Sex Differences in Striatal Dopamine Release in Young Adults After Oral Alcohol Challenge: A Positron Emission Tomography Imaging Study With [11C]Raclopride

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Background: We used a positron emission tomography paradigm with the D2/3 radiotracer [11C]raclopride and an alcohol challenge to examine the magnitude of alcohol-induced dopamine release and compare it between young men and women.

Methods: Twenty-one nonalcohol-dependent young social drinkers completed two positron emission tomography scans on separate days following ingestion of a juice mix containing either ethanol (.75 mg/kg body water) or trace ethanol only. The extent of dopamine released after alcohol was estimated by the percentage difference in [11C]raclopride binding potential (ΔBPND) between days.

Results: Alcohol administration significantly displaced [11C]raclopride in all striatal subregions, indicating dopamine release, with the largest effect observed in the ventral striatum. Linear mixed model analysis across all striatal subregions of regional ΔBPND with region of interest as repeated measure showed a highly significant effect of sex (p < .001). Ventr striatal dopamine release in men, but not in women, showed a significant positive correlation to alcohol-induced measures of subjective activation. Furthermore, we found a significant negative correlation between the frequency of maximum alcohol consumption per 24 hours and ventristriatal ΔBPND (r = .739, p = .009) in men.

Conclusions: This study provides definitive evidence that oral alcohol induces dopamine release in nonalcoholic human subjects and shows sex differences in the magnitude of this effect. The ability of alcohol to stimulate dopamine release may contribute to its rewarding effects and, thereby, to its abuse liability in humans. Our report further suggests several biological mechanisms that may mediate the difference in vulnerability for alcoholism between men and women.

Key Words: Alcoholism, dopamine, PET imaging, sex differences

Alcohol is one of the most commonly abused substances, and alcoholism is one of the leading causes of disability in the United States (1,2). In most developed countries, the lifetime risk for alcohol use disorders is 20% in men (twofold higher than in women) (3), with a risk of 15% for alcohol abuse and 10% for dependence (4,5). The heaviest drinking in the general population occurs between the ages of 18 and 22 years (6), and consequently, the highest risk to develop alcohol use disorders is at the beginning of the third decade of life (7).

Little is known about the mechanisms through which alcohol produces its rewarding effects in humans, in part because of the diversity of ethanol targets in the brain (8). Principally based on preclinical studies, primarily the ability of alcohol to stimulate dopaminergic (DA) transmission in the ventral striatum has been hypothesized to contribute to its abuse liability in humans. Alcohol administration induces DA release in the dorsal caudate and nucleus accumbens in rats (9). The rewarding and euphoriant properties of alcohol-induced mesolimbic DA stimulation (10–12) are believed to play a major role in reinforcing its consumption (11,13). However, in rats habituated to alcohol exposure, self-administration of an ethanol solution raised DA levels in the accumbens only during the early phase after onset of drinking, and there was no DA increase after cue presentation, suggesting that while DA may play a significant role, it is not the only or central substrate producing the reinforcement from alcohol (14).

Alcohol-prefering rats have been found to have lower extracellular DA levels at baseline than abstainer rats and decreased D2 receptor density (15), as well as lower DA concentrations in the mesolimbic terminals (16), and intraperitoneal ethanol induced a twofold greater increase of DA release in the nucleus accumbens measured by microdialysis (17). Greater magnitude of alcohol-induced DA release was also found to be a predictor of degree of alcohol preference in rats in some (18) but not other studies (19). These findings may suggest that both a low dopaminergic tone and a strong mesolimbic DA response to ethanol are associated with ethanol-seeking behavior.

Human studies have evaluated dopamine transmission in the striatum of both chronic alcohol users and healthy control subjects. Dopamine release after amphetamine administration is reduced in the ventral striatum (VST) of detoxified subjects with alcohol dependence (20,21).

Despite this evidence, the dopaminergic response to alcohol itself has not been extensively studied in humans. Four studies quantifying in vivo alcohol-induced displacement of [11C]raclopride from DA D2/3 receptors have reported mixed findings: two studies suggested that alcohol-induced DA release within the striatum in humans can be measured with [11C]raclopride displacement (22,23), one reported no overall effect on binding but a relationship between subjective effects of alcohol and the magnitude of [11C]raclopride displacement (24), and one found no effect of alcohol on difference in [11C]raclopride binding potential (ΔBPND) (25).
Here, we present a study designed to evaluate the capacity of oral alcohol to stimulate DA release in the human striatum with a larger sample of subjects providing greater statistical power and robustness to the sources of variance reported in prior studies. We hypothesized that sex is an important moderator of alcohol effects on DA release with greater effect to be expected in men.

Methods and Materials

Study Population
The study was approved by the Institutional Review Board of the New York State Psychiatric Institute and informed consent was obtained from all subjects. Male and female social drinkers not meeting criteria for alcohol abuse or dependence, aged 21 to 27 years, were included. Subjects were required to have sufficient experience with alcohol to minimize adverse effects associated with the administration of alcohol, based on consumption of at least 10 to 15 standard drinks (standard drinking unit in United States = 14 g alcohol) per week. This was ascertained by self-reported drinking history and Alcohol Time Line Follow Back Interview (26), used to estimate drinking patterns and the amount consumed over the past 30 days and past 12 months. In addition, all subjects completed questionnaires assessing their prior experiences with alcohol (26). Smoking was not an exclusion criterion.

Study Design
Two \(^{11}\text{C}\)raclopride positron emission tomography (PET) scans on two separate days following consumption of either a placebo or an alcohol drink were obtained in counterbalanced order (11 out of 21 received alcohol on the first day, randomly chosen). The placebo consisted of cranberry juice and soda alone, while the alcohol drink in addition contained the equivalent of three standard drinks of 100 proof vodka designed to deliver an average of .75 g alcohol per kilogram body weight. The individual amount of alcohol was calculated based on the subject’s amount of body water according to the equation: total body water (g/liter) = \(-2.097 + .1069 (height\, in\, cm) + .2466 (weight\, in\, kg)\) (27). For men, the volume of the drink amounted to 500 mL, while women received 350 mL. This difference intended to keep the alcohol concentration per drink similar between groups. Participants were blinded to the drink content. We disguised olfactory cues that might have indicated the nature of the drink before consumption by covering the rim of the drink containers with a paper napkin doused in vodka. The alcohol challenge was administered in a nonfasting condition. Subjects were asked to refrain from alcohol the night before, from smoking tobacco for the 2 hours before the PET scan, and from using any recreational drugs after the time of screening. Subjects underwent screening for substances of abuse including alcohol (AlcoMate Pro digital alcohol detector, KHN Solutions, San Francisco, California) on the first day of screening and on scan days. Oral consumption of alcohol or alcohol-free mixture had to be completed within 5 to 10 minutes.

PET Data Acquisition
Five minutes after the drink, \(^{11}\text{C}\)raclopride was delivered as a bolus plus constant infusion (28,29). Emission data were collected using an ECAT EXACT HR+/H11001 scanner (Siemens Medical Systems, Knoxville, Tennessee) starting 40 minutes into the constant infusion. Blood samples for plasma alcohol levels were drawn at 25, 40, 55, and 70 minutes after the drink (Figure S1 in Supplement 1). Subjective effects of alcohol were assessed with the Biphasic Alcohol Effects Scale for rating subjective activation (elation, feeling up, energy, excitement, stimulation, vigor, talkativeness) and sedation (difficulty concentrating, feeling down, heavy head, inactive, sedated, slowed thoughts, sluggishness) on scales from 1 to 10 (30), given at baseline and every 30 minutes after drink administration for 90 minutes. Subjects underwent structural magnetic resonance imaging (MRI) (GE Signa 1.5 or 3 Tesla scanner, General Electric Healthcare, Waukesha, Wisconsin) on a separate day for co-registration and regions of interest (ROI) analysis.

PET Data Analysis
Image analysis was performed as described previously (29). Positron emission tomography data were co-registered to the structural MRI images using maximum of mutual information as implemented in the SPM2 software environment (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) (31). Regions of interest were drawn on each individual’s MRI and applied to the co-registered PET images. Regions of interest included precommisural caudate and putamen (preDCA, preDPU), postcommissural caudate and putamen (postCA, postPU), and ventral striatum (28). Cerebellum was used as a reference region to measure free and nonspecifically bound \(^{11}\text{C}\)raclopride activity, as the concentration of D2 receptors in the cerebellum is negligible (32). Equilibrium analysis was used to derive the specific to nondisplaceable equilibrium partition coefficient \(BP_{ND}(\text{unitless})\) as \((\text{ROI activity/cerebellum activity} - 1)\) during steady state (20).

The primary outcome measure for the study was the percentage change in \(BP_{ND}\), between conditions, calculated as:

\[
\Delta BP_{ND} = (BP_{ND,alcohol} / BP_{ND,placebo}) - 1 \times 100\%.
\]

This expresses the relative reduction in DA D2/3 receptor availability for \(^{11}\text{C}\)raclopride binding after alcohol-induced DA release.

Statistical Analysis
Comparisons between drink conditions were performed with paired \(t\) tests; comparisons between groups were performed with two-group \(t\) tests at the ROI level. A linear mixed model across all stratal subregions with regional \(\Delta BP_{ND}\) as the dependent variable and region of interest as repeated measure was performed to test for a global effect of sex on \(\Delta BP_{ND}\). Correlation analysis between PET measures and other variables (\(\Delta BP_{ND}\) for all ROIs vs. measures of drinking history and subjective response to alcohol) were performed. Data were inspected for normality. Pearson product-moment coefficients were computed for normally distributed data and the Spearman rank correlation coefficient was applied to nonnormally distributed data. A two-tailed probability value of \(p < .05\) was chosen as statistically significant. The false discovery rate method (33) was applied to the correlations between drinking history and VST DA release to correct for multiple comparisons.

Results

Subjects
Twenty-one subjects, ages 24 \(\pm\) 1.7 (mean \(\pm\) SD) years, including 11 males and 10 females completed the study (Table 1).

Drinking History
Table 2 shows drinking history over the last 12 months before enrollment. Regular drinking (i.e., number of drinks per average drinking session), as well as binge drinking (defined as more than five drinks in 2 hours for men and more than four drinks for women [34]) were similar in both groups. The measure M, maximum number of drinks per 24 hours (35), a quantitative trait expected to be related to alcohol tolerance (36), showed slightly different patterns. Men had a higher magnitude of M during the past 12
Correlations of Drinking Behavior with $\Delta$BP$_{ND}$

Of nine measures of drinking behavior tested for correlation with VST DA release (Table 2), only frequency of M over the past 12 months showed a negative correlation in men, i.e., the less frequently men drank their maximal amount, the larger the $\Delta$BP$_{ND}$. As the data for this parameter were not normally distributed, correlations were analyzed with the Spearman’s rank order coefficient: $\rho = .72, p = .012$; this did not survive false discovery rate multiple comparisons correction at the .05 alpha level but did survive at trend level ($p = .06$) but not for women ($p = .01$). Because frequency of M was binned into several distinct levels, we also applied ordinal logistic regression with frequency of M as an ordinal dependent variable and $\Delta$BP$_{ND}$ in VST as continuous independent variable. This model reached significance for men and the entire cohort but not for women alone (Figure 1).

Blood Alcohol Levels

Subjects were distinctively, but not heavily, intoxicated with blood alcohol levels slightly above the legal limit. Blood alcohol level peaked at 55 minutes after drink ($1.15 \pm 0.3$ mg/mL in men and $1.02 \pm 0.4$ mg/mL in women, $p = .37$, Figure S1 in Supplement 1) and did not differ between groups at any time point (25, 40, 55, and 70 minutes). There was no correlation between blood alcohol level at any of the time points and ventrostriatal DA release. Table S1 in Supplement 1 shows mean alcohol content of the drink.

Subjective Effects of Alcohol

The group as a whole showed a significant increase in total scores (sum of scores for each item) of subjective activation and sedation, at all time points (alcohol vs. placebo condition, Table S2 in Supplement 1). Baseline scores for activation or sedation did not differ significantly between conditions; however, activation at baseline was higher on the first scan day, independent of the nature of the drink ($35 \pm 14$ first day vs. $28 \pm 12$ second day, $p < .01$). For men, difference in activation scores between conditions was significant after 30 minutes and for women only after 60 minutes. Total scores for subjective sedation differed between conditions: peak total scores (at 60 minutes) were $27.8 \pm 9.5$ for alcohol and $19.2 \pm 11.7$ for placebo drink ($p < .01$) but were not different between groups.

Table 1. Demographics and Scan Parameters

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Men (n = 11)</th>
<th>Women (n = 10)</th>
<th>t Test (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>24.4 ± 1.8</td>
<td>23.0 ± 1.5</td>
<td>.07</td>
</tr>
<tr>
<td>Smokers (&lt;10 Cigarettes/Day)</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (C, AA, H, As)</td>
<td>6.2,2,1</td>
<td>7.0,1,2</td>
<td></td>
</tr>
<tr>
<td>Family History of EtOH</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PET Parameters (All, n = 21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID (mCi)</td>
<td>7.99 ± 1.09</td>
<td>7.80 ± 1.53</td>
<td>.65</td>
</tr>
<tr>
<td>IM (µg)</td>
<td>3.34 ± 1.93</td>
<td>2.99 ± 1.33</td>
<td>.35</td>
</tr>
<tr>
<td>SA (Ci/mmol)</td>
<td>1787 ± 1090</td>
<td>1726 ± 1031</td>
<td>.84</td>
</tr>
<tr>
<td>$V_{ND}$ (mL/cm$^3$)</td>
<td>.43 ± .08</td>
<td>.45 ± .1</td>
<td>.32</td>
</tr>
<tr>
<td>fp (unitless)</td>
<td>4.2 ± 1.6%</td>
<td>4.1 ± 0.7%</td>
<td>.68</td>
</tr>
</tbody>
</table>

Sample composition and scan parameters. Injected dose, injected mass, specific activity, distribution volume of the reference region, and plasma free faction are shown.

AA, African American; As, Asian; C, Caucasian; EtOH, ethanol; fp, plasma free faction; H, Hispanic; ID, injected dose; IM, injected mass; PET, positron emission tomography; SA, specific activity; $V_{ND}$, distribution volume of the reference region.

Table 2. Drinking History: Pattern of Drinking Behavior for Men and Women Over the Past 12 Months Before Enrollment

<table>
<thead>
<tr>
<th>Drinking History: Pattern of Drinking Behavior for Men and Women Over the Past 12 Months Before Enrollment</th>
<th>Men (n = 11)</th>
<th>Women (n = 10)</th>
<th>Sex Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset Regular Alcohol Consumption (Years)</td>
<td>18.6 ± 1.6</td>
<td>18.6 ± 1.4</td>
<td>.96</td>
</tr>
<tr>
<td>Duration Regular Alcohol Consumption (Years)</td>
<td>5.5 ± 2.7</td>
<td>4.2 ± 1.5</td>
<td>.22</td>
</tr>
<tr>
<td>Average Number of Drinking Days/Week (Past 12 Months)</td>
<td>2.8 ± 1.0</td>
<td>3.8 ± 1.0</td>
<td>.05</td>
</tr>
<tr>
<td>Average Number Drinks/Week (Past 12 Months)</td>
<td>14.9 ± 5.9</td>
<td>17.6 ± 14.4</td>
<td>.57</td>
</tr>
<tr>
<td>Average Number Drinks/Regular Drinking Occasion</td>
<td>5.5 ± 2.1</td>
<td>4.5 ± 2.5</td>
<td>.32</td>
</tr>
<tr>
<td>Number of Drinking Binges (Past 12 Months)</td>
<td>23.5 ± 28.8</td>
<td>12.5 ± 15.0</td>
<td>.29</td>
</tr>
<tr>
<td>Maximum Number Drinks/24 Hours (Last 12 Months); M</td>
<td>14.4 ± 6.6</td>
<td>7.5 ± 2.3</td>
<td>.01</td>
</tr>
<tr>
<td>Number Days M Is Consumed (Past 12 months); Frequency of M</td>
<td>5.2 ± 3.4</td>
<td>33.6 ± 42</td>
<td>.04</td>
</tr>
<tr>
<td>Lifetime Maximum Number Drinks/24 Hours</td>
<td>17.6 ± 9.5</td>
<td>10.3 ± 3.2</td>
<td>.03</td>
</tr>
</tbody>
</table>

