SUPPLEMENTAL MATERIALS

Amino acid Beverages

Amino acid mixtures were prepared by Nutricia (Liverpool, UK). The control beverage consisted of (in g): L-alanine, 4.1; L-arginine, 3.7; L-cysteine, 2.0; L-glycine, 2.4; L-histidine, 2.4; L-isoleucine, 6; L-leucine, 10.1; L-lysine, 6.7; L-methionine, 2.3; L-phenylalanine, 4.3; L-proline, 9,2; L-serine, 5.2; L-threonine, 4.9; L-tryptophan, 3.0; L-tyrosine, 5.2; and L-valine, 6.7. The P/T-depleted beverage had the same composition except that P and T were omitted. Beverages were mixed with cold water and a lemon-lime flavor packet from Nutricia North America (Gaithersburg, MD) in an 11 oz sterile container. Using identical recipes and procedures, we previously reported that 5 hr after drinking the beverage, the P/T depleted beverage reduces the ratio of P/T to the other large neutral amino acids (P+T/$\sum$ LNAA) in plasma by an average of 76% relative to the placebo beverage [1]. Based on PET imaging, this ratio is a measure of the availability of DA the brain [2].

Carolina Alcohol Use Patterns Questionnaire (CAUPQ)

The Carolina Alcohol Use Patterns Questionnaire (CAUPQ, below) assessed adolescent binge drinking before age 18 (question 4) and between 18-21 years (question 5). Responses ranged from “Never” to “More than once a week.” These frequency bins were recoded to estimate the number of binge episodes before age 18 and between 18-21 years (Supplemental Table 1), which were summed to estimate a total number of adolescent (0-21 years) binge episodes.

1 Standard Drink is Equal to

One 12 oz can/bottle of beer

One 5 oz glass of regular (12%) wine

1 ½ oz of hard liquor (e.g. rum, vodka, whiskey)

1 mixed or straight drink with 1 ½ oz hard liquor

Carolina Alcohol Use Pattern Questionnaire

1. During the last 12 months, how many alcoholic **drinks** did you have on a typical day when you drank alcohol? _____

2. During the last 12 months, how often did you have 5 or more **drinks** (4 or more if you are female) containing any kind of alcohol within a two-hour period? Please circle the correct response.

Never	1-3 times	4-6 times	7-12 times	2-3 times/month	weekly	>once/week

3. At what age did you have your first alcoholic **drink**? _____

4. Before the age of 18, how often did you have 5 or more **drinks** (4 or more if you are female) containing any kind of alcohol within a two-hour period? Please circle the correct response.

Never	1-3 times	4-6 times	7-12 times	2-3 times/month	weekly	>once/week

5. From age 18 to age 21, how often did you have 5 or more **drinks** (4 or more if you are female) containing any kind of alcohol within a two-hour period? Please circle the correct response.

Never	1-3 times	4-6 times	7-12 times	2-3 times/month	weekly	>once/week

6. How old were you when you first drank 4 or more drinks in a row (females), or 5 or more drinks in a row (males)? _____

7. How old were you the first time you became drunk from alcohol? _____

Supplemental Table 1. Approximated number of binge episodes based on responses to the CAUPQ.

	Before the age of 18	From age 18 to age 21
Never	0	0
1-3 times	2	2
4-6 times	5	5
7-12 times	9.5	9.5
2-3 times/month	48	48
weekly	N/A	156
>once/week	N/A	312

Psychoactive medication use

No participants reported ever taking psychotropic medications ("medications for your nerves or psychological medications"), aside from one who reported taking Xanax when flying (rare use). Ten participants reported having used over-the-counter cold medicines within the previous 3 months, and one also reported using an inhaler occasionally when needed, which should not have central effects, but might make them feel jittery. Use of such medications was not in the previous 24 hours and was generally one week or more before any sessions.

Behavioral Inventories

Participants completed standardized questionnaires to capture demographic information, and to quantify factors that may account for individual differences in attentional bias to alcohol, sensitivity to reward conditioning, or brain connectivity. We quantified past and current drug and alcohol use with the Alcohol Use Questionnaire [AUQ; 3], the Carolina Alcohol Use Patterns Questionnaire (CAUPQ), the Drug Use Screening Inventory-Domain I [DUSI-I; 4], the Alcohol Use and Disorders Inventory Test [AUDIT; 5], and drinking motivations with Coopers Drinking Motivations Scale-Revised [DMQ-r; 6]. We used the NIAAA definition of binge drinking for males: 5 or more drinks in a 2-hour period (National Institute on Alcohol Abuse and Alcoholism, 2017). We also used a more refined measure of binge drinking, the AUQ binge drinking score (BDS), which is based on the speed of drinking, the frequency of intoxication in the past 6 months, and the percentage of time the individual becomes intoxicated when drinking, rather than a purely alcohol intake quantity measure [3]. The CAUPQ assesses the age of drinking onset, and the frequency of binge drinking. Binge drinking frequency was assessed in three questions on the CAUPQ, addressing binge drinking before age of 18, binge drinking between 18-21 years, and current binge drinking frequency. Responses range from "Never" to "More than once a week," and are coded numerically from 0-

6 (see Appendix). To assess the effect of familial history of alcohol abuse we administered the Family Tree Questionnaire [7]. Impulsivity was measured by the Barrett Impulsivity Scale [BIS-11; 8].

Heavy binge drinkers differed significantly from moderate drinkers on several psychometric measures (Supplemental Table 2). Heavy drinkers reported higher rates of current (ADQ binge score) and adolescent binge drinking (between 0-21 years of age) and significantly more hazardous drinking behavior based on AUDIT scores. Heavy and moderate drinkers also differed significantly in their self-reported motivations to drink alcohol, based on the DMQ-r.

Supplemental Table 2. Demographics and Alcohol Use Measures

	MD (*n*=19)	HD (*n*=15)	*t*-statistic	*p*-value
Demographics				
Age (yrs)	27±5.0	25.4±5.2	-0.89	0.392
Education (yrs)	16.9±2.2	16.5±1.6	-0.55	0.586
Familial Alcohol Density (%)	12±15	18±18	1.02	0.317
Substance Use Measures				
Binge Score	8.0±5.2	32.3±28.0	3.26	**<0.001**
Age of Drinking Onset (yrs)	15.9±3.3	15.8±3.3	-.071	0.994
Binges 0-21 yrs [median (range)]	2 (0-360)	48 (0-312)	2.07	**0.046**
DMQ-r Social	11.8±3.9	15.3±3.8	2.66	**0.012**
DMQ-r Enhancement	10.1±4.2	14.0±3.5	2.98	**0.005**
DMQ-r Coping	7.3±3.4	9.1±3.8	1.41	0.170
DMQ-r Conformity	7.5±3.9	7.5±2.2	-0.07	0.995
AUDIT	4.1±2.7	12.6±3.7	7.55	**<0.001**
Barratt Impulsiveness Scale Total	57.0±9.5	61.2±8.7	1.36	0.184

Structural fMRI

Structural brain images were obtained using the MP-RAGE sequence with FOV 256×256 mm^2, 176 sagittal slices, 1 mm thick with 0.5 mm spacing, TR/TE=2530/2.3 ms, TI = 1100, echo spacing time 6.9 ms, flip angle 9°, bandwidth 190 Hz/pixel, total scan time 6 min and 3 sec. Parallel acquisition was conducted in the GRAPPA mode, with reference line phase encoding (PE)=32, and an acceleration factor of 2.

Dot-Probe Task

We assessed selective attention capture using a dot-probe task consisting of 48 trials and implemented in E-Prime 2.0. Trials began with a non-predictive white fixation cross, followed by two grayscale images (11.1°×9.0°) that appeared simultaneously on either side of the fixation cross, for 150ms. Following a 50ms inter-stimulus interval (ISI), the target, a white asterisk (36 pt font), appeared in one of the image locations for 200ms. This timing structure yields a 200 ms stimulus-onset asynchrony (SOA) between the cue and target, well below the ~300 ms SOA at which attention capture effects decline [9]. In each trial, one image depicted alcohol-related content, while the other depicted neutral (kitchen-related) content. Alcohol and neutral images were otherwise similar in basic visual properties. Alcohol images appeared with equal frequency on the left and right in a pseudo-random order. Subjects were instructed to respond to the target's location via keypress as quickly as possible. Faster RT in trials with alcohol-cue congruent targets indicates AB toward alcohol-related cues via selective attention capture. This design is modified from our previous studies assessing AB toward smoking cues in cigarette smokers [10,11].

Modified Attentional Blink Task

To measure extended attention hold, participants completed a modified attentional blink task [12,13] implemented in E-Prime 2.0 based on the emotional blink of attention paradigm [14-18]. The task included

four blocks of 48 trials each. Trials began with a non-predictive white fixation crosshair (18pt font), followed by a rapid serial visual presentation of 17 grayscale photos (11.1°×9.0°) for 100 ms each, with a 0 ms ISI. Stimuli within each stream consisted of upright landscape or house photographs [12,13], except for two images: the critical distractor and the target stimulus. Critical distractor images were either a neutral or an alcohol-related image (ratio: 50:50). Targets occurred 2 or 8 images after the distractors and were house photos rotated 90º left or right. At the end of each trial, the response screen was presented for 2000 ms and participants were instructed to indicate the target orientation by pressing one of two keys in response to the query, "Was the target rotated right or left?" Reduced lag 2 accuracy relative to lag 8 accuracy indicates a greater attentional blink, and a greater blink following an alcohol distractor relative to neutral distractor is interpreted as greater AB to alcohol cues.

Reward Task

We assessed each participant's reward conditioning sensitivity using a value-driven attention capture task identical to one described elsewhere [19], programmed in Matlab (The MathWorks Inc., Natick, MA, 2000) using the Psychtoolbox-3 extensions [20]. Briefly, the task is separated into two phases: a reward-conditioning phase and a test phase. For the conditioning phase, target stimuli were red or green circles, and participants were rewarded for quickly and correctly reporting (via keypress) the orientation of a white bar (horizontal or vertical) appearing within the target circle. One of the two target colors yielded a reward of 10¢ in 80% of trials, and 2¢ in the remaining 20% of trials (high-reward target); these contingencies were reversed for the other color target (low-reward target). Incorrect or omitted responses yielded 0¢. The high-reward color was red for half the participants and green for the other half.

The test phase was structured similarly to the training phase, with key differences. First, the search array included a target shape (diamond or circle) among 5 non-target shapes (circles or diamonds); participants were instructed to disregard color, instead reporting the orientation of the bar within the target shape. Second, feedback after the search array only informed participants whether their response was

correct; no rewards were given. Critically, 25% of trials included a red circle in the search array, 25% included a green circle in the search array, and the remaining 50% lacked any reward-conditioned distractor shapes. Prolonged RTs in trials containing a distractor for which the color was previously associated with reward represent AB to reward-conditioned cues.

Supplemental Table 3. Effects of P/T depletion on VTA whole-brain functional connectivity.

	# Voxels	x	y	z	*t*-statistic
L intraparietal sulcus	118	-36	-74	36	-6.01
	48	-34	-46	36	-5.81
	12	-42	-56	54	-4.72
L orbitofrontal cortex and ventral striatum	70	-18	8	-18	-5.85
L superior frontal sulcus	42	-26	18	52	-5.53
	30	-20	32	30	-5.05
	27	-28	64	12	-5.04
	7	-22	58	-4	-4.71
	2	-28	52	0	-4.59
	2	-16	20	60	-4.34
R superior frontal sulcus	37	32	56	22	-5.88
	15	26	30	44	-5.03
	11	30	64	12	-4.59
	6	20	22	54	-4.48
L caudate tail	31	-22	-18	22	4.95
L postcentral gyrus	30	-8	-42	72	-5.54
L inferior temporal gyrus	26	-44	-18	-28	5.43
L superior temporal gyrus	25	-70	-24	-2	-5.43
cerebellar vermis	24	6	-62	-16	5.01
	5	0	-46	-22	4.74
R middle cingulate gyrus	23	6	-32	32	-5.39
R intraparietal sulcus	22	36	-64	36	-5.00
	8	40	-44	38	-4.77
R insula	16	32	2	14	5.83
L precentral gyrus	13	-12	-28	76	-5.30
L middle temporal gyrus	5	-42	10	-32	5.37
L brainstem	5	-4	-26	-16	4.69
R brainstem	4	8	-26	-10	4.81
	2	6	-26	-16	4.34
L precentral gyrus	4	-52	-4	50	-4.44
R superior temporal gyrus	3	66	-6	-4	-4.75
R ventral striatum	2	8	6	-12	-4.39

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