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Alcohol Use Disorder and Cannabis Use Disorder symptomatology in adolescents and Aggression: Associations with recruitment of neural regions implicated in retaliation

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Abstract

Background: Alcohol and cannabis are commonly used by adolescents in the United States. Both Alcohol Use Disorder (AUD) and Cannabis Use Disorder (CUD) have been associated with an increased risk for aggression. One form of aggression seen during retaliation is reactive aggression to social provocation. The current study investigated the association between AUD and CUD symptom severity and recruitment of neural regions implicated in retaliation.

Methods: In this study, 102 youths aged 13-18 years (67 male; 84 in residential care) completed self-report measures of aggression-related constructs and participated in a retaliation task during functional magnetic resonance imaging to investigate the association between relative severity of AUD/CUD and atypical recruitment of regions implicated in retaliation.

Results: AUD Identification Test (AUDIT) scores were positively associated with irritability and reactive aggression scores. CUD Identification Test (CUDIT) scores were positively associated with callous-unemotional traits and both proactive and reactive aggression scores. In fMRI analyses, only AUDIT (not CUDIT) scores were associated with an exaggerated recruitment of regions implicated in retaliation (dorsomedial frontal, anterior insula cortices, caudate and, to a lesser extent, periaqueductal gray).

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Conclusions: These data suggest that relative severity of AUD is associated with a disinhibited, exaggerated retaliation response that relates to an increased risk for reactive aggression. Similar findings were not related to severity of CUD.

Keywords

Adolescent; Alcohol Use Disorder; Cannabis Use Disorder; fMRI; Retaliation; Aggression

Introduction

Alcohol use disorder (AUD) and cannabis use disorder (CUD) are two of the most common substance use disorders (SUDs) in the United States, with lifetime prevalence rates of 29% and 6%, respectively (1, 2). Alcohol and cannabis use during adolescence are associated with an increased risk of developing AUD/CUD in adulthood (3). AUD and CUD are associated with a multitude of negative behavioral outcomes that peak during adolescence including risky sexual behavior (4, 5) and aggression (6–9). This increased disease severity may be due in part to adverse neurodevelopmental effects of these substances on the adolescent brain (10, 11).

AUD and CUD are significantly co-morbid with Conduct Disorder (CD) (12, 13) and are both associated with a significantly increased risk for aggression (6–9). But an understanding of the associations between AUD, CUD, CD and aggression remains in its infancy. Data generally indicate that early conduct problems are associated with an increased risk for later cannabis (14, 15) and alcohol use (16, 17). As such, common vulnerability factors, including neuro-cognitive risk factors, for the development of conduct problems likely overlap with those for substance use (9). However, there are also strong indications that chronic heavy use of alcohol and/or cannabis can in turn disrupt the neuro-cognitive systems that are implicated in CD (9). Specifically, AUD severity in adolescence has been linked to impaired functioning of neural systems engaged in reinforcement signaling and response control (18–20) – both of which are seen in participants with CD and related to an increased risk for aggression (21, 22). CUD severity in adolescence is associated with reduced neural activity during threat and socio-emotional processing, including the processing of other individual's facial expressions, such as distress cues (23, 24). Again, both of these impairments are seen in participants with CD (22, 25, 26) and are related to an increased risk for aggression (27).

Complicating matters, aggression is not a unitary construct mediated by a single set of neuro-cognitive systems (28, 29). Instead, a distinction can be drawn between reactive and instrumental aggression (28). "Reactive aggression" describes retaliatory actions in response to perceived threat, frustration, or provocation. "Instrumental aggression" is goal-directed - the individual decides to use aggression to achieve their goals (28, 29). This study focuses on the neural systems involved in retaliation, and potential associated perturbations with AUD and/or CUD.