Drinking binge is defined as >5 drinks in 2 hours for men and >4 drinks in 2 hours for women. Sex differences for each parameter evaluated by t test, p values shown (significant differences in bold).
Correlations of Subjective Effects with VST DA Release

The difference in activation total scores between conditions over 90 minutes was significantly correlated to VST DA release for the group as a whole at all time points. For men, there was significant correlation at 30 minutes and 60 minutes but not for women (Figure 2; Table S2 in Supplement 1). There was no significant correlation between subjective sedation and ΔBPND at any time.

Imaging Results

There were no differences in ROI volumes or scan parameters (Table 1 (all subjects)).

Effect of Alcohol on DA Release

The effect of alcohol on DA release in the group as a whole was significant for all striatal substructures with the greatest effect observed in the VST (ΔBPND = -9 ± 8%, p < .0001). The ΔBPND were -7 ± 8% in the preDPU, -5 ± 8% in the preDCA, -6 ± 8% in the postCA, -5 ± 6% in the postPU, -6 ± 7% for associative striatum, -6 ± 6% in the putamen, and -6 ± 7% for the striatum as a whole (p < .05 for all ROI). When separated by sex, men showed a significant effect of alcohol on ΔBPND in all ROIs (VST: -12 ± 8%, p < .001) and an overall greater magnitude of change than women (VST: -6 ± 8%, p = .02; statistically significant also in preDPU: 5 ± 7%, p < .05; Table 3).

Two group t-tests for effect of sex on ΔBPND did not reach statistical significance in individual ROIs (for VST, p = .10), but application of a linear mixed model across all striatal subregions with regional ΔBPND as the dependent variable and regions of interest as repeated measures showed a highly significant effect of sex (p < .001) with larger DA release in men. Because drink order was balanced for the group as a whole but not across sex (three women and seven men had alcohol on the first day), the model was repeated with drink order as a covariate. Effect of sex remained significant (p = .027). There was also a significant independent effect of scan order (p < .001), but there was no sex by order interaction (p = .35). Figure 2 illustrates the sex difference with binding potential maps averaged across subjects.

The BPND for the placebo condition only was not significantly different between men and women for any ROI apart from the postCA (BPNDmen = 1.83 ± .25, BPNDwomen = 2.09 ± .28, p = .04).

There was no difference in ΔBPND between smokers (n = 4) and nonsmokers (n = 17) in any ROI. A two-way test with sex and smoking as covariates and ΔBPND as the dependent variable showed no effect of smoking status (p = .92).

To further explore the effect of drinking history on DA release, we used general linear model analysis of ΔBPND in VST with fre-
Table 3. Binding Potential: [11C]Raclopride Binding for All Regions of Interest After Each Condition (Placebo Versus Alcohol) and Percent Change of [11C]Raclopride Displacement for Both Men and Women

<table>
<thead>
<tr>
<th>ROI</th>
<th>Men (n = 11)</th>
<th>Women (n = 10)</th>
<th>Men Versus Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BPND (Placebo)</td>
<td>BPND (Alcohol)</td>
<td>% ΔBPND</td>
</tr>
<tr>
<td>VST</td>
<td>2.28 ± .23</td>
<td>2.00 ± .18</td>
<td>-12.1% ± 8%</td>
</tr>
<tr>
<td>PreDCA</td>
<td>2.51 ± .31</td>
<td>2.32 ± .29</td>
<td>-7.3% ± 8%</td>
</tr>
<tr>
<td>PreDPU</td>
<td>3.02 ± .33</td>
<td>2.75 ± .28</td>
<td>-8.3% ± 8%</td>
</tr>
<tr>
<td>PostCA</td>
<td>1.83 ± .25</td>
<td>1.68 ± .26</td>
<td>-8.5% ± 7%</td>
</tr>
<tr>
<td>PostPU</td>
<td>3.17 ± .25</td>
<td>2.93 ± .25</td>
<td>-7.6% ± 6%</td>
</tr>
</tbody>
</table>

ΔBPND = difference in [11C]raclopride binding potential; BPND = [11C]raclopride binding potential; postCA, postcomissural caudate; postDPU, postcommissural putamen; preDCA, precommissural caudate; preDPU, precommissural putamen; ROI, region of interest; VST, ventral striatum.

*Changes were significant for all regions in men. VST: p < .001.
*Changes were only significant for VST and preDPU in women. VST: p = .02, preDPU: p = .04.
*Analysis with a linear mixed model across all striatal subregions showed a highly significant effect of sex (p < .001) with significantly greater ΔBPND in men.

Discussion

This report presents conclusive evidence in a large group of young adults for alcohol-induced DA release measured in vivo and shows, for the first time, sex differences in the magnitude of release. Although exposed to similar levels of alcohol, men had greater DA release than women. Furthermore, we show that alcohol stimulates DA release throughout the human striatum but most significantly in striatal regions implicated in reward and motivation. Whereas large effects were seen in both VST and postDPU following amphetamine (28,37,38) with smaller effects in other striatal subregions, only the VST displayed large ΔBPND after alcohol. We can estimate the level of fractional increase in ventrostriatal DA induced by our alcohol administration by using the simplifying assumptions that 1) the interaction between DA and [11C]raclopride at the D2/D3 receptor is purely competitive, 2) DA dissociation constant for D2/D3 receptors does not change between conditions, and 3) receptor-bound DA during the placebo condition is comparable with baseline values. Using the baseline occupancy of D2/D3 receptors by DA in healthy volunteers estimated by Laruelle et al. (39) (10%) and in vivo estimates of the fraction of D2/D3 receptors in a high-affinity state for agonists (80%) (40), we estimate that the alcohol challenge increased extracellular DA levels by 138% in men and 69% in women. The magnitude of the effect of alcohol is comparable with that measured with a low dose of amphetamine in young subjects (41,42) and similar to that reported for challenge with nicotine or smoking (43). Similar sex differences have been previously reported after an amphetamine challenge (38) showing greater change in [11C]raclopride binding in men in several striatal subregions (VST: 12 ± 6% in men, 7 ± 5% in women, p = .01) but no difference in baseline D2 binding.

The effect of sex was apparent across the whole striatum, suggesting that alcohol affects a broader dopaminergic pathway than the classic ventral tegmental area-VST circuit.

While amphetamine works by a mechanism of facilitated exchange diffusion at the DA transporter (44,45), it is not clear how alcohol stimulates dopamine release, and it may have direct and indirect effects. Ethanol has been reported to remove gamma-amino-nobutyric acidergic inhibition of DA neurons (46) and to directly excite DA ventral tegmental area neurons and reduce the afterhyperpolarization that follows spontaneous action potentials by reducing a quinidine-sensitive K+ current (47). Additionally, alcohol promotes DA release by a local calcium-dependent effect at the DA terminals in the striatum and accumbens (48–50), possibly mediated by an effect on DA transporters (51). In animals, ethanol administered at doses typically associated with human drinking enhances DA release in the accumbens via actions at other brain sites (52,53). In rats habituated to alcohol exposure, this may be limited to the early phase after the onset of drinking, suggesting a blunted striatal DA release as an effect of habituation as seen in chronically alcohol dependent humans (20,21) but also that DA may not be the central substrate producing the reinforcement in habituated rats (14). While passively administered intravenous ethanol can stimulate DA release, ethanol-related cues evoke an additional component of DA release (54,55). Repeated alcohol intake may induce salience attribution to alcohol-associated cues.

In this study, we did not test for the effect of cues but endeavored to minimize olfactory cues. Comparison of the placebo condition BPND in our study with baseline [11C]raclopride BPND values from a cohort of age- and sex-matched healthy control subjects (n = 20, mean age 24.8 ± 3 years, 11 men, 9 women, unpublished observations) shows no statistically significant differences in binding potential in any region: BPND in the baseline cohort was 2.21 ± .3 in the VST (vs. 2.26 ± .2 after placebo drink in this study, p = .57) and 2.8 ± .3 for the striatum as a whole (vs. 2.7 ± .2 after placebo, p = .31). This suggests that the placebo drink in our hands was associated with negligible or no change in DA release and provided a neutral stimulus rather than an appetitive cue. This interpretation is limited by the fact that we are comparing different cohorts. A better paradigm would include an additional baseline scan to test the effects of all sensory cues.

The alcoholic drink supplied both the sensory properties of alcohol (taste and smell), as well as the pharmacological effects once absorbed, which may both contribute to dopamine release and are not easily separated in this study design.

The fact that women received drinks with slightly lower concentrations of alcohol may support the contribution of sensory stimuli to the difference in VST DA release; however, as sensory organs generally respond logarithmically to increase in stimuli intensity, rather than linearly (56), it is unlikely that the absolute difference in concentrations of 10% (49% in women and 59% in men) was detectable. We consider it unlikely that sensory properties of alcohol alone are able to explain the large effect on ΔBPND and the signifi-

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cant sex differences in the striatum as a whole. The effects sizes for alcohol (1.25 total group, 1.5 for men, .75 for women) and sex (= .75) here are comparable with those in the Boileau et al. (22) study; alcohol effect size of 1.03 in an all male sample. As a further caveat, we did not control for estrogen levels among subjects and its possible effect on the magnitude of DA release in women. However, so far, only behavioral and biochemical studies in animals indicate central dopaminergic neurotransmission may be modulated by sex steroids, while human studies have not confirmed these findings (57,58).

Correlations with Clinical Measures

We observed correlations in men between magnitude of release and subjective activation, as well as with maximal number of drinks per 24 hours. These observations should be regarded as preliminary, but they allow us to speculate on the functional significance of the observed DA release.

Alcohol induced greater subjective activation than placebo and the difference in activation scores across days between conditions correlated with greater DA release in the VST (p < .05). Greater activation between alcohol and placebo was no longer observed when the ratings were corrected for baseline for each day, due to an order effect where subjective activation at baseline on the first day was higher than second day regardless of the nature of the drink. This effect is possibly related to the novelty of the situation on the first day. This is an unexpected effect of the 2-day paradigm and presents a limitation in our study. To bypass this order effect, we compared ratings of subjective activation at specific time points across days, and we observed that men showed greater activation in the early phase after alcohol consumption (Figure 2), which correlated with ABPND in VST only in men. It is tempting to speculate, based on this observation, that the larger effect on DA transmission may contribute to the initial reinforcing properties of alcohol and may be related to the higher incidence of alcoholism in men.

We also observed an effect of scan order on ABPND, alcohol administered in the first PET session evoked greater DA release. However, sex was an independent factor: men still had greater alcohol-evoked DA release than did women after controlling for the order effect; there was no sex by order interaction.

Finally, we observed that larger DA release was associated with smaller frequency of maximum number of drinks per 24 hours (M), a strong relationship that survived correction for multiple comparisons. This observation is interesting, as it could suggest that habitual drinking of large numbers of alcoholic drinks at individual occasions, as measured by M, a parameter proposed to indicate greater potential for addiction (35) and withdrawal symptoms (36), is associated with smaller release. In other terms, the beginning of a transition to habit, detected here by frequent drinking, may be associated with a decrease in the magnitude of DA release in men. In women, this relationship was not significant, possibly due to lack of power in the presence of large variance. When outliers among women were removed, the same relationship of lower DA release with higher frequency was true for the group as a whole but not for women. Our interpretation of lowered DA release as a correlate of transition to habit is consistent with preclinical animal models of addiction (59).

In summary, the current findings indicate that alcohol stimulates DA release in humans, and this effect is greater in men than in women. We also observe that DA release is associated with subjective activation in men and inversely related to the frequency of heavy drinking. Together, these findings suggest that the ability of alcohol to stimulate DA release may play an important and complex role in its rewarding effects and abuse liability in humans. Our report further suggests a biological mechanism that may mediate the difference in vulnerability for alcoholism between men and women.

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