When What You See Isn't What You Get: Alcohol Cues, Alcohol Administration, Prediction Error, and Human Striatal Dopamine

Karmen K. Yoder, Evan D. Morris, Cristian C. Constantinescu, Tee-Ean Cheng, Marc D. Normandin, Sean J. O'Connor, and David A. Kareken

Background: The mesolimbic dopamine (DA) system is implicated in the development and maintenance of alcohol drinking; however, the exact mechanisms by which DA regulates human alcohol consumption are unclear. This study assessed the distinct effects of alcohol-related cues and alcohol administration on striatal DA release in healthy humans.

Methods: Subjects underwent 3 PET scans with [^{11}C]raclopride (RAC). Subjects were informed that they would receive either an IV Ringer's lactate infusion or an alcohol (EtOH) infusion during scanning, with naturalistic visual and olfactory cues indicating which infusion would occur. Scans were acquired in the following sequence: (1) Baseline Scan: Neutral cues predicting a Ringer's lactate infusion, (2) CUES Scan: Alcohol-related cues predicting alcohol infusion in a Ringer's lactate solution, but with alcohol infusion *after* scanning to isolate the effects of cues, and (3) EtOH Scan: Neutral cues predicting Ringer's, but with alcohol infusion *during* scanning (to isolate the effects of alcohol without confounding expectation or craving).

Results: Relative to baseline, striatal DA concentration decreased during CUES, but increased during EtOH.

Conclusion: While the results appear inconsistent with some animal experiments showing dopaminergic responses to alcohol's conditioned cues, they can be understood in the context of the hypothesized role of the striatum in reward prediction error, and of animal studies showing that midbrain dopamine neurons decrease and increase firing rates during negative and positive prediction errors, respectively. We believe that our data are the first in humans to demonstrate such changes in striatal DA during reward prediction error.

Key Words: Alcohol, Alcohol Cues, Dopamine, PET, Prediction Error.

CONDITIONED CUES ASSOCIATED with alcohol can induce craving in humans (Carter and Tiffany, 1999), which results in alcohol-seeking and consumption (e.g., Cooney et al., 1997; Litt et al., 2000). It has been hypothesized that cue-induced activation of the mesolimbic dopamine (DA) system leads to drinking behavior (Weiss et al., 1993). Animal studies of alcohol self-administration have shown that extracellular DA concentration ([DA]) in the nucleus accumbens (NAc) increases while animals wait in operant chambers for access to alcohol. (Gonzales and Weiss, 1998; Katner et al., 1996; Melendez et al., 2002; Weiss et al., 1993). While these studies observed the effects of environmental cues on DA levels, Doyon et al. (2003, 2005) concluded that the initial perception of the olfactory/gustatory properties of alcohol transiently elevates NAc [DA]. Similarly, others have shown that NAc [DA] increases as a result of exposure to conditioned stimuli associated with cocaine (Ito et al., 2000; Phillips et al., 2003; Weiss et al., 2000). Taken together, these studies support a relationship between dopaminergic activity in the NAc and presentation of alcohol- and drug-related cues (Berridge, 2007; Robinson and Berridge, 1993).

In humans, brain areas associated with reward are activated during cues that elicit craving. Using fMRI, we showed that alcoholic drink odors increased blood oxygen level dependent (BOLD) responses in the NAc of risky drinkers (Bragulat et al., 2008; Kareken et al., 2004a). Myrick and colleagues (2004) found that images of alcoholic beverages increased ventral striatal BOLD signals in alcoholic patients (see also Braus et al., 2001; Wrase et al., 2007). Cue-induced limbic, cortical, and striatal activity have also been correlated with craving (Modell and Mountz, 1995; Myrick et al., 2004) and alcohol intake (Grusser et al., 2004).

The neurochemical basis of cue reactivity and craving in humans is less clear. In parallel with the animal studies cited

From the Department of Radiology (KKY, EDM, CCC, TEC, MDN, DAK), Stark Neurosciences Research Institute (KKY, EDM, DAK), Department of Psychiatry (EDM, SJO, DAK), Department of Neurology (DAK), Indiana University School of Medicine, Indianapolis, IN; Weldon School of Biomedical Engineering (EDM, CCC, MDN), Purdue University, West Lafayette, IN; and Department of Biomedical Engineering (EDM, TEC), Indiana University-Purdue University at Indianapolis, Indianapolis, IN.