In previous work, we have outlined three interacting components of the neuro-cognitive response during retaliation (29): First, systems mediating the acute threat response (amygdala and particularly periaqueductal gray [PAG]) (cf. 30, 31). The suggestion is that if

these are overly responsive, as they appear to be in some more emotionally labile cases of CD (32, 33), the individual will be more likely to retaliate/respond with reactive aggression (29). Second, ventromedial prefrontal cortex's (vmPFC) role in either inhibiting the acute threat response (e.g., 34) or representing the costs of retaliation such that another action may be chosen (i.e., having an impact on the motivation to perform the action; 29). The suggestion is that if this is dysfunctional, as is seen in CD (32, 35), the individual will be more likely to retaliate (29). Third, dorsomedial frontal (dmFC), anterior insula/inferior frontal cortices and caudate have been implicated in the retaliation response (29, 36). The suggestion is that these regions play a role in controlling the retaliation response (29), similar to suggestions of the importance of these regions in response control more generally (37) – though it could alternatively be argued, given that both regions are key regions in the salience network (38, 39), that their increasing activation reflects the increasing salience (actionability) of the retaliation.

With respect to implications for aggression associated with AUD/CUD, the situation is largely equivocal. Regarding the acute threat response, there have been some suggestions that AUD and/or CUD might be related to increased threat responsiveness (40, 41). However, other work has indicated that heavy alcohol and cannabis use might be related to reduced emotional responsiveness (e.g., 23, 24, 42, 43). Regarding vmPFC functioning, there have been some previous findings indicating that individuals with AUD show reduced vmPFC responses to monetary reward (44, 45). However, other studies have not found atypical vmPFC responding to reward as a function of AUD or CUD severity (20, 46). Only with respect to systems engaged in response control is there more consistent data. The literature indicates that substance use generally can disrupt the function of the neural systems engaged in response control (for reviews, see 47, 48). Consistent with this, with respect to AUD specifically, neuroimaging work has revealed that, relative to controls, adolescents and adults with heavy alcohol use histories show disrupted regions of core neural regions implicated in response control during the performance of response control tasks (19, 49–51). However, it should be noted that there is less consistency regarding whether recruitment of these systems is dysfunctional in adolescent and adult cannabis users (e.g., 19, 51–53).

In the present study, we used fMRI to examine associations between AUD and CUD severity and neuro-cognitive responses during retaliation using data from a large transdiagnostic sample of youth with varying AUD and CUD severities performing a retaliation task adapted from previous work (32, 36). Three predictions were made: First, if AUD and/or CUD is associated with heightened threat processing, then increasing AUD and/or CUD severity would be associated with greater recruitment of regions implicated in the acute threat response (amygdala, PAG) during retaliation. Second, if AUD and/or CUD is associated with vmPFC dysfunction then increasing AUD and/or CUD severity would be associated with decreased modulation of activity within this region as a function of retaliation. Third, if AUD and/or CUD is associated with dysfunction in the neural systems engaged in response control, then increasing AUD and/or CUD severity would be associated with atypical recruitment of dorsomedial frontal and anterior insula cortices as a function of retaliation.

Methods

Participants

Study participants included 112 youths aged 13-18 from a residential treatment program or the surrounding community. They were recruited as part of a broader study determining neural correlates of youth with behavioral and emotional problems, specifically substance use disorders (at least 40% of the population) and mental health concerns (Attention Deficit/Hyperactivity Disorder [ADHD], CD, Major Depressive Disorder [MDD] and Generalized Anxiety Disorder [GAD]). None of these participants have been included in previous papers on this task. However, a number of the participants have been involved in previously published studies associating specific forms of neuro-cognitive dysfunction with severity of alcohol and/or cannabis use disorder (18–20, 23, 24, 54). Ten youths were excluded due to excessive head movement (>5mm maximum displacement) during functional MRI scanning (details below) (e.g., 55). This resulted in a final sample of 102 youths (84 from the residential treatment program and 18 from the community); average age=16.54 (*SD*=1.26), average IQ=98.76 (*SD*=10.90), 67 males. Participants recruited from Boys Town were enrolled a highly supervised residential treatment program where they received random drug testing and did not have access to alcohol or drugs. All Boys Town participants were abstinent from any substance for at least 4 weeks prior to scanning. Task administration and scanning occurred as shortly after this period was reached as possible. See Supplemental Methods for information on recruitment, consent/assent, and exclusion criteria.

Measures

The Retaliation Task -—Participants were presented with a version of the Ultimatum game, the Retaliation task, that has been previously described (32); see Supplementary Material (Figure S1). Participants were offered either a fair ($10 to participant; $10 to partner) or unfair ($6 or $4 or $2 to participant; $14/$16/$18 to partner) division of a $20 pot (Allocation phase). Participants could then either accept the offer or reject it and, by spending $1, $2 or $3 punishment dollars, punish the partner (Retaliation phase). Each punishment dollar spent by the participant caused the partner to lose $7 from the $20 pot (Figure 1). Retaliatory propensity was defined as the participant's average punishment level per offer level.

Substance Use Disorder Assessments.—Participants completed both the AUD Identification Test (AUDIT; 56) and CUD Identification Test (CUDIT; 57) assessing symptom levels over the previous 12 months. These scales assess overall symptom severity of AUD and CUD, respectively, including overall quantity/frequency of use, abuse symptoms, and dependence symptoms. They show high validity, as higher scores on these scales are associated with a high likelihood of an AUD and/or CUD diagnosis, respectively (57, 58). Cigarette smoking status was determined via the Monitoring the Future Survey (59). Although participants were subject to random urine drug screening drug testing as part of the treatment program, they were not drug tested on the day of scanning.

Aggression Assessments.—Participants completed the Reactive–Proactive Aggression Questionnaire (RPQ; 60), the Inventory of Callous-Unemotional Traits (ICU: 61) and the

Affective Reactivity Index (ARI: 62). More complete descriptions of these measures are provided in the Supplemental Material.

Functional MRI Parameters and Analysis.—Whole-brain BOLD functional MRI data were acquired via a 3T MAGNETOM Skyra magnetic resonance imaging scanner. Imaging data were preprocessed and analyzed in Analysis of Functional NeuroImages (AFNI) (63). Both individual and group level analyses were conducted. At the individual level, functional images from the first four repetitions, collected prior to equilibrium magnetization, were discarded. The participants' anatomical scans were then individually registered to the Talairach and Tournoux atlas (64). The individuals' functional EPI data were then registered to their Talairach anatomical scan. The EPI datasets for each participant were spatially smoothed (isotropic 6 mm^3 Gaussian kernel) to reduce variability among individuals and generate group maps. Next, the time series data were normalized by dividing the signal intensity of a voxel at each time point by the mean signal intensity of that voxel for each run and multiplying the result by 100, producing regression coefficients representing percent-signal change. Every TR on which motion exceeded 1 mm was censored.

A model was generated using six motion regressors and the following task regressors: indicator functions for the (i) offer-phase; (ii) decision-phase; (iii) outcome-phase; (iv) offer-phase multiplied by offer unfairness (0 [fair: $10 kept; $10 offered to partner], 8 [unfair: $14 kept; $6 offered to partner], 12 [unfair: $16/$4], 16 [unfair: $18/$2]); and (v) decision-phase multiplied by the sample average punishment level at each level of unfairness (average response to $10/$10=1.176, $14/$6=2.358, $16/$4=2.726, $18/$2=3.23). GLM fitting was performed with these regressors, six motion regressors, and a regressor modeling baseline drift. All regressors were convolved with a canonical hemodynamic response function (HRF) to account for the slow hemodynamic response (with time point commencing at time of first image onset). This produced an unmodulated β coefficient and associated *t* statistic and a β coefficient and associated *t* statistic modulated by punishment level for each voxel and regressor. There was no significant regressor collinearity.

Details on the statistical analyses conducted are provided in the Supplemental Material.

Results

Clinical Data

Of the final sample of 102 adolescents, 81 youths endorsed past-year use of either alcohol and/or cannabis. AUDIT scores ranged from 0-21 [M=3.30, SD=4.85] and CUDIT scores ranged from 0-32 [M=9.26, SD=8.94]. Fifty-six youths met the clinical cutoffs on the AUDIT and/or CUDIT suggestive of adolescent AUD (AUDIT≥4) or CUD (CUDIT≥8) (58, 65, 66). Thirty participants had an AUDIT score≥4 and 51 participants had a CUDIT score≥8. In line with prior work indicating high rates of poly-substance use in adolescents (65), 24 participants had both an AUDIT score≥4 and CUDIT score≥8 (20 participants had AUDIT and CUDIT scores=0).

Correlation analyses revealed a significant positive association between AUDIT and CUDIT scores [r=0.43, p<.001]; see Table 1. AUDIT scores were significantly positively associated

with a MDD diagnosis and CUDIT scores were significantly positively associated with diagnoses of ADHD, CD and prescription of antidepressants; see Table 1. In all cases, except ADHD status, follow-up Steiger's z tests showed no significantly stronger associations between AUDIT/CUDIT scores and any of these indices (Steiger z's= −0.50-1.78, *p*'s=.62-.08). There was a stronger association between CUDIT scores and ADHD status than AUDIT scores and ADHD status (Steiger's z=2.58, $p<.01$). There were no significant associations between age, IQ, stimulant use, or antipsychotic use and AUDIT scores or CUDIT scores (see Table 1).

Two-sample t-tests revealed no sex differences in either AUDIT [$t(100)=1.50$, $p=0.14$]. or CUDIT scores [$t(100)=-1.01$, $p=0.32$]. The average AUDIT score for females was 4.29 (SD=5.82) and the average AUDIT score for males was 2.77 (SD=4.21). The average CUDIT score for females was 8.03 (SD=7.81) and the average CUDIT score for males was 9.91 (SD=9.47).

Aggression Data (Self and Parent Report)

Correlation analyses revealed a significant positive association between AUDIT and CUDIT scores and the self and parent report aggression data (see Table 2). Notably, AUDIT scores were only significantly positively correlated with reactive, and not proactive, aggression on the RPQ while CUDIT scores were significantly positively correlated with both. Moreover, only CUDIT scores were significantly positively correlated with ICU scores.

Retaliation Behavioral Data

The one-way ANCOVA conducted on the retaliation data revealed a main effect of offer level [$F(3,297)=427.09$, $p<.001$]; participants retaliated more strongly as offers became progressively less fair [$M_{10}=1.14$, SD=0.27; $M_6=2.65$, SD=0.72; $M_4=2.90$, SD=0.64; $M_2=3.29$, SD=0.62). In addition, there was a significant offer level-by-CUDIT score interaction [$F(3,297)=3.09$, $p=.028$]. Participants with higher CUDIT scores were more prone to retaliate at lower levels of unfairness compared to higher levels of unfairness (CUDIT correlation with retaliation $Level_{10}$-$Level_6$=0.28, p=0.004; with retaliation $Level_{10}$-$Level_4$=0.26, p=0.008). The offer level-by-AUDIT score interaction was not significant [$F(3,297)=0.867$, $p=.459$].

fMRI Results

The goal of this study was to explore whether either AUDIT or CUDIT scores might be associated with atypical responding when retaliating to unfair offers. Main effects of Phase are reported in the Supplemental Material (Table S1 & Figure S2). Our main analysis revealed the following interaction effects:

AUDIT-by-Phase Interaction:

There was a significant AUDIT-by-Phase interaction within regions including bilateral caudate, bilateral dorsal ACC, left anterior insula cortex and right lateral frontal cortex (Figure 1, Table 3). In all brain regions there was a significant positive association between AUDIT scores and BOLD responses modulated by level of retaliation; i.e., as AUDIT score increased, the positive response within these regions as a function of increasing retaliation

was exaggerated [r_p=0.363 to 0.482 respectively; p<0.001]. This was more positive than the association between AUDIT scores and BOLD responses modulated by level of offer unfairness. This AUDIT-by-Phase Interaction was also seen within PAG at a slightly more lenient initial threshold (p<0.005);as AUDIT score increased, the positive response as a function of increasing retaliation was exaggerated [r_p=0.277; p<0.005]; see Figure 1.

No regions showed either a CUDIT-by-Phase interaction or AUDIT-by-CUDIT-by-Phase Interaction that survived correction for multiple comparisons.

Potential Confounds:

There were three main potential confounds with the current data: (i) ADHD diagnosis was more related to CUDIT than AUDIT scores. However, repeating our main analysis adding an ADHD diagnosis status group variable largely replicated our main results (see Table S2); (ii) CD diagnosis which was significantly related to CUDIT but not AUDIT scores (though the correlational strengths were not significantly greater). However, repeating our main analysis adding a CD diagnosis status group variable largely replicated our main results (see Table S3); and (iii) The significant association between SSRI prescription and CUDIT scores. However, repeating our main analysis excluding participants prescribed SSRIs largely replicated our main results (see Table S4). Re-analysis of the data following removal of the two participants who had a significant alcohol and/or cannabis use history but who were not residents of the highly supervised residential treatment facility, and thus not subject to random drug testing, also largely replicated our main results (see Table S5).

Analyses examining the AUDIT and CUDIT separately (to ensure that inter-covariate suppressor effects could not obscure potential individual covariate associations) largely replicated our BOLD response main results. The AUDIT ANCOVA revealed significant comparable AUDIT score-by-Phase interactions in proximal regions (see Table S6) while the CUDIT ANCOVA failed to identify regions showing significant CUDIT score-by-Phase interactions. The comparable CUDIT single covariate ANCOVA on the behavioral data replicated the findings with respect to CUDIT scores (offer level-by-CUDIT score interaction: $F(3,300)=5.24$, $p=.002$). However, the AUDIT single covariate ANCOVA on the behavioral data *also* revealed a significant offer level-by-AUDIT score interaction ($F(3,300)=2.95$, $p=.033$).

Discussion

The current study investigated whether severity of AUD and/or CUD was related to atypical recruitment of neural regions during retaliation. Our data suggested that AUDIT scores, but not CUDIT scores, were associated with dysfunctional recruitment of regions including dmFC, aIC and caudate (and to a lesser extent, PAG) during retaliation.

In previous work, we have outlined three interacting components of the neuro-cognitive response during retaliation (29). In line with our previous work with this task (32, 36), the participants in the current study as a group showed responses within particularly the PAG, vmPFC, dmFC, aIC and caudate that were varied as a function of the participant's level of retaliation (see Figure S2). Notably, responsiveness within all these regions, except vmPFC,

was positively moderated by participants' AUDIT but not their CUDIT scores (though the PAG results were seen at a slightly more lenient threshold).

DmFC, aIC and caudate are all regions implicated in response control (37), a function considered to be disrupted by substance use (for reviews, see 47, 48), particularly AUD (19, 49–51) rather than CUD (e.g., 19, 51-53). Consistent with this, we observed that AUDIT (but not CUDIT) scores were associated with atypical responses within implicating dmFC, aIC and caudate during retaliation.

Notably, AUDIT scores were *positively* associated with activity within dmFC, aIC and caudate as a function of retaliation level. Typically developing individuals show increased responses within these regions as a function of level of retaliation (32, 36). As such, AUDIT scores were associated with an exaggeration of the typical response. It could be suggested that this reflects failed attempted behavioral inhibition of retaliation. However, we believe instead that it reflects response selection – something seen in other decision-making tasks involving multiple response options (67–69). Moreover, in the context of retaliation, we believe it reflects an integration of the activity of these systems involved in response selection/control with those mediating reactive aggressive retaliation responses that allows an organized angry response (29). Indeed, these regions have been implicated in anger in a number of other studies (70–73). In the current study, AUDIT scores were not only positively associated with the exaggeration of the responsiveness of dmFC, aIC and caudate as a function of retaliation level but also the responsiveness of PAG, consistent with an increased angry, retaliation response. Moreover, AUDIT scores were significantly positively associated with irritability (ARI scores) and selectively associated with reactive, but not proactive, aggression as indexed by the RPQ (see Table 2). In short, we believe that severity of impact of alcohol use in adolescents, as indexed by the AUDIT, is associated with an increased responsiveness of neural regions implicated in the organization of angry, retaliation responses and can manifest as increased irritability and an increased risk for reactive aggression.

The absence of a significant association between AUDIT scores and responsiveness within vmPFC is of some interest. An extensive region of vmPFC showed reduced activity as a function of retaliation level (see Figure S2). However, activity within this region was not associated with AUDIT or CUDIT scores (even at more lenient initial thresholds; $p<.005$). We hypothesize that this region tracks the non-optimal nature of retaliation (29) - the individual loses (spends) money so ends up with even less – with a purpose of motivating behavior that will maximize reward. Some studies examining reward responsiveness in individuals with AUD have reported reduced vmPFC responses to monetary reward (44, 45) but others have not (18, 20, 54). As such, our data suggests that the impact of alcohol and cannabis use in adolescents, at least as it manifests in AUD and CUD symptoms indexed by the AUDIT and CUDIT, on the vmPFC's role in representing reward is relatively minor.

To our surprise, the current study observed no association between CUDIT scores and atypical BOLD responses during retaliation. However, data indicate that there is an association between cannabis use and aggression (74, 75) though not impulsivity (76). In this study, CUDIT scores were positively associated with aggression scores on the RPQ,

conduct problems score on the SDQ and task performance suggesting that youth with higher CUD symptomatology may retaliate more to lower levels of unfairness. They were also positively associated with both reactive *and* proactive aggression on the RPQ and level of callous-unemotional (CU) traits as indexed by the ICU. CU traits are associated with reduced guilt and empathy and an increased risk for both reactive and proactive aggression (77). Notably, the neurobiology underpinning CU traits and an increased risk for both reactive and proactive aggression appears different from that incurring a selectively increased risk for reactive aggression and irritability (for a review, see 29). It is thus plausible that the problematic use of cannabis and alcohol during adolescence may increase the risk for aggressive responding via different neurobehavioral pathways.

The results of this study should be viewed in light of several limitations. First, we did not conduct urine or breathalyzer testing for alcohol or cannabis use on scan days. However, all but two participants with a significant alcohol and/or cannabis use history were residents of a highly supervised residential treatment facility and subject to random drug testing as part of treatment for at least 4 weeks prior to scanning. Exclusion of these 2 participants elicited highly similar results (see Table S4). Second, this study was cross-sectional. As such, the associations reported in the present study might reflect neurotoxic/neuroplastic effects of alcohol use on the developing brain *or* could alternatively represent pre-existing risk factors for AUD. However, no case has been made relating responsiveness within these systems as a selective risk factor for the development of AUD but not CUD. Third, there was a high degree of psychiatric co-morbidity in the residential treatment sample. It could be argued that the current findings are reflective of psychiatric co-morbidities of AUD rather than AUD/CUD itself. Prior work has often excluded participants with psychiatric conditions (44, 66, 78). However, this approach is problematic as approximately 80% of adolescents with a SUD present with one or more co-morbid psychiatric conditions (79, 80) and AUD and CUD are associated with a number of co-morbid psychiatric conditions (81, 82). As such, studies that exclude youth with psychiatric comorbidities are clinically atypical and may not generalize. Moreover, there were no significant differences in the strength of the association between AUDIT and CUDIT scores and probability of these diagnoses – except ADHD. Controlling for ADHD (or CD) in our analyses did not significantly alter our main study findings (see Table S2 & S3). Therefore, the current findings likely reflect severity of AUD rather than any psychiatric co-morbidity. Fourth, while the study observed no sex differences in the current study, almost two thirds of the sample were male. For that reason, caution should be excised when drawing conclusions with respect to the current results and sex. Fifth, the current study did not include personality traits such as sensation-seeking and impulsivity/disinhibition (though we did index ADHD) which have been related to externalizing behavior (83, 84). As such, we cannot determine whether AUD (or CUD) severity interacts with these variables with respect to task performance/BOLD response.

In summary, AUDIT scores were positively associated with the exaggeration of the responsiveness of dmFC, aIC, caudate and (to a lesser extent) PAG, as a function of retaliation level. Moreover, AUDIT scores were significantly positively associated with irritability and selectively associated with reactive but not proactive aggression. On this basis, we hypothesize that alcohol use in adolescents, as indexed by the AUDIT, is positively associated with responsiveness of neural regions implicated in the organization of angry,

