Alcohol Use Disorder, But Not Cannabis Use Disorder, Symptomatology in Adolescents Is Associated With Reduced Differential Responsiveness to Reward Versus Punishment Feedback During Instrumental Learning

Supplemental Information

Supplemental Methods

Youths recruited from Boys Town had been referred for behavioral and mental health problems, including substance use disorders. Participants from the community were recruited through flyers or social media. Clinical characterization was done through psychiatric interviews by licensed and board-certified child and adolescent psychiatrists with the participants and their parents/caregivers, to adhere closely to common clinical practice.

The Boys Town National Research Hospital institutional review board approved this study. A doctoral level researcher or a member of the clinical research team obtained written informed consent and assent. In all cases, youth had the right to decline participation at any time before or during the study.

Exclusion criteria for the broader project included IQ<75 assessed with the Wechsler Abbreviated Scale of Intelligence (WASI two-subtest form; Wechsler, 2011), pregnancy, non-psychiatric medical conditions that require the use of medication that may have psychotropic effects (e.g., beta blockers or steroids), current psychosis, pervasive developmental disorders, Tourette's disorder, neurological disorders, presence of metallic objects in the body (e.g., metal plates, pacemakers, etc.), and claustrophobia. Current psychiatric conditions (other than psychotic disorders or pervasive developmental disorders) were not exclusionary. Use of psychotropic medications for psychiatric indications (e.g., stimulants, selective serotonin reuptake inhibitors)

were not exclusory. However, participants on stimulant medication were asked to withhold medication on the day of scanning.

MRI Parameters

All data were collected on a 3T Siemens Skyra scanner. A total of 313 functional images were taken with a T2* weighted gradient echo planar imaging (EPI) sequence (repetition time=2500 ms; echo time=27 ms; 240 mm field of view; 94x94 matrix; 90^{o} flip angle). Whole-brain coverage was obtained with 43 axial slices (thickness, 2.5 mm; voxel size 2.6x2.6x2.5 mm^{3}). A high-resolution T1 anatomical scan (MP-RAGE, repetition time=2200 ms; echo time=2.48 ms; 230 mm field of view; 8^{o} flip angle; 256x208 matrix; thickness, 1 mm; voxel size .9x.9x1 mm^{3}) in register with the EPI data set was obtained covering the whole brain with 176 axial slices.

fMRI Preprocessing

Functional MRI data were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (2). The anatomical scan for each participant was registered to the Talairach and Tournoux atlas (3) and each participant's functional EPI data were registered to their Talairach anatomical scan in AFNI. Functional images were motion corrected to a reference volume and spatially smoothed with a 6-mm full width at half maximum Gaussian kernel. The data then underwent time series normalization to a T1 image, and these results were multiplied by 100 for each voxel. Therefore, the resultant regression coefficients are representative of a percentage of signal change from the mean.

Correction for Multiple Comparisons

Correction for multiple comparisons was performed using a spatial clustering operation in AFNI's 3dClustSim utilizing the autocorrelation function (-acf) with 10,000 Monte Carlo simulations for the whole-brain analysis. Spatial autocorrelation was estimated from residuals

from the individual-level GLMs. The initial threshold was set at p=.001 (4, 5). This process yielded an extent threshold of k=16 contiguous voxels for the whole brain (NN1/facewise neighbor clustering). Follow-up analyses were conducted on the percent signal change taken from all significant voxels within each functional ROI generated by AFNI to examine significant main effects and interactions with planned follow-up testing within SPSS 22.0 (6).

Supplemental Results

AUDIT and CUDIT Skewness and Kurtosis

For AUDIT scores, pre-transformation skewness and kurtosis values were 2.59 and 7.48, respectively. Post-transformation, skewness and kurtosis values for AUDIT scores were 0.65 and -0.44. The skewness and kurtosis values for CUDIT scores were 0.81 and -0.48, respectively, so no transformation was applied to the CUDIT scores.

Main Effect of Feedback

There was a significant main effect of feedback within dorsomedial prefrontal/anterior cingulate cortex, bilateral anterior insular cortex/inferior frontal gyrus, left lingual gyrus, right middle temporal gyrus, right lingual gyrus, right middle frontal gyrus, left supramarginal gyrus, middle cingulate cortex, left middle temporal gyrus, brainstem, right supramarginal gyrus, and precuneus. In all brain regions, there was greater activation for punishment feedback relative to reward feedback. See Table S1 for more details.

Movement Data

Volumes were censored if there was >0.5 mm motion across adjacent volumes. Thirteen out of 154 participants were due to excessive motion (>20% censored volumes) on the task. This

resulted in a final sample of N=141 participants. There was no relationship between AUDIT scores or CUDIT scores and number of censored TR's, average motion per TR, or maximum displacement during the task [*r*'s=-0.01-0.10, *p*'s>.05]

Demographic and Clinical Variables

Tables S1-S3 break down demographic and clinical variables by i) group comparisons of demographic/clinical variables for adolescents with AUDIT scores=0 versus AUDIT scores≥4; ii) group comparisons of demographic/clinical variables for adolescents with CUDIT scores=0 versus CUDIT scores≥8; and iii) demographic and clinical variables for adolescents with both AUDIT<4 and CUDIT<8, AUDIT≥4 and CUDIT<8, AUDIT<4 and CUDIT≥8, and both AUDIT≥4 and CUDIT≥8.

Potential Confounds

Given that our sample reflected clinical reality, there were a number of potential confounds, including medication usage, co-morbid psychiatric conditions, placement, and sex differences. Briefly, we identified nine potential confounds and for each potential confound we conducted an additional analysis that repeated the main analysis controlling for that specific confound. We chose to run separate models for each confounding variable because including all of these variables in one model would substantially reduce the statistical power of our analyses, as 11 regressors would be included in our model. In addition, we wished to interrogate these potential confounds individually so that each could be evaluated on its own merits.

Since AUDIT and CUDIT scores were associated with antidepressant use and the participants were permitted to use those medications on the day of scanning, the same analysis was repeated with antidepressant use entered as a covariate. This analysis revealed a pattern of results highly similar to the main analysis; specifically, the striatal, parietal cortex, and posterior cingulate

cortex findings remained significant after covarying for antidepressant use (Table S5). To rule out the possibility that pathology related to psychiatric co-morbidities influenced our results, our main analysis was repeated with each of the four most common psychiatric diagnoses as a covariate (ADHD, CD, MDD, GAD). Each of these analyses revealed a pattern of results highly similar to the main analysis; specifically, the striatal, parietal cortex, and PCC findings remained significant after controlling for each of the diagnostic categories (Tables S6-S9). To rule out the possibility that our results could be attributed to smoking status, we repeated the same analysis with smoking as a covariate; the striatal and parietal cortex findings remained significant in this analysis (Table S10). Although many participants with significant substance use histories in this study were members of the residential treatment program and were subject to random drug testing in the weeks prior to scanning, one participant with a significant substance use history was recruited from the community and not subject to random drug testing. We repeated the same analysis with this participant excluded from the sample; the striatal and parietal cortex remained significant in this analysis (Table S11). We also repeated the same analysis with placement (Boys Town versus Community) as a covariate; the striatal and parietal cortex remained significant in this analysis (Table S12). Since there was a significant difference between females and males on AUDIT scores, we repeated the same analysis with sex a categorical variable. The striatal, parietal, and PCC findings remained significant (Table S13).

Supplemental References

1. Wechsler D (2011): *Wechsler Abbreviated Scale of Intelligence–Second Edition*. San Antonio, TX: NCS Pearson.

2. Cox RW (1996): AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. *Comput Biomed Res*. 29: 162–173.

3. Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain: 3-D Proportional System: An Approach to Cerebral Imaging*, 1st ed. Stuttgart: Thieme.

4. Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA (2017): FMRI Clustering in AFNI: False-Positive Rates Redux. *Brain Connect*. 7: 152–171.

5. Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA (2017): FMRI Clustering and False Positive Rates. *Proc Natl Acad Sci U S A*. 114. doi: 10.1089/brain.2016.0475.

6. *IBM SPSS Statistics For MacOSX* (2012): Armonk, NY: IBM Corp.

Table S1. Group Comparisons of Demographic Variables between Adolescents with AUDIT=0 and Adolescents with AUDIT≥4 (n=102)

Variable	AUDIT=0 (N=59)	AUDIT≥4 (N=43)	t/chi-square value
Age (SD)	16.5 (1.06)	16.9 (0.99)	-2.18*
IQ (SD)	98.1 (9.35)	99.6 (10.82)	-0.79
% Male	72.9%	58.1%	2.42
MDD Diagnosis	10.2%	23.3%	3.22
GAD Diagnosis	15.3%	46.5%	11.94*
CD Diagnosis	28.8%	69.8%	16.79*
ADHD Diagnosis	45.8%	65.1%	3.75
Antidepressant Use	13.6%	32.6%	5.31*
Stimulant Use	16.9%	14.0%	0.17
Antipsychotic Use	10.2%	7.0%	0.32

*indicates significant t/chi-square value at $p<.05$ (to be interpreted with caution, as all other analyses utilize a dimensional approach)

Table S2. Group Comparisons of Demographic Variables between Adolescents with CUDIT=0 and Adolescents with CUDIT≥8 (n=117)

Variable	CUDIT=0 (N=55)	CUDIT≥8 (N=62)	t/chi-square value
Age (SD)	16.5 (1.03)	16.6 (1.02)	-0.44
IQ (SD)	98.8 (9.29)	100.3 (10.51)	-0.85
% Male	61.8%	66.1%	0.24
MDD Diagnosis	5.5%	21.0%	5.94*
GAD Diagnosis	18.2%	38.7%	5.96*
CD Diagnosis	21.8%	71.0%	26.28*
ADHD Diagnosis	32.7%	69.4%	15.67*
Antidepressant Use	12.7%	30.6%	5.41*
Stimulant Use	14.5%	17.7%	0.22
Antipsychotic Use	9.1%	9.7%	0.01

*indicates significant t/chi-square value at $p<.05$ (to be interpreted with caution, as all other analyses utilize a dimensional approach)

Table S3. Demographic and Clinical Variables between Adolescents with AUDIT<4 and CUDIT<8, AUDIT≥4 only, CUDIT≥8 only, and both AUDIT≥4 and CUDIT≥8

Variable	AUDIT<4 and CUDIT<8 (N=71)	AUDIT≥4 only (N=8)	CUDIT≥8 only (N=27)	AUDIT≥4 and CUDIT≥8 (N=35)
Age (SD)	16.5 (1.18)	17.7 (0.57)	16.35 (1.07)	16.7 (0.97)
IQ (SD)	99.8 (10.00)	104.5 (7.82)	102.6 (9.26)	98.5 (11.18)
% Male	62.0%	62.5%	77.8%	57.1%
MDD Diagnosis	9.9%	12.5%	14.8%	25.7%
GAD Diagnosis	16.9%	37.5%	18.5%	48.6%
CD Diagnosis	25.4%	50.0%	66.7%	74.3%
ADHD Diagnosis	38.0%	50.0%	70.4%	68.6%
Antidepressant Use	8.5%	25.0%	25.9%	34.3%
Stimulant Use	14.5%	0.0%	18.5%	17.1%
Antipsychotic Use	8.5%	0.0%	11.1%	8.6%

*indicates significant t/chi-square value at $p<.05$ (to be interpreted with caution, as all other analyses utilize a dimensional approach)

Table S4. Brain regions demonstrating significant responses to feedback type

			Coordinates of Peak Activation[b]					
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
			Punishment>Reward					
Dorsomedial Prefrontal Cortex/Anterior Cingulate Cortex	R/L	6/8	5	14	56	44.23	0.244	700
Anterior Insular Cortex/Inferior Frontal Gyrus	R	45	50	20	8	38.01	0.217	278
Anterior Insular Cortex/Inferior Frontal Gyrus	L	47	-37	20	-1	38.08	0.218	266
Lingual Gyrus	L	18	-22	-55	2	26.56	0.162	131
Middle Temporal Gyrus	R	38	44	11	-31	32.77	0.193	90
Middle Temporal Gyrus	R	21	53	-28	-4	34.61	0.202	85
Lingual Gyrus	R	30	20	-58	5	26.46	0.162	74
Middle Frontal Gyrus	R	9	41	8	35	27.39	0.167	62
Supramarginal Gyrus	L	40	-58	-43	26	22.93	0.143	46
Middle Cingulate Cortex	R/L	23	2	-19	32	20.13	0.128	35
Middle Temporal Gyrus	L	21	-52	-19	-1	22.38	0.140	29
Middle Temporal Gyrus	L	39	-49	-52	14	18.50	0.119	25
Brainstem	R/L	-	5	-16	-22	23.39	0.146	23
Supramarginal Gyrus	R	40	56	-46	23	19.15	0.123	23
Supramarginal Gyrus	R	40	35	-52	35	17.46	0.113	22
Middle Frontal Gyrus	R	6	41	-1	50	19.78	0.126	22
Precuneus	L	7	-4	-49	47	16.64	0.108	16

Note: [a] According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/), [b] Based on the Tournoux & Talairach standard brain template, BA= Brodmann's Area

Table S5. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for Prescribed Antidepressant Usage

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	20.68	0.132	27
Putamen*	L	-	-19	8	2	16.87	0.110	19
Posterior Cingulate Cortex*	L	29/30	-10	-49	5	17.52	0.114	19
Superior Parietal Lobule*	R	7	38	-55	50	18.92	0.122	27
Occipital Cortex*	R	19/39	32	-73	26	17.77	0.116	30
Cerebellum	R	-	11	-49	-22	18.96	0.122	16

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 relationship between AUDIT scores and the reward > punishment contrast, , * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S6. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for ADHD Diagnosis

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	20.43	0.131	27
Putamen*	L	-	-19	8	2	16.66	0.109	20
Posterior Cingulate Cortex*	L	29/30	-10	-49	5	17.63	0.115	19
Superior Parietal Lobule*	R	7	38	-55	50	17.75	0.115	17
Occipital Cortex*	R	19/31	32	-73	17	16.86	0.110	20

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 relationship between AUDIT scores and the reward > punishment contrast, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S7. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for CD Diagnosis

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	19.83	0.127	25
Posterior Cingulate Cortex*	L	30	-16	-52	8	18.19	0.118	26
Superior Parietal Lobule*	R	7	38	-55	50	22.27	0.141	49
Precuneus	R	7	29	-67	38	17.10	0.112	21
Postcentral Gyrus	L	3	-43	-25	53	14.17	0.094	16
Occipital Cortex*	R	-	35	-67	20	17.24	0.112	21

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 relationship between AUDIT scores and the reward > punishment contrast, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S8. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for GAD Diagnosis

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	19.58	0.126	24
Posterior Cingulate Cortex*	L	30	-10	-43	-1	18.79	0.121	26
Superior Parietal Lobule*	R	7	38	-55	50	18.27	0.118	21
Occipital Cortex*	R	-	35	-67	20	17.14	0.112	26
Cerebellum	R	-	11	-49	-22	19.95	0.128	19

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 relationship between AUDIT scores and the reward > punishment contrast, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S9. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for MDD Diagnosis

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	20.38	0.130	26
Putamen[d]*	L	-	-19	8	2	16.64	0.109	15
Posterior Cingulate Cortex*	L	29/30	-10	-49	5	17.93	0.117	19
Superior Parietal Lobule*	R	7	38	-55	50	17.62	0.115	16
Occipital Cortex*	R	19	32	-73	26	17.28	0.113	25

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 relationship between AUDIT scores and the reward > punishment contrast, [d] Below the Clustsim threshold, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S10. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for Smoking

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	19.53	0.127	25
Superior Parietal Lobule*	R	7	38	-55	50	18.26	0.120	25

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 relationship between AUDIT scores and the reward > punishment contrast, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S11. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Excluding Community Participants with significant substance use

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	19.96	0.128	21
Superior Parietal Lobule*	R	7	38	-55	50	19.20	0.124	29
Posterior Cingulate Cortex[d]*	L	29/30	-10	-49	5	15.44	0.102	10

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 relationship between AUDIT scores and the reward > punishment contrast, [d] Below the clustsim threshold, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S12. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for Placement (Boys Town versus Community)

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	19.39	0.125	21
Superior Parietal Lobule*	R	7	38	-55	50	18.26	0.113	27

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 relationship between AUDIT scores and the reward > punishment contrast, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area

Table S13. Brain regions demonstrating significant AUDIT-by-Feedback Interactions Covarying for Sex

		Coordinates of Peak Activation[b]						
Region[a]	Hemisphere	BA	x	y	z	*F*	Partial η^2	Voxels
		AUDIT-by-Feedback[c]						
Caudate/Putamen*	L	-	-13	14	8	16.80	0.110	21
Posterior Cingulate Cortex*	L	29/30	-10	-49	5	13.47	0.090	18
Superior Parietal Lobule*	R	7	38	-55	50	22.44	0.142	20
Occipital Cortex*	R	19	32	-73	17	20.42	0.131	20

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 relationship between AUDIT scores and the reward > punishment contrast, * denotes clusters that overlap with significant clusters found in the main analysis, BA= Brodmann's Area