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Reprint requests: David A. Kareken, PhD, Department of Neurology (CL 298), 541 Clinical Drive, Indianapolis, IN 46202; Fax: 317-274-1337; E-mail: dkareken@iupui.edu

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above, Boileau et al. (2007) reported that conditioned contextual cues of amphetamine administration lead to increased ventral striatal [DA] release. Although several studies have examined the relationship between DA and drug craving, the literature is equivocal. In detoxified alcoholics, low DA synthesis capacity and low DA receptor availability are associated with higher craving (Heinz et al., 2005; Heinz et al., 2004). Nicotine-induced striatal DA release is associated with diminished urge to smoke in nicotine-dependent subjects (Brody et al., 2004), which similarly suggests an underlying hypoactive DA system. In contrast, both Wong et al. (2006) and Volkow et al. (2006b) reported that the intensity of cue-induced craving is correlated with cue-induced increases in [DA] in the dorsal striatum of cocaine users.

We used [^{11}C]raclopride (RAC) PET to study the relationship between striatal [DA] and the sight and smell of preferred alcoholic drinks, which were used to predict intravenous (IV) alcohol administration. As PET methodology cannot resolve the individual contributions of multiple stimuli (e.g., anticipation of administration, physiological effects of alcohol) to changes in [DA], we isolated the effects of cue-induced anticipation from the pharmacological effects of alcohol by using separate scan sessions. Generalizing from the animal literature and our work with IV alcohol (Yoder et al., 2005, 2007), we initially hypothesized that conditioned cues predicting alcohol would increase striatal [DA], while alcohol administration would not. However, ventral striatal [DA] instead varied systematically in response to alcohol cues and unexpected alcohol exposure in a manner consistent with the hypothesized role of the dopamine system in detecting reward prediction errors (Mirenowicz and Schultz, 1994; Pan et al., 2005; Schultz et al., 1993, 2000).

MATERIALS AND METHODS

Subjects

Eight healthy Caucasian subjects (Table 1) signed informed consent statements agreeing to participate in the study, which was approved by the Indiana University Institutional Review Board. None had any history of psychiatric or neurological disease as determined by interview, and none were drug or alcohol dependent according to the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994). Two subjects had a family history of alcoholism. Five subjects (2 female) surpassed the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) threshold of 8 for hazardous drinking (Conigrave et al., 1995). All were screened with the University of Pennsylvania Smell Identification Test to rule out problems smelling the olfactory cues (Doty et al., 1984, 1989). All subjects completed the Timeline Followback Interview (Sobell et al., 1986) for assessment of drinking habits.

Table 1. Subject Characteristics

	Mean	SD	*n*	%
Age	23.8	4.03	—	—
Male	—	—	5	62.5
AUDIT	7.0	2.88	—	—
Drinks/week[a]	11.14	8.18	—	—
Drinks/month[a]	46.5	34.4	—	—
Drinks/drinking day[a]	4.57	1.76	—	—
Subjects reporting FHA[b]	—	—	4	50.0
# Relatives	2.25	(Range: 1–4)	—	—

SD, standard deviation; AUDIT, Alcohol Use Disorders Identification Test; FHA, family history of alcoholism; includes report of any first- or second degree relatives with alcohol use disorders.

[a]Assessed by the Timeline Followback Interview (Sobell et al., 1986).

[b]Two subjects were "unambiguously" family-history positive for alcoholism (defined as reporting at least 2 relatives, with at least one being a first-degree relative). One subject reported only 1 first-degree relative; the other reported 2 second-degree relatives.

Scanning Procedures

[^{11}C]raclopride (RAC, a selective DA D_2/D_3 receptor antagonist) was synthesized as reported previously (Fei et al., 2004). Subjects underwent 3 RAC PET scans (EXACT HR+, CTI; Knoxville, TN) over 2 days. PET data were acquired with septa retracted (3D mode). Full width half maximum (FWHM) was 9 mm when images were reconstructed with a 5 mm Hanning filter. Radiochemical purity was > 99%. Scans were initiated with the IV injection of (mean ± SD) 14.1 ± 0.99 mCi of RAC; total mass injected was 15.1 ± 5.69 nmol per subject per scan. Dynamic data acquisition lasted 45 minutes [An analysis of ventral striatal time-activity curves (TACs) from a previous study (Yoder et al., 2005) demonstrated that BP_{ND} values from 45 minutes of scan data were only 2.5% lower than BP_{ND} values estimated from 60 minutes of data. BP_{ND} values from the 45- and 60-minute datasets were highly correlated ($R^2 = 0.99$; $p < 3.4 \times 10^{-14}$)]. A heavily T1-weighted, spoiled gradient recalled (SPGR) magnetic resonance image (MRI; 1.5T GE Echospeed LX, GE; Waukesha, WI) was acquired in each subject for subsequent spatial normalization of image data into Montreal Neurological Institute (MNI) stereotactic space.

Behavioral Paradigm

A schematic of the 3 conditions is presented in Fig. 1. Subjects were informed that what they saw and smelled would predict what would happen to them during scanning. Specifically, they were instructed that if they saw and smelled leather and lilac, they would receive an infusion of Ringer's lactate (no alcohol), and that if they saw and smelled their favorite alcoholic beverages, they would receive an alcohol infusion to an intoxicating level.