retaliation responses and can manifest as increased irritability and an increased risk for reactive aggression. CUDIT scores, in contrast, were not associated with atypical BOLD responses on the current task though they were positively associated with reactive and proactive aggression and CU traits. We speculate on this basis, and previous findings, that, in adolescents at least, cannabis use sufficient to induce symptom level changes as indexed by the CUDIT, may increase propensity for aggression by compromising neural systems associated with CU traits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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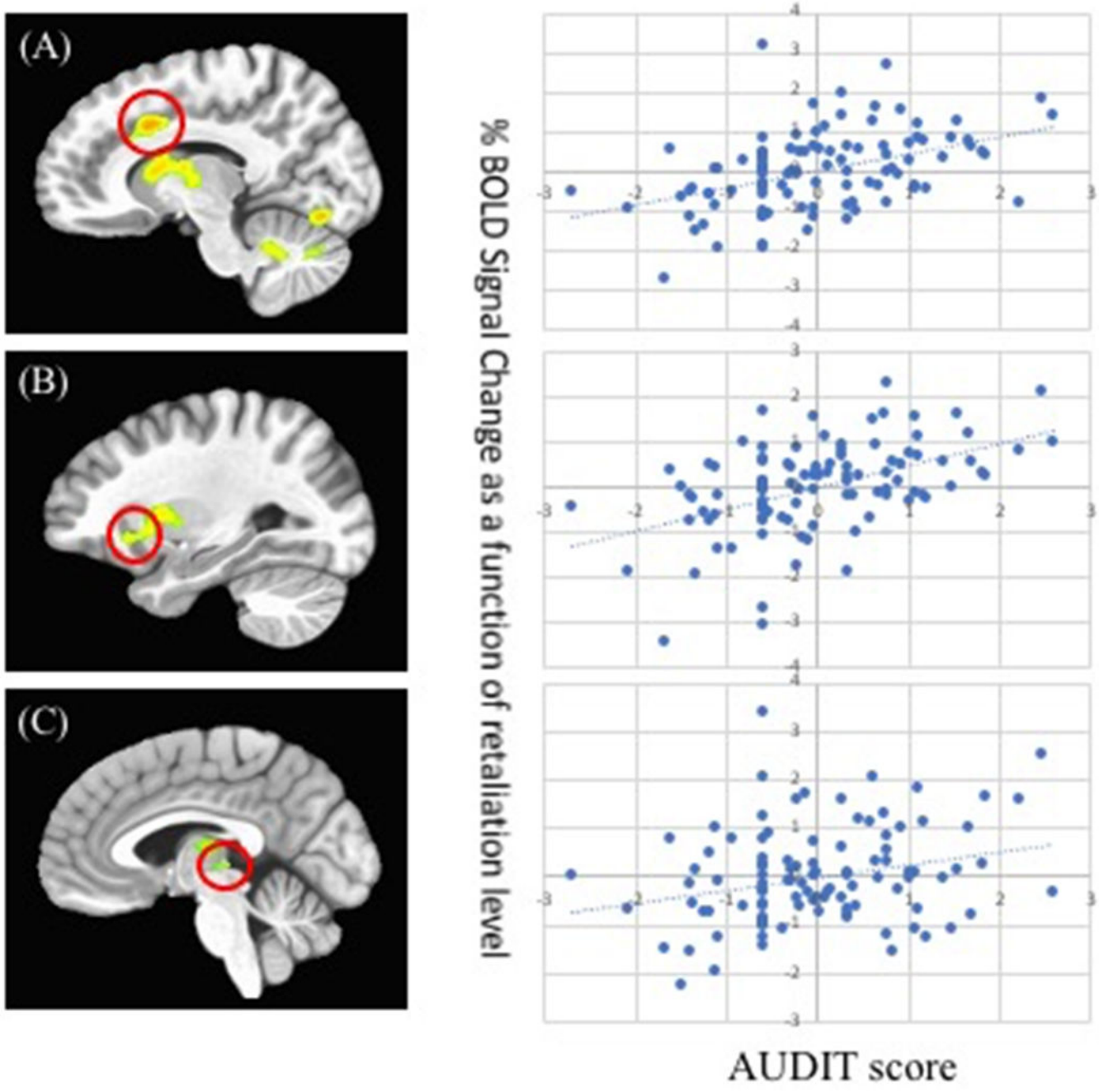

Figure 1. AUDIT-by-Phase interaction

within: (A) right anterior cingulate cortex; (B) an extensive region of right caudate/striatum extending into anterior insula cortex; and (C) PAG. Scatterplots depict the partial correlations and adjusted residuals for each of the regions. Adjusted residuals for the Rankit transformed z-scored AUDIT scores (x-axis) are plotted against adjusted residuals for the BOLD responses as a function of retaliation level.

Table 1.

Demographic and Clinical Variables

	Average (SD) (N=102)	ADHD (N=52)	CD (N=50)	MDD (N=14)	GAD (N=32)	Stimulants (N=16)	SSRIs (N=16)	Antipsychotics (N=5)	Age	IQ	AUDIT	CUDIT	Smoking
Age	16.54 (1.26)												
IQ	98.76 (10.90)								0.036				
AUDIT	3.30 (4.85)	0.062	0.142	0.210 †	0.192	0.044	0.178	−0.128	0.184	−0.100			
CUDIT	9.26 (8.94)	0.322 *	0.319 *	0.046	0.108	0.187	0.233 †	−0.185	0.175	−0.106	0.434 *		
Smoking	1.45 (1.47)								0.220 †	0.057	0.483 *	0.557 *	
Sex	67 males								−0.055 [a]	−0.117 [a]	−0.145 [a]	0.100 [a]	0.008

† significant at $p<0.05$,

* significant at $p<0.01$,

[a] correlations coded as male=1, female=0; ADHD=Attention Deficit/Hyperactivity Disorder, CD=Conduct Disorder, MDD=Major Depressive Disorder, GAD=Generalized Anxiety Disorder, AUDIT=Alcohol Use Disorder Identification Test, CUDIT=Cannabis Use Disorder Identification Test

Table 2.

Associations between AUDIT and CUDIT scores and aggression measures.

	RPQ Total	RPQ Reactive	RPQ Proactive	ARI	ICU	SDQ CP
AUDIT	0.225 *	0.230 *	0.161	0.228 *	0.178	0.220 *
CUDIT	0.273 **	0.240 *	0.254 *	0.179	0.287 **	0.389 **
RPQ Total		0.937 **	0.825 **	0.685 **	0.541 **	0.391 **
RPQ Reactive			0.576 **	0.714 **	0.451 **	0.357 **
RPQ Proactive				0.449 **	0.538 **	0.329 **
ARI					0.463 **	0.252 *
ICU						0.283 *

RPQ=Reactive Proactive Questionnaire, ARI-Affective Reactivity Index, ICU=Inventory of Callous Unemotional Traits, SDQ CP=Conduct Problems subscale of the Strengths and Difficulties Questionnaire, AUDIT=Alcohol Use Disorder Identification Test, CUDIT=Cannabis Use Disorder Identification Test

* significant at $p<0.05$,

** significant at $p<0.001$.

Table 3.

Brain regions demonstrating significant AUDIT-by-Phase Interactions

Region[a]	Hemisphere	BA	Coordinates of Peak Activation[b] x	y	z	*F*	Partial η^2	Voxels
AUDIT-by-Phase[c]								
Anterior cingulate cortex	R	24	15	20	31	26.771	0.213	102
Anterior cingulate cortex	L	32	−11	23	31	21.12	0.176	36
Lentiform nucleus/caudate extending to anterior insula cortex	R	--	18	−5	1	23.616	0.193	167
Caudate extending to anterior insula cortex	L	--	−19	8	14	28.045	0.221	225
Lentiform nucleus	L	--	−33	−12	2	17.882	0.153	22
Middle frontal gyrus	R	9	31	34	23	17.309	0.149	80
Middle frontal gyrus	L	6	−17	15	52	23.434	0.191	78
Superior Temporal Gyrus	R	13/38	47	4	−20	25.043	0.202	76
Lingual Gyrus	R	18	8	−72	−11	21.152	0.176	54
Culmen	R	--	12	−48	−29	20.933	0.175	41
Culmen	L	--	−8	−53	−9	23.682	0.193	86

Note:

[a]According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/),

[b]Based on the Tournoux & Talairach standard brain template,

[c]Note that all interactions reflect a negative association between AUDIT scores and neural response as a function of retaliation level, BA= Brodmann's Area