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Enhanced Striatal Dopamine Release to Expectation of Alcohol: A Potential Risk Factor for Alcohol Use Disorder

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Abstract

BACKGROUND: We used positron emission tomography imaging with [¹¹C]raclopride to examine the effects of consumption of alcohol or placebo beverage by participants with alcohol use disorder (AUD) compared with healthy participants with and without family history of AUD. We sought to assess dopamine release following alcohol exposure in relation to AUD risk.

METHODS: Three groups were enrolled: participants with AUD ($n = 15$) and healthy participants with family history negative ($n = 34$) or positive ($n = 16$) for AUD. Participants consumed a placebo ($n = 65$) or alcohol ($n = 63$) beverage in counterbalanced order before positron emission tomography scanning (128 scans). Binding potential (BP_{ND}) in the two drink conditions and the percent change in BP_{ND} between conditions were evaluated across striatal subregions. Subjective effects of beverage consumption were rated. Effects of group, drink order, and sex were evaluated.

RESULTS: Alcohol resulted in greater dopamine release than did placebo in the ventral striatum ($p < .001$). There were no main effects of group, drink order, or sex on ventral striatum BP_{ND} or percent change in BP_{ND}. However, there was a drink order-by-group interaction ($p = .02$) whereby family history-positive participants who received placebo first had both lower placebo BP_{ND} and less difference between placebo and alcohol BP_{ND} than all other groups, consistent with expectation of alcohol powerfully evoking dopamine release in this group. Subjective responses showed the same order-by-group interaction.

CONCLUSIONS: Hyper-responsivity of the dopaminergic system in family history-positive participants to expectation of alcohol may contribute to the expression of familial risk for AUD.

Keywords

Alcohol use disorder; [¹¹C]raclopride; Dopamine; Familial risk; PET; Ventral striatum

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The capacity of alcohol and alcohol-related cues to activate mesolimbic dopamine (DA) release may reinforce alcohol consumption (1,2) and contribute to the risk for alcohol use disorder (AUD). Alcohol stimulates DA release in humans, especially in the ventral striatum (VST) (3), although reports have been variable (4–7). Alcohol-stimulated DA release has been reported to differ according to risk-related traits (8) and between AUD and social drinkers (9). In individuals with a family history of AUD (family history–positive [FHP]) compared with those without this family history (family history–negative [FHN]), there is greater cue-induced DA release (10), raising the possibility that it reflects a heritable AUD risk mechanism.

However, in individuals with chronic AUD, stimulant-induced DA signaling in the VST appears to be blunted. After detoxification, individuals with chronic AUD have decreased DA $D_{2/3}$ receptor availability in the striatum (11,12) as well as VST blunting of DA release after amphetamine (11) or methylphenidate (12) administration. The same markers have been investigated in individuals with family history of AUD, with findings of higher baseline receptor density than those without family history, but no difference in amphetamine-induced DA release (13). This pattern of changes is consistent with VST DA release contributing to the reinforcing effects of alcohol and learning alcohol use–related behaviors, while alcohol-seeking behaviors are represented in other brain regions and may not be dependent on VST DA release (14,15).

Across the spectrum of risk, there have been reports that individuals at risk for addictions exhibit elevated DA responses to a drink of alcohol (8) yet a diminished response to amphetamine (16,17), and that individuals with AUD release more DA on alcohol administration than social drinkers (9)—also an opposite DA abnormality to that elicited by stimulants.

The current study evaluated alcohol-induced DA release across the spectrum of AUD risk, i.e., FHN, FHP, and AUD. DA release was assessed by comparing the binding potential (BP_{ND}) of the $D_{2/3}$ receptor radioligand [^{11}C]raclopride following oral placebo to that after an alcohol beverage in a counterbalanced-order design. We sought to confirm that oral alcohol induces striatal DA release in AUD and across all participants. We investigated whether FHP and AUD participants would show altered alcohol-induced DA release in the VST relative to FHN participants.

In addition, we previously reported an order effect in a comparison of placebo drink to alcohol (6), but drink order was balanced by neither sex nor family history of participants in that study. We designed the current study with matched cells for each group and drink order, with the goal of identifying the sex and diagnostic group(s) exhibiting the order effect. To interpret the order effect we made the assumption that a placebo response of DA release to expectation of alcohol would be reflected in a lowering of BP_{ND} . Comparing expectation-induced with alcohol-induced DA release across the risk spectrum provides a fuller characterization of this measure as a possible risk factor for AUD.

METHODS AND MATERIALS

Participants

The study was approved by the New York State Psychiatric Institute/Columbia University Institutional Review Board and the Yale Human Investigation Committee, and all participants provided written informed consent. All participants in all groups were completers (underwent 2 positron emission tomography [PET] scans preceded by each of the 2 study beverages) except for 2 participants in the FHN group who underwent one PET scan preceded by the placebo beverage. Additional details on recruitment, demographics, inclusion/exclusion criteria, and safety monitoring of participants are presented in Table 1 and in the Supplement.

AUD participants were between 21 and 55 years of age and met DSM-IV criteria for alcohol abuse or dependence. They were enrolled regardless of their family history of AUD and were not treatment seeking. Participants at risk for withdrawal symptoms were admitted to an inpatient unit for monitoring and treatment as needed.

FHP and FHN participants were recruited as healthy volunteers who were moderate drinkers (so they could tolerate the study beverage). Family history was ascertained through questionnaires presented in a neutral way to all candidates on intake.

FHP participants were between 21 and 30 years of age and had a family history of AUD in a biological parent and at least one additional first- or second-degree relative. FHP participants were by inclusion criteria younger than the AUD group, as they were an at-risk group and thus could not exceed the age of risk, in contrast to the AUD group, whose greater age helped to establish their diagnosis (see Table 1 for age comparisons). In case of maternal AUD, we screened out fetal alcohol syndrome by using the Fetal Alcohol Syndrome Pre-Screen (18).

FHN participants were age and sex matched in two cohorts, one to the FHP participants and the other to the AUD participants. The FHN participants had no family history of substance dependence or abuse (including alcohol or any other substance) in any first-degree relatives.

FHN and FHP participants had a history of consuming at least 10 standard drinks per week (with no upper limit but no history of AUD) and a history of having consumed three to four drinks within a 3- to 4-hour period at least once within the past month, to ensure that they would tolerate the alcohol beverage administration during the protocol.

Smoking status for all participants was a binary evaluation of current cigarette smoking.

Procedures

Each participant underwent two scans at least 2 weeks apart, with each scan preceded by one of the two study beverages in a counterbalanced-order design (except for the 2 FHN non-completers, as noted). Participants were informed that they would receive both alcohol and placebo in blinded counterbalanced order. Participants were asked what they thought they received and accurately identified the drink content across all groups, effectively unblinding

participants to drink composition for the second drink. Ten minutes before initiation of the [¹¹C]raclopride dose administration, research staff provided the beverage, which was consumed over the intervening 10-minute period. The placebo drink consisted of 500 mL of tonic water and cranberry juice in a 3:1 ratio, with the top of the container doused in alcohol. The alcohol drink was designed to deliver 0.75 g alcohol per kilogram of body water (19–21), the equivalent of three standard drinks, using 100-proof vodka, with the remainder of the 500-mL drink consisting of tonic water and cranberry juice in a 3:1 ratio. Participants were asked to refrain from alcohol consumption for 48 hours before each PET scan, smoking tobacco for 2 hours before the scan, and consuming food for 6 hours before the scan. Participants underwent screening for substances of abuse including alcohol (AlcoTester breath alcohol detector; Testing Solutions LLC, Macomb Township, MI) on the first day of screening and on scan days.

PET Data Acquisition.—[¹¹C]Raclopride was administered as a bolus plus constant infusion over an 80-minute period as previously described (6,22,23), with emission scanning beginning at 40 minutes and proceeding in eight successive 5-minute frames. Data were acquired using identical ECAT EXACT HR+ scanners (CTI-Siemens, Knoxville, TN) at Yale and Columbia for the FHP and matched FHN participants or a Biograph mCT scanner (Siemens Healthcare, Malvern, PA) at Columbia for the AUD and their FHN control subjects. Blood samples for alcohol level assays were drawn at 25, 40, 55, and 70 minutes after beginning the drink consumption.

Subjective Effects of Alcohol.—Participants completed the Subjective Effects of Alcohol Scale (SEAS) (24) after initiation of the [¹¹C]raclopride infusion, immediately on completion of beverage consumption. The SEAS is a 15-item self-rated questionnaire with ratings ranging from 0 (not at all) to 10 (extremely) on subjective feelings of differing valence and arousal characteristics. Instructions were, “The following adjectives describe feelings that are sometimes produced by drinking alcohol. On a scale of 1–10, please rate the extent to which the drink has produced these feelings in you at the present time,” followed by a listing of the adjectives. Factor analysis has shown that the 15 scale items group into four factors corresponding to the four quadrants defined by high and low arousal and by positive and negative valence.

Magnetic Resonance Imaging.—Each participant underwent a structural magnetic resonance imaging (MRI) scan (GE MR 750 3T scanner, GE Healthcare, Port Washington, NY), in some cases on a separate day, for coregistration and region-of-interest analysis.

Discharge Criteria.—Participants were discharged from the PET scan procedure when blood pressure, heart rate, electrocardiography, physical and mental status exam, and field sobriety test were within normal limits and when breath alcohol concentration of <0.04 mg/dL was attained. In addition, participants were free of symptoms of alcohol withdrawal. AUD participants were informed that referrals for treatment would be provided on request at any point if they chose to leave the study for treatment, or on study completion.

PET Data Analysis

Image analysis was performed as previously described (22). In brief, PET data were coregistered to the structural MRI images using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) (25). Regions of interest were drawn on each individual's MRI and applied to the coregistered PET images. Regions of interest included the striatal subregions, precommissural dorsal caudate and putamen, postcommissural caudate and putamen, and VST (23), with the cerebellum as a reference region. The BP_{ND} (unitless) was given by (region-of-interest activity/cerebellum activity - 1) during steady state, which was attained during the latter 40 minutes of the constant infusion. The primary outcome measure was the percent change in BP_{ND} (ΔBP_{ND}) between scan (drink) conditions, calculated as

$$\Delta BP_{ND} = \left[\left(\frac{BP_{ND \text{ alcohol}}}{BP_{ND \text{ placebo}}} \right) - 1 \right] \times 100\% .$$

This outcome measure has become standard in the field of PET measurement of induced neurotransmitter release (9,12,26) because of its quantitative relationship to magnitude of release or receptor occupancy (27) by neurotransmitter.

Statistical Analysis

The overall effect of alcohol for the full sample and for each diagnostic group was evaluated by *t* test across all participants and within each group to test whether BP_{ND} differed from zero. Effects of drink order, sex, group, and smoking status (determined as currently smoking cigarettes) on BP_{ND} were assessed with a univariate general linear mixed-effects model with age included as a covariate. The two FHN cohorts were included as distinct groups, but the model showed no impact of pooling them into a single FHN group, which was then adopted for the summary and presentation. A two-tailed probability value of $p < .05$ was chosen as statistically significant.

We analyzed the SEAS data by focusing on the eight positive-valence items (24), noting the number of these that exhibited the same group and order response pattern as the changes in PET BP_{ND} . To protect against multiple-comparisons risk we used a permutation test to determine whether this number was greater than expected by chance. In this permutation test, data were randomly reshuffled by condition and group on each of 100,000 iterations to assess statistical significance at $p < .05$.

RESULTS

Drinking History

The Timeline Followback Interview (28,29) was used to assess recent drinking history (past 30 days) for all participants. On average AUD participants consumed 8.1 ± 8.6 drinks per drinking occasion, FHN participants consumed 3.5 ± 1.5 drinks per drinking occasion, and FHP participants consumed 3.9 ± 2.0 drinks per drinking occasion. Age when participants began regular drinking was 21 ± 3 years for FHP, 21 ± 4 years for FHN, and 22 ± 6 years for AUD, who had 15 ± 11 years of drinking history. AUD participants were ascertained under

DSM-IV criteria, but all met DSM-5 AUD criteria: 3 met two criteria, 8 met three criteria, and 4 met four criteria. In the AUD group there were several participants who began regular drinking relatively late (2 in their mid-20s and 2 over 30 years of age), and the median in this group was 20 years.

Alcohol-Induced DA Release (BP_{ND})

BP_{ND} , the percent reduction in BP_{ND} from the placebo scan to the alcohol scan, was greatest in VST (Table 2). VST BP_{ND} following alcohol was significantly lower than following the placebo drink across all participants ($BP_{ND} < 0$, $p < .001$, two-tailed t test). The same comparison was significant within each group ($p < .01$, two-tailed t test). PET scanning characteristics (injected dose, mass) did not contribute to the difference between alcohol and placebo scans (Supplemental Table S2). There were no main effects of group, drink order, or sex on VST BP_{ND} , nor was age a significant covariate. Years of drinking history did not correlate with VST BP_{ND} . Cigarette smoking showed a trend-level impact of enhancing BP_{ND} . There was a significant group-by-drink order interaction ($p = .02$) in which post hoc analysis showed that BP_{ND} was significantly different from zero in both FHN groups, FHP participants who consumed alcohol first (FHP-AP), and AUD participants who consumed placebo first (AUD-PA), but not FHP participants who consumed placebo first (FHP-PA) or AUD participants who consumed alcohol first (AUD-AP). Among the FHP participants, those who consumed alcohol first exhibited a much greater BP_{ND} ($11.7 \pm 4.0\%$) than those who consumed placebo first ($2.7 \pm 5.4\%$, $p = 0.002$) (Figure 1; Supplemental Table S3).

Binding Potential

A secondary analysis for both VST $BP_{ND \text{ placebo}}$ and VST $BP_{ND \text{ alcohol}}$, pooled across drink order, found that there was no difference between groups, and there was no main effect of drink order or sex.

Subjective Effects of Alcohol

Ratings on the positive valence items of the SEAS (24) similarly showed a unique pattern for the FHP participants in contrast to the other two participant groups as observed for BP_{ND} . To test this, a set of three criteria was defined that described this pattern: 1) in the FHP group, the difference between the effect of placebo when it was administered on the first day versus the second day was greater than the difference between the effect of alcohol when it was administered on the second day versus the first day (i.e., there was an interaction between drink-content group and order of administration); 2) in the FHP group, the smallest effect across group and order was that for placebo when it was administered on the second day; and 3) the interaction effect described by criterion 1 was greater for FHP than for the average of the other two groups (FHN and AUD). Five of eight items (mellow, relaxed, secure, lively, talkative) met all three criteria describing the BP_{ND} pattern, a proportion that was above the chance level ($p = .012$, permutation test). Thus, mirroring DA release, positive subjective experiences were more accentuated for alcohol in both drink orders and the placebo-first condition than for the placebo-second condition, and this pattern was more pronounced in the FHP group than in the other two.

Blood Alcohol Levels

Participants became notably but not heavily intoxicated, with only 1 of 65 enrollees unable to proceed to the PET scan following the drink because of nausea and emesis. Mean blood levels (assessed at 25, 40, 55, and 70 minutes) reached their maximum at 55 minutes following the drink (1.04 ± 0.31 mg/mL) (Supplemental Figure S1), plateaued at that level (1.04 ± 0.25 mg/mL) at 70 minutes, and did not differ between groups at any time point. Blood alcohol levels and VST BP_{ND} were not correlated at any of the time points.

DISCUSSION

The main finding of this relatively large ($n = 128$ PET scans) study was a highly significant DA-releasing effect of alcohol compared with placebo across all participants and all striatal subregions, with greatest effect observed in VST (Table 2), confirming the observations that alcohol consumption induces DA release. However, there were no differences in BP_{ND} across the FHP, FHN, or AUD groups, indicating similar magnitude of alcohol-induced DA release across all three groups. There were also no significant effects of drink order, sex, or smoking status on BP_{ND} or BP_{ND} . Additionally, we found significantly lower BP_{ND} compared with the other groups in the placebo condition in FHP when placebo was consumed first, consistent with a DA-releasing effect of placebo when placebo was consumed first.

Alcohol-Induced DA Release (BP_{ND})

The highly significant DA-releasing effect of alcohol compared with placebo across all participants and all striatal subregions, greatest in the VST, confirms prior observations that alcohol consumption, combined with its expectation, induces net DA release (3–6). The absence of a main effect of group on BP_{ND} indicated normal alcohol-induced DA release in those participants with AUD. This is in contrast to prior reports of blunted DA release in individuals with AUD using distinct DA releasing agents [amphetamine (11,30) and methylphenidate (12)] as well as elevated release under intravenous alcohol administration (9). This contrast may be due to lower severity of AUD in our cohort, as discussed below in connection with the BP_{ND} findings. It is also possible that this difference is related to the administration of alcohol rather than amphetamine or methylphenidate, which probe different aspects of dopaminergic transmission. Amphetamine and methylphenidate increase synaptic DA by blocking or reversing transporters and at high doses, releasing DA from vesicles (31). Mechanisms that contribute to the ability of alcohol to stimulate DA release include direct excitation of DA ventral tegmental area neurons and reduction of the afterhyperpolarization that follows spontaneous action potentials by reducing a quinidine-sensitive K^+ current (32). Ventral tegmental area DA neurons from adult rats have been found to exhibit increased inhibitory tone after adolescent alcohol exposure leading to potentiation of stimulus-evoked phasic DA release, driving risky choice behavior in adulthood (33). Particular subsets of medial ventral tegmental area DA neurons have shown enhanced alcohol sensitivity, specifically attributed to adolescent drinking, over a range of alcohol concentrations associated with social drinking in humans (34,35). Furthermore, alcohol may promote DA release by a local calcium-dependent effect at the DA terminals in the striatum and accumbens (36,37). Consistent with our own findings, passively

administered intravenous alcohol can stimulate DA release, while alcohol-related cues evoke additional DA release (38,39). Also consistent with the idea of distinct DA-releasing mechanisms of alcohol and stimulant challenges is the lower effect of alcohol-induced release in control subjects (FHP and FHN) than under stimulant-induced release, comparable to that seen in AUD under both types of challenge administration. It is also possible that use of an ethanol-scented placebo drink might have decreased the probability of observing a main effect of alcohol ingestion but increased the probability of observing an effect of potent cues.

Binding Potential

Our findings of similar BP_{ND} across groups contrast with prior literature reporting elevations in DA $D_{2/3}$ receptors in unaffected members of AUD families (13,40), considered in those reports potentially to be a protective factor [but see Munro *et al.* (41)], or decreases in AUD participants (11,12). These prior measurements were made under baseline conditions with no pharmacological challenge (40) or intravenous placebo (saline) infusion (13), while our BP_{ND} measurements were made under placebo or alcohol beverage conditions. Furthermore, there were no decreases in BP_{ND} in AUD compared with the FHP and FHN groups, unlike previous findings, possibly owing to lower severity of AUD in our cohort. Our AUD sample consumed 8 ± 9 drinks per day with a history of 15 ± 11 years of drinking, while in Martinez *et al.* (11) the AUD sample drank 20 ± 8 drinks per day with a history of 18 ± 7 years of drinking, and in Volkow *et al.* (12) these figures were 16 ± 6 drinks per day with 23 ± 8 years of drinking.

Group-by-Drink Order Interaction

The counterbalanced-order design showed that, when the two drink orders were pooled, there were no differences among the groups in BP_{ND} or BP_{ND} attributable to the combined effects of alcohol consumption and the anticipation of alcohol consumption. However, tracking the effects by drink order within each group addressed differences in the effects of alcohol alone from those of expectation of alcohol.

The significant group-by-drink order interaction indicates contrasting DA release responses to placebo and alcohol beverages by the different diagnostic groups, depending on which beverage was consumed first. To interpret this finding, post hoc analysis showed significantly smaller BP_{ND} in the FHP-PA group ($2.7 \pm 5.4\%$) compared with in the FHP-AP group ($11.7 \pm 4.0\%$; $p = .002$) (Figure 1). Contributing to the small 2.7% BP_{ND} in the FHP-PA group was the low BP_{ND} for FHP-PA on the placebo day (Figure 2A; see also Figure 2B for voxelwise data), similar to BP_{ND} for both FHP subgroups on their alcohol days. One potential explanation for the low BP_{ND} for FHP-PA participants on the placebo day is provided by the principle that in every [^{11}C]raclopride measurement, BP_{ND} is proportional to receptor density but is reduced by binding to endogenous DA (42). In other words, lower BP_{ND} in Figure 2A is consistent with greater DA availability within the perisynaptic space. Thus, BP_{ND} values within each condition shown in Figure 2A can be thought of relative to a hypothetical baseline measurement (not acquired in this study) under plausible assumptions about the baseline (see Supplement for a full derivation). In short, the markedly lower BP_{ND} values in the FHP-PA group than in the FHP-AP group might have

resulted from as great a release of DA under placebo in the FHP-PA group as under the alcohol in either the PA or the AP order. We note as well the contribution to the high FHP-AP BP_{ND} from the minimal DA release on the placebo-second day, when participants (who already received alcohol) know not to expect alcohol; however, this feature is shared with the FHN-AP group and therefore does not fully account for the group contrast. For the FHN and AUD groups, BP_{ND} was moderate and comparable in both drink orders (Figure 1; Supplemental Table S3), ranging from 4% to 7%, corresponding to more modest BP_{ND} differences by order in Figure 2A. The similarity of BP_{ND} for the FHN and AUD groups was not due to predominance of negative family history among the AUD group: 7 AUD participants had negative family history, 6 had positive family history, and 2 declined to specify their family history; analysis showed that the FHP and FHN AUD subgroups each showed the same behavior as the total group (greater BP_{ND} in the PA order than in the AP order). This contrast with the FHP group is consistent with a recent report of greater cue-induced DA release compared with a neutral flavor stimulus in individuals with family history of AUD (10), although that study made no comparison to alcohol itself.

Subjective Effects

Alcohol-related cues such as place-conditioned anticipation of alcohol or initial olfactory sensations have generally been found in rodents to induce DA release in the nucleus accumbens (38,43,44). In humans, alcohol-related conditioned cues induce craving and lead to consumption (45,46), although their effect on DA release is less well established.

In our study the apparently heightened release of DA under the placebo-first drink, interpreted as a response to expectation of alcohol, occurs particularly in the group at risk for AUD by family history. This pattern of enhanced response was observed for both BP_{ND} and the positive subjective effects of alcohol, suggesting enhanced subjective value associated with alcohol cues in FHP individuals. Many functional MRI studies have consistently shown that the human VST encodes a subjective value signal (47) that is widely thought to depend on DA.

Limitations

One limitation of the study is the use of two scanners; however, we compensated for this by acquiring the FHP and matched FHN subjects on the same scanner (ECAT EXACT HR+). Similarly, the AUD participants and matched FHN control subjects were acquired on the same scanner (Biograph mCT). We did not detect a site or scanner effect for any of the outcome measures acquired on the Siemens HR+ scanners or the Biograph mCT. The study was also limited by the absence of baseline BP_{ND} measurements (without placebo or alcohol), which would have necessitated at least a third scan for each participant, and a fourth if a baseline measurement was acquired in association with each drink administration. This makes the interpretations based on BP_{ND} comparisons in Figure 2A tentative and dependent on our assumptions regarding baseline BP_{ND} values (see Supplement).

In summary, our study shows similar magnitude of alcohol-induced DA release in FHP, FHN, and AUD, with an exaggerated response to expectation of alcohol in FHP participants.

Further investigation is needed to determine whether this exaggerated DA release under expectation of alcohol is an independent risk factor for AUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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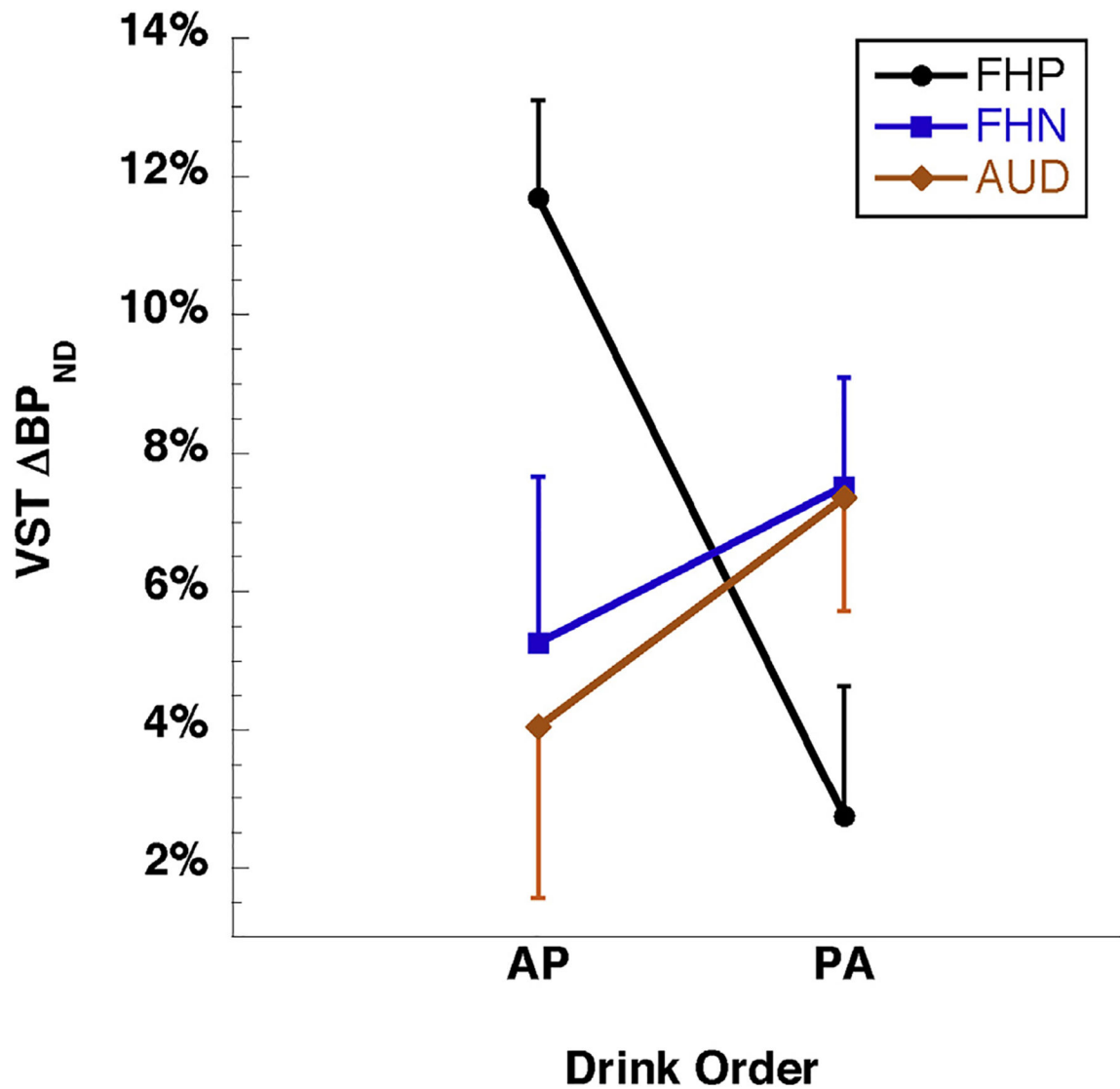


Figure 1.

Alcohol-induced change in ventral striatal $D_{2/3}$ receptor binding (ventral striatum [VST] percent change in binding potential [BP_{ND}], the percent decrease from placebo day to alcohol day) by group and drink order. The family history–positive (FHP) group showed an opposite response to the drink conditions compared with the family history–negative (FHN) and alcohol use disorder (AUD) groups ($p = .02$, group-by-order interaction). Plot symbols indicate group mean and error bars indicate SEM. Participant group sizes were FHP: $n = 8$ alcohol beverage at first scan (AP) and $n = 8$ alcohol beverage at second scan (PA); FHN: $n = 15$ AP and $n = 17$ PA; AUD: $n = 8$ AP and $n = 7$ PA (data shown in Supplemental Table S3).

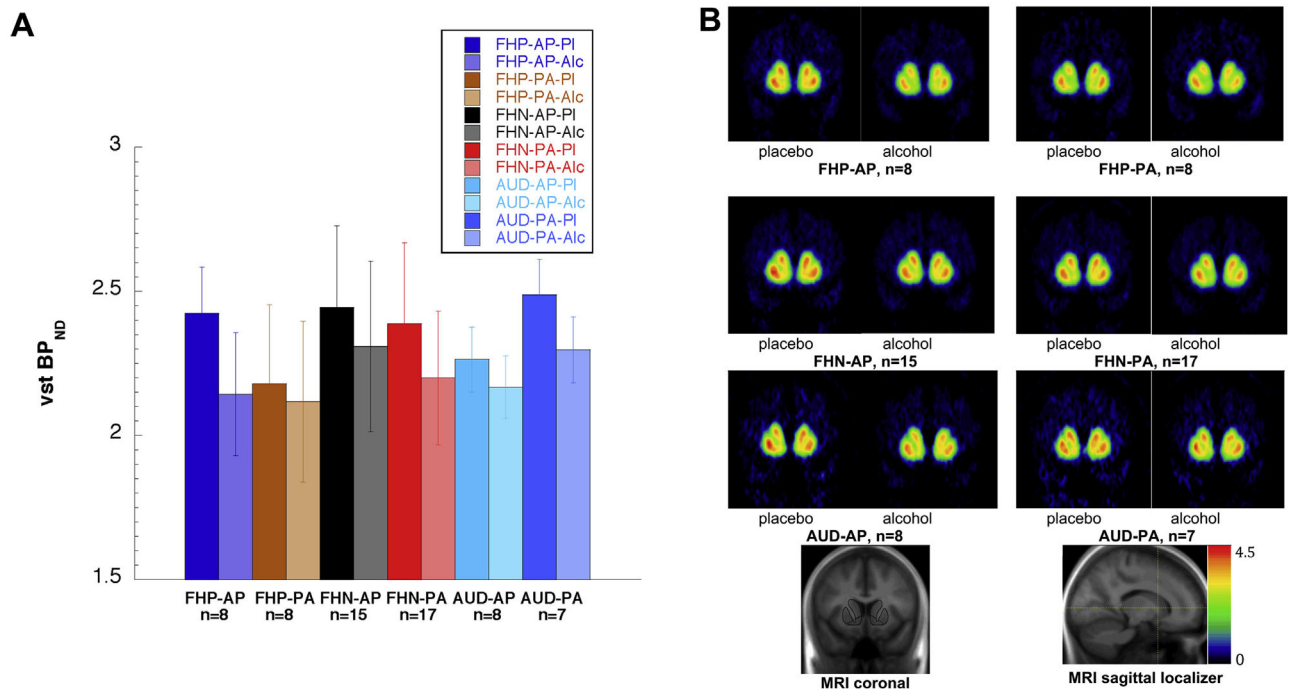


Figure 2.

(A) [^{11}C]Raclopride binding potential (BP_{ND}) for each group and drink order. Each group (family history–positive [FHP], family history–negative [FHN], alcohol use disorder [AUD]) is represented by four bars: the placebo day (PI) and the alcohol day (Alc) for each order (alcohol beverage at first scan [AP]; alcohol beverage at second scan [PA]). In all three groups, alcohol (second bar in each pair) resulted in greater dopamine release (reduction in BP_{ND}) than placebo did. However, the FHP participants showed much smaller alcohol-induced reduction in BP_{ND} when placebo was first (FHP-PA) than when placebo was second (FHP-AP). In contrast, the FHN and AUD participants showed moderate BP_{ND} reductions between placebo and alcohol day that were similar regardless of drink order. The six within-group differences between the placebo and alcohol day for each order (as percent of placebo) are the six data points in Figure 1. Bar heights indicate group mean BP_{ND} and error bars indicate SD (data shown in Table 3). (B) [^{11}C]Raclopride BP_{ND} for each group and drink order, voxelwise maps. These images display the BP_{ND} values shown as regional means in panel (A). Note that the greatest intensity changes from placebo to alcohol scan occur for the FHP-AP group, and the smallest changes occur for the FHP-PA group. MRI, magnetic resonance imaging; VST, ventral striatum.

Table 1.

Participant Demographics

Variable	FHP	FHN	AUD	<i>p</i>
<i>n</i>	16	34 (2 noncompleters) ^a	15	
Age, Years, Mean ± SD	25 ± 3	29 ± 7	36 ± 10	<.05 ^b
Sex, Female/Male, <i>n</i>	8/8	17/17	8/7	.97 ^c
Ethnicity, AA/As/CH/Mixed, <i>n</i>	1/0/11/4/0	13/1/11/8/1	9/0/3/3/0	.09 ^c
Smokers (Currently Smoke Cigarettes), <i>n</i>	1	4	6	.02 ^c

AA, African American; As, Asian; AUD, alcohol use disorder; C, Caucasian; FHN, family history–negative; FHP, family history–positive; H, Hispanic; PET, positron emission tomography.

^aAll participants in all groups were completers (underwent 2 PET scans preceded by each of the 2 study beverages) except for 2 participants in the FHN group who underwent one PET scan preceded by the placebo beverage.

^bTwo-group *t* test, all 2-way comparisons: FHP vs. FHN; FHN vs. AUD; FHP vs. AUD.

^c χ^2 test.

Table 2.

[¹¹C]Raclopride BP_{ND} for Striatal Subregions in Placebo and Alcohol Conditions and Percent Change in BP_{ND} (BP_{ND}) for FHP, FHN, and AUD Groups

ROI	FHP (n = 16)			FHN (n = 32)			AUD (n = 15)		
	BP _{ND} Placebo	BP _{ND} Alcohol	BP _{ND} (%)	BP _{ND} Placebo	BP _{ND} Alcohol	BP _{ND} (%)	BP _{ND} Placebo	BP _{ND} Alcohol	BP _{ND} (%)
VST	2.30 ± 0.25	2.13 ± 0.24	-7.2 ± 6	2.43 ± 0.28	2.25 ± 0.26	-6.5 ± 8	2.37 ± 0.27	2.23 ± 0.21	-5.6 ± 6
PreDCA	2.44 ± 0.23	2.33 ± 0.26	-4.7 ± 7	2.77 ± 0.37	2.62 ± 0.36	-3.7 ± 8	2.76 ± 0.30	2.62 ± 0.20	-4.6 ± 7
PreDPU	3.00 ± 0.31	2.88 ± 0.34	-4.0 ± 7	3.30 ± 0.37	3.14 ± 0.35	-3.5 ± 7	3.27 ± 0.27	3.16 ± 0.21	-3.2 ± 6
PostCA	1.84 ± 0.40	1.78 ± 0.36	-2.4 ± 10	1.89 ± 0.34	1.78 ± 0.31	-4.1 ± 14	1.92 ± 0.29	1.75 ± 0.28	-5.0 ± 8 ^b
PostPU	3.21 ± 0.33	3.10 ± 0.27	-3.0 ± 7	3.34 ± 0.32	3.21 ± 0.33	-3.0 ± 6	3.33 ± 0.42	3.24 ± 0.30	-2.1 ± 8

Values represent mean ± SD.

AUD, alcohol use disorder; BP_{ND}, binding potential; FHN, family history–negative; FHP, family history–positive; PostCA, postcommissural caudate; PostPU, postcommissural putamen; PreDCA, precommissural dorsal caudate; PreDPU, precommissural dorsal putamen; ROI, region of interest; VST, ventral striatum.

^a Paired *t* test; note that *p* < .001 for each striatal subregion when all subjects' data are pooled across groups.

^b After removal of one outlier in the AUD group with PostCA BP_{ND} more than 3 SDs above the mean.

Table 3.

Ventral Striatal BP_{ND} by Group, Drink Order, and Beverage Day

	Group			
	FHP	FHN	AUD	
	Drink Order			
	AP (n = 8)	PA (n = 8)	AP (n = 15)	PA (n = 8)
VST BP _{ND} Placebo Day	2.42 ± 0.16	2.18 ± 0.27	2.44 ± 0.28	2.39 ± 0.28
VST BP _{ND} Alcohol Day	2.14 ± 0.21	2.12 ± 0.28	2.31 ± 0.30	2.20 ± 0.23
			2.17 ± 0.23	2.30 ± 0.17

Values represent mean ± SD.

AP, alcohol beverage at first positron emission tomography scan; AUD, alcohol use disorder; BP_{ND}, binding potential; FHN, family history–negative; FHP, family history–positive; PA, alcohol beverage at second positron emission tomography scan; VST, ventral striatum.