Cue Stimulation. Neutral or alcohol cues were started 2 minutes after RAC injection, and were maintained for 15 minutes. Visual cues were placed on a rotating table behind the scanner gantry (viewed through mirror goggles). Two sets of objects (neutral cues: scraps of tanned leather and plastic lilac flowers; alcohol cues: a subject's 2 favorite alcoholic beverages, e.g., a filled glass of beer next to a beer bottle, a glass of wine next to a wine bottle) were set on the table and separated by an opaque divider. The table rotated every 75 seconds, and each side was displayed 6 times. Visual displays were accompanied by presentation of the corresponding olfactory stimulus.

Olfactory stimuli were delivered with a computer-controlled olfactometer (Kareken et al., 2004a,b) through a polytetrafluoroethylene (PTFE) nasal cannula that was mounted on the scanner gantry and positioned approximately one inch in front of the subject's nose. The cannula delivered a constant airflow of 2.0 liters per min of airflow throughout the imaging session, with odors injected into the constant air-stream during two 10 second odor periods during each visual display period. The first odor in the 75-second display period began 3 seconds after the visual display came into view; the second odor began 27 seconds later. Lilac and leather odors were provided by International Flavors and Fragrances (Union Beach, NJ).

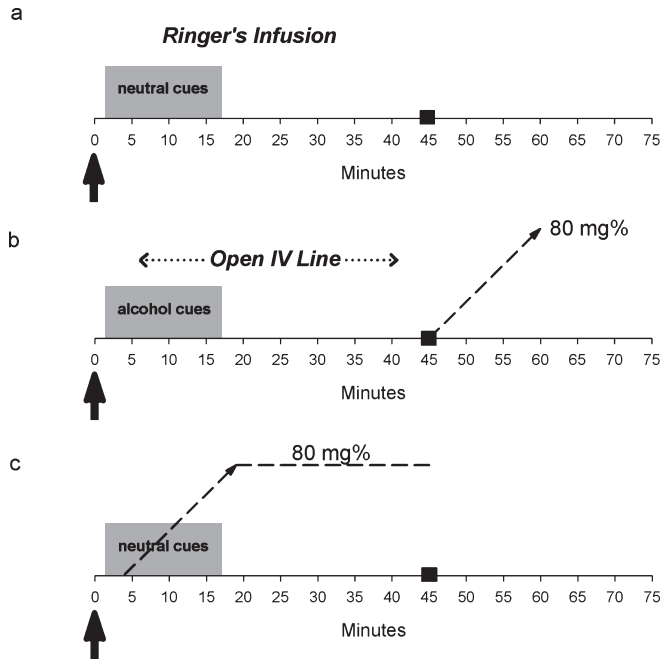

Fig. 1. Graphic depiction of scanning protocols. See text for details. Arrows indicate [^{11}C]raclopride injection and beginning of image acquisition. Dotted lines represent the alcohol infusion profiles, with black box at 45 minutes indicating scan end time. (**A**) Baseline (BL) scan; Ringer's solution was infused using the same infusion rate parameters determined for each subject's alcohol scan. (**B**) Olfactory and visual alcohol cues (CUES) scan; the IV line was kept open during scanning, alcohol infusion was started after scanning. (**C**) Alcohol (EtOH) infusion scan.

Alcohol-related odors were produced by bubbling air from the olfactometer through each subject's 2 most preferred alcoholic beverages.

The 3 scan conditions occurred in the following fixed order: (1) Baseline (BL): Neutral cues with a lactated Ringer's infusion; (2) Alcohol cues (CUES): Alcohol cues, with alcohol infusion *after* scanning to fulfill the promise of alcohol delivery; (3) Alcohol (EtOH): Neutral cues, but with alcohol infusion *during* scanning (thus violating the subject's expectation and avoiding anticipation of alcohol). A fixed-order design was used for several reasons. The last scan, the alcohol condition, involved a direct deception. A critical factor in execution of this experiment was that the subjects maintain faith in the veracity of the predictive stimuli. Had a randomized scan order been used, the deception condition could have come either first or second. In that scenario, a subject would have been deceived before completing the entire protocol, and would have been highly unlikely to believe anything that the stimuli were supposed to have predicted in subsequent conditions, thus confounding the remaining scan(s).

Alcohol Infusion. The physiologically-based pharmacokinetically (PBPK) modeled IV alcohol clamp (O'Connor et al., 1998; Ramchandani et al., 1999) was used to control the exact timing of alcohol delivery and minimize the experimental variation in the brain's exposure to alcohol across subjects. Oral ingestion of alcohol causes highly variable rates and concentrations of brain alcohol exposure as a result of inter-subject differences in stomach pH, volume of stomach contents, age, gender, and first-pass metabolism. Different brain alcohol concentrations are likely to cause different magnitudes of dopamine responses across subjects. In addition, