a total of six alcohol and six neutral blocks took approximately 9 minutes to complete. Each participant completed two runs of the task.

Imaging Protocol and Data Preprocessing

The imaging protocol is described in detail in the Supplement. Data were analyzed with SPM 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 function and with the temporal derivative of the canonical hemodynamic response function 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 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 contrast (difference in beta) images of the first-level analysis were then used for the second-level group statistics (random-effects analysis). Following current reporting standards, all imaging results were evaluated with voxel $p < .001$, uncorrected, in combination with cluster $p < .05$, familywise error corrected, on the basis of Gaussian random field theory, as implemented in SPM.

In ROI analysis, we used MarsBaR (http://marsbar.sourceforge.net/) to derive for each individual subject the activity (beta contrast) for the ROIs. Functional ROIs were defined based on clusters obtained from whole-brain analysis. All voxel activations were presented in Montreal Neurological Institute coordinates.

General Psychophysiological Interaction

To explore circuit activities, we examined psychophysiological interaction (PPI) of the ROIs with differential response to alcohol versus neutral cues. PPI describes functional connectivity between brain regions contingent on a psychological context. We used a generalized form of context-dependent PPI (general PPI [gPPI]; http://brainmap.wisc.edu/PPI) (33). Briefly, in gPPI the hemodynamic responses to 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 coactivation. The extracted mean time series of the blood oxygen level–dependent signals were temporally filtered, mean corrected, and deconvolved 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 reconvolved with the canonical hemodynamic response function to obtain the interaction term or PPI variable. Finally, the psychological regressors of alcohol picture and neutral picture, 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-effects group analysis. Likewise, the results were evaluated at voxel $p < .001$, uncorrected, in combination with cluster $p < .05$, familywise error corrected, according to current reporting standards.

Mediation Analysis

Owing to space limitations, mediation analyses are presented in the Supplement.

RESULTS

Cue-Induced Craving and Regional Activations to Alcohol Cue Exposure

Alcohol, as compared with neutral cue, elicited a higher craving rating (3.1 ± 2.5 vs. 1.9 ± 2.1, $p < .0001$, paired t test). Alcohol- but not neutral cue–elicited craving was also correlated positively with GP score across subjects ($r = .43$, $p < .0006$ and $r = .16$, $p = .2141$, respectively).

In examining regional responses to alcohol versus neutral cues, we first conducted a two-sample t test to compare men and women. Even at a relaxed threshold at voxel $p < .005$, uncorrected, no clusters showed a significant sex difference. Thus, men and women were combined in the analysis. Exposure to alcohol as compared with neutral cues engaged higher activation of cortical and subcortical structures, including the occipital cortex, medial OFC, 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 with alcohol cues involved higher activation in the superior parietal gyrus/cuneus, supramarginal gyrus, and posterior cingulate gyrus (Figure 1). These clusters are summarized in Table 2. We extracted the beta contrast of alcohol versus neutral cue response for each of these clusters, and none showed a significant correlation with craving rating during the alcohol block (all ps $> .24$) or with difference in craving rating between the alcohol and neutral blocks (all ps $> .13$).

Cue Reactivity in Relation to AE and Problem Drinking

As with the analyses of regional responses to alcohol versus neutral cues, we compared men and women in voxelwise regression against GP score and observed no sex differences at voxel $p < .005$, uncorrected. With men and women combined and in a whole-brain linear regression of alcohol versus neutral cue exposure against GP score for all subjects with age as a covariate, bilateral thalamus (x = 12, y = −13, z = 13, volume = 1971 mm^3, $Z = 3.43$; x = −15, y = −19, z = 10, volume =1458 mm^3, $Z = 3.29$), in the area of the 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 = 1944 mm^3; x = −15, y = −19, z = 10, $Z = 3.34$, volume = 1404 mm^3. We extracted the beta contrast of thalamic activation to alcohol versus neutral cue for individual subjects. Figure 2B, C shows the linear regression of GP and AUDIT scores 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 score and that with AUDIT score did not differ between men and women ($p = .95$ and $p = .44$, 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 versus neutral cue blocks (Figure 3 and Table 3). Of these nine clusters, we examined whether any of these regional interactions correlated with the GP and AUDIT scores. Because GP and AUDIT scores were highly correlated, we corrected for the number of clusters with a $p = .05/9 = .0056$ in examining the results. The gPPI magnitude of the cluster located at the left superior frontal gyrus (SFG)/superior frontal sulcus showed a positive correlation with both the GP score ($r = .38$, $p = .0023$) and AUDIT score ($r = .39$, $p = .0022$) (Figure 4A). A slope test showed no difference between men and women in the regression of the gPPI against GP score ($p = .79$) or AUDIT score ($p = .27$) (Figure 4B, C).

Mediation Analysis

With mediation analysis, we further examined the interrelationship among thalamic activation to alcohol (vs. neutral) cue exposure, AE (GP score), and problem drinking (AUDIT score). AUDIT score was highly correlated with GP score in men and women combined ($r = .5934$, $p = 4.66 \times 10^{-7}$), and thalamic activity during alcohol versus neutral cue exposure was correlated with GP score ($r = .4218$, $p = .0007$) and with AUDIT score ($r = .2708$, $p = .03476$). However, the interrelationships between these neural and clinical measures remained open. We performed mediation analyses to test two specific hypotheses, namely that 1) thalamic activity contributed to higher AE and, in turn, problem drinking, and 2) higher AE 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 versus 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 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

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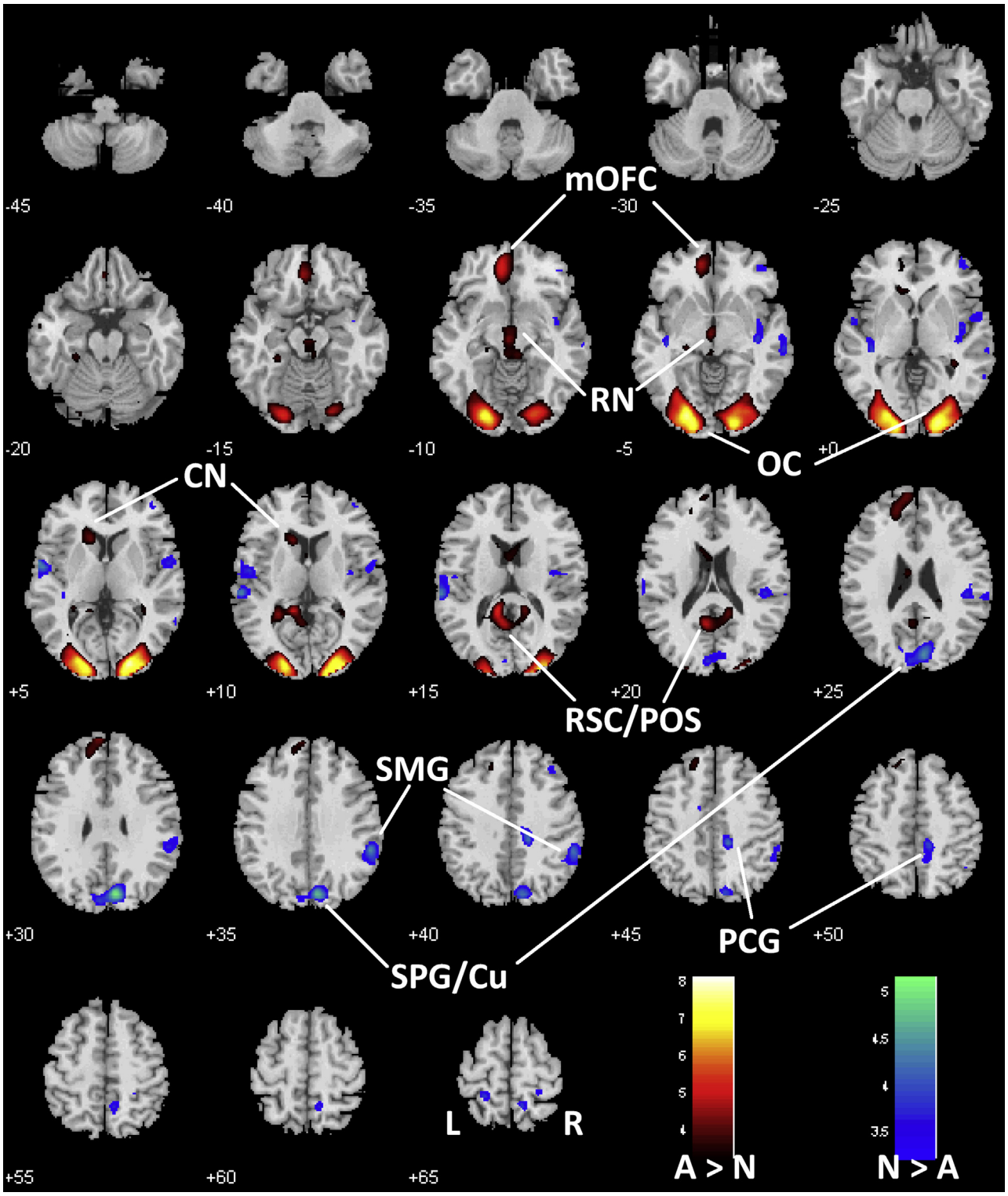

Figure 1. Regional activations to alcohol (A) vs. neutral (N) cues at $p < .001$, uncorrected. All clusters with cluster $p < .05$, familywise error corrected, are shown in Table 2. CN, caudate nucleus; L, left; mOFC, medial orbitofrontal cortex; OC, occipital cortex; PCG, posterior cingulate gyrus; R, right; RN, red nucleus; RSC/POS, retrosplenial cortex/parieto-occipital sulcus; SMG, supramarginal gyrus; SPG/Cu, superior parietal gyrus/cuneus.

Table 2. Regional Activations to Alcohol vs. Neutral Cue Exposure

Volume (mm^3)	Peak Voxel (Z)	MNI Coordinates (mm) x	y	z	Side	Identified Brain Region
Alcohol > Neutral Cues						
19,494[a]	6.66	21	−91	4	R	Superior/Middle occipital gyrus/Cuneus
20,412[a]	6.48	−24	−85	−5	L	Superior/Middle occipital gyrus/Cuneus
7263[a]	5.42	−12	−43	13	L/R	Retrosplenial cortex/Parieto-occipital sulcus
5481[a]	4.77	−9	44	−11	L/R	Medial orbitofrontal cortex
3699	4.08	−6	59	31	L/R	Dorsomedial prefrontal cortex
3807	4.01	−3	−16	−8	L/R	Red nucleus
3402	4.00	−12	20	7	L	Caudate nucleus
Neutral > Alcohol Cues						
7857[a]	4.69	9	−79	31	L/R	Superior parietal gyrus/Cuneus
4617	4.33	−60	−28	13	L	Superior temporal gyrus
5643	4.14	57	−40	37	R	Supramarginal gyrus
3780	4.05	15	−34	46	L/R	Posterior cingulate gyrus

Voxel $p < .001$, uncorrected, and cluster level $p < .05$, familywise error corrected.
L, left; MNI, Montreal Neurological Institute; R, right.
[a]Clusters with voxel peak meeting $p < .05$, familywise error corrected.

(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 versus neutral cues in the occipital, retrosplenial, and medial OFC as well as in the left caudate head and red nucleus, in accordance with earlier imaging studies of cue-related responses (35) and reward-related responses (36,37). Although not showing higher responses to alcohol versus neutral cues, the bilateral thalamus demonstrated a positive correlation in cue response with GP score and 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 SFG during cue exposures. Thalamic SFG connectivity was also correlated with both GP and AUDIT scores. Furthermore, 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 AE 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

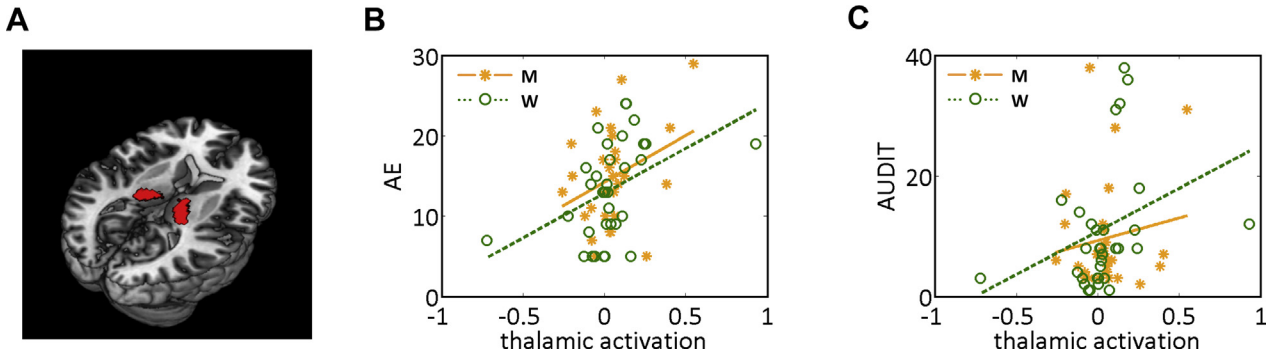

Figure 2. **(A)** Bilateral thalamus showing regional activations to alcohol > neutral cues in correlation with global positive alcohol expectancy (AE) score in all subjects at voxel $p < .001$, uncorrected, in combination with cluster $p < .05$, familywise error corrected. **(B)** Regression of thalamic activity (beta contrast: alcohol > neutral cue) against AE score separately for men (M) ($p = .05$, $r = .37$) and women (W) ($p = .007$, $r = .46$) and for all subjects ($p = .0007$, $r = .42$). A slope test showed no difference between men and women ($p = .95$). **(C)** Regression of thalamic activity (alcohol > neutral cue) against Alcohol Use Disorder Identification Test (AUDIT) score separately for men ($p = .05$, $r = .34$) and women ($p = .43$, $r = .15$) and for all subjects ($p = .03$, $r = .27$). A slope test showed no difference between men and women ($p = .44$).

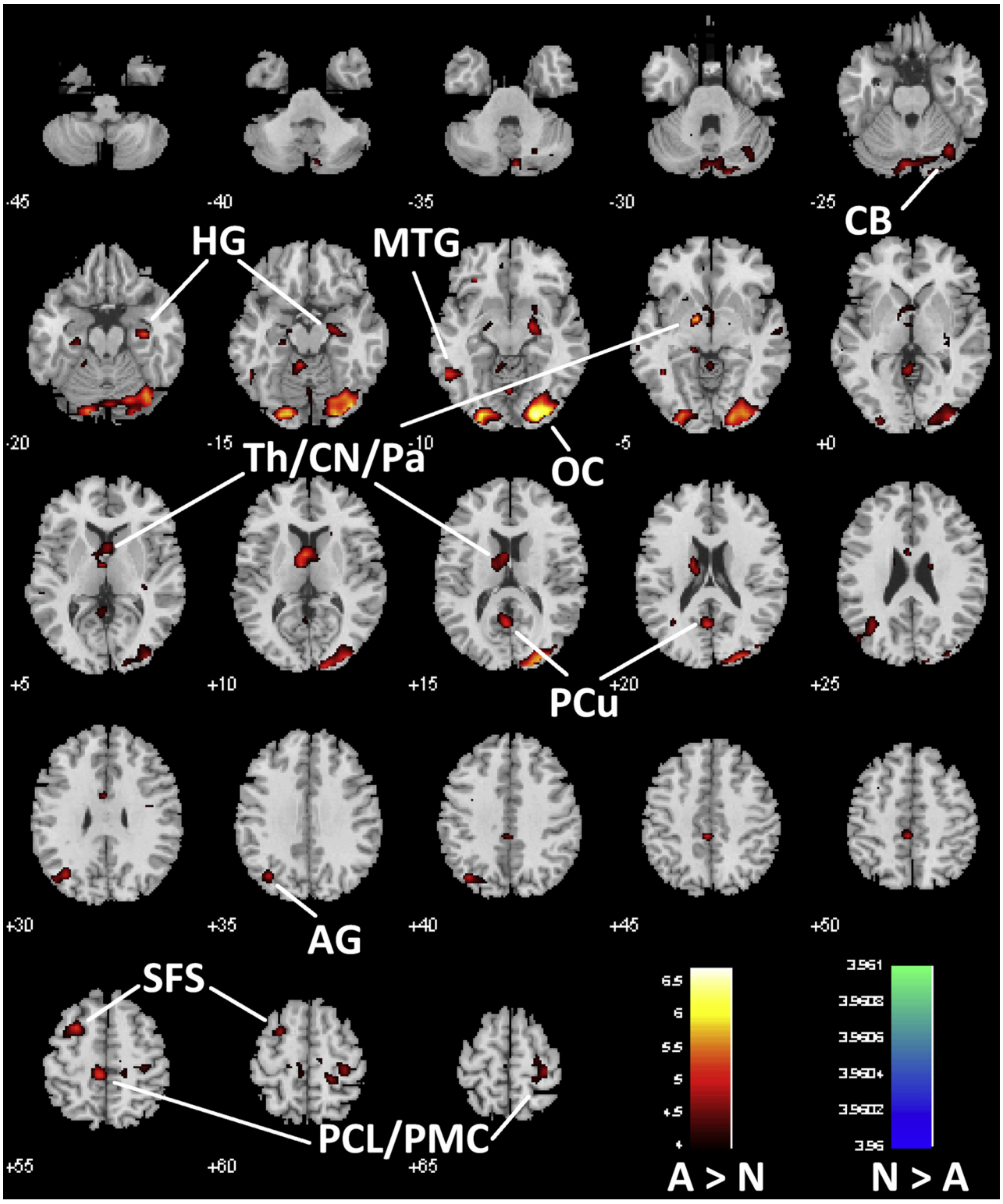

Figure 3. Brain regions showing a higher psychophysiological interaction with the bilateral thalamus during alcohol (A) vs. neutral (N) cue blocks (warm color) and during neutral vs. alcohol cue blocks (cool color) at $p < .001$, uncorrected. Clusters meeting cluster $p < .05$, familywise error corrected, 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.

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		
Positive						
32,184	5.79	24	−88	−11	R	Occipital cortex/cerebellum
	5.42	−24	−88	−11	L	Occipital cortex/cerebellum
2511[a]	4.87	33	−16	−20	R	Hippocampus
1593[a]	4.85	−54	−52	−11	L	Middle temporal gyrus
8154[a]	4.82	−6	−31	55	L/R	Paracentral lobule/PMC
1620[a]	4.81	−3	−61	19	L/R	Precuneus
7398[a]	4.75	−6	−7	10	L/R	Thalamus/caudate/pallidum
1782[a]	4.75	−27	11	55	L	Superior frontal sulcus
2457[a]	4.68	−9	−46	−14	L/R	Cerebellum
3672[a]	4.59	−36	−70	37	L	Occipital cortex
Negative						
None						

Voxel $p < .001$, uncorrected, and cluster level $p < .05$, familywise error corrected.
L. left; MNI, Montreal Neurological Institute; PMC, premotor cortex; R, right.
[a]Clusters with voxel peak $p < .05$, familywise error corrected.

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 nondrinkers.

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 PFC, posterior cingulate cortex, and striatum, although ventral striatal activations were reported largely in studies that interrogated only the limbic circuits with ROI analysis (16). There was substantial intra- and interstudy 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 more than 300 participants, authors reported robust thalamic response to alcohol versus litchi juice drinks (13), suggesting that gustatory stimulation may have more powerful effects on the thalamus than visual stimulation. Furthermore, of the clinical variables that influenced cue-elicited brain responses, length of use and addiction severity appeared to influence activities of the thalamus, amygdala, and dorsal ACC, 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 versus neutral cues. However, bilateral thalamus clusters exhibited higher response to alcohol versus

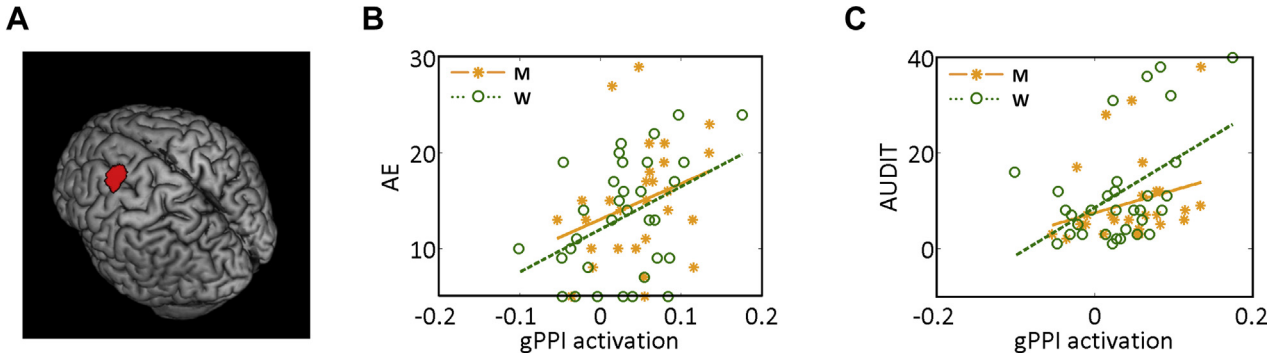

Figure 4. **(A)** Left superior frontal sulcus/gyrus showing a higher psychophysiological interaction with the bilateral thalamus during alcohol vs. neutral cue blocks at voxel $p < .001$, uncorrected, in combination with cluster $p < .05$, familywise error corrected. **(B)** Regression of the general psychophysiological interaction (gPPI) magnitude against global positive alcohol expectancy (AE) score separately for men (M) ($p = .01$, $r = .42$) and women (W) ($p = .11$, $r = .30$) and for all subjects ($p = .0023$, $r = .38$). A slope test showed no difference between men and women ($p = .79$). **(C)** Regression of the gPPI magnitude against Alcohol Use Disorder Identification Test (AUDIT) score separately for men ($p = .0034$, $r = .50$) and women ($p = .18$, $r = .26$) and for all subjects ($p = .0022$, $r = .39$). A slope test showed no difference between men and women ($p = .27$).

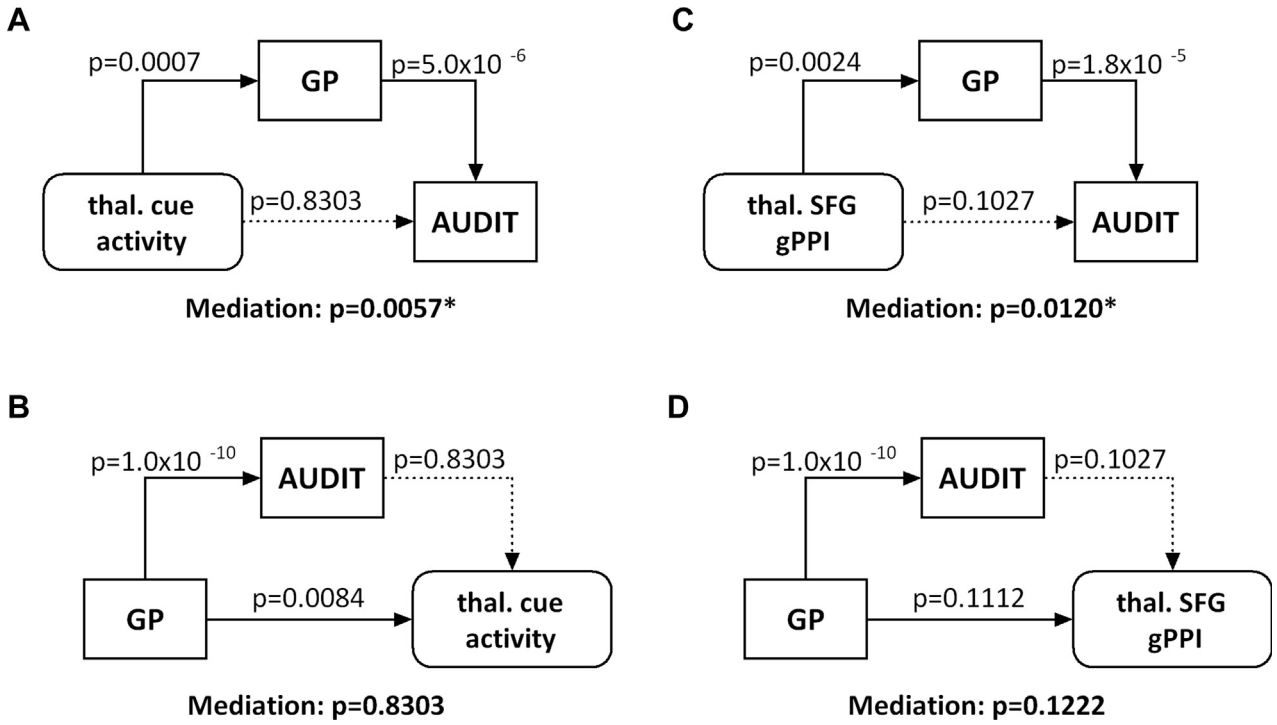

Figure 5. Mediation analysis. **(A)** The global positive (GP) alcohol expectancy score completely mediated the correlation between the thalamic response to alcohol vs. neutral cue and Alcohol Use Disorder Identification Test (AUDIT) score in men and women combined. **(B)** The alternative model where AUDIT score mediated the correlation between the GP score and thalamic response was not supported. **(C)** Likewise, the GP score completely mediated the correlation between the strength of thalamic superior frontal gyrus (SFG) connectivity and AUDIT score. **(D)** The alternative model where AUDIT score mediated the correlation between the GP score and connectivity strength was not supported. The *p* values associated with mediation are for the *a*b* path (see Supplemental Methods). *$p < .05$. gPPI, general psychophysiological interaction; thal., thalamic.

neutral cues in association with AE. These clusters comprised primarily the dorsomedial nucleus and pulvinar in the area of the frontal and parietal association thalamus, according to a tractography study (38), integrating multiple modalities of sensory inputs to support cognition. Interestingly, although the thalamus did not show higher response to alcohol versus neutral cues, thalamic responses appeared to play an important role in distinguishing relapsers from nonrelapsers in treatment studies and in predicting individual vulnerability to relapse (50–53), as recently reviewed (54). Because AE is conducive 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 SFG during cue exposure, and the magnitude of psychophysiological connectivity was also positively correlated with both 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 PFCs and the exact locale of cortical regions in these executive processes. Whereas the right-hemispheric PFC 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 their right-hemispheric counterparts. For instance, in studies of the stop signal task, we showed that response speeding as compared with slowing, as a behavioral index of risk taking, engaged predominantly left prefrontal and subcortical structures, whereas post-error slowing involved the right-hemispheric ventrolateral PFC (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, which increased neuronal activity as compared with cathodal stimulation, of the left dorsolateral PFC 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 transcranial anodal direct current stimulation of the dorsolateral PFC 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 PFC in facilitating approach and avoidance behavior. The current findings of increased thalamic–left SFG connectivity in association with higher AE 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 did not use alcohol regularly in the left SFG, despite similar behavioral performance, in an imaging study of the go/no-go 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 the 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, AE was highly correlated with cue-elicited craving during the alcohol blocks but not the neutral blocks. Notably, imaging studies showed that placebo effects involved reduced activation of the ACC and thalamus to pain stimulation (66). In contrast, the nocebo effect—negative expectation of the manipulation or treatment—was associated with increased activation of the thalamus, amygdala, and hippocampus (68). These results suggested flexible thalamic response to expectancy that associated individual variation in expectancy, acquired via conditioning or instrumental learning, with 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 8, 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. Furthermore, 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 interrelationship remained to be clarified. Mediation analyses delineated how AE mediated the contribution of thalamic effect size to at-risk drinking, but the causal link among thalamic cue response, AE, 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 AE. To our knowledge, these findings are the first to relate AE to cue-elicited brain responses and provide new markers of alcohol misuse. The etiologies of alcohol misuse are multifaceted. The current findings of altered thalamic activation and connectivity in relation to AE 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 noninvasive brain stimulation, of individuals with alcohol use disorders (71,72).

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ARTICLE INFORMATION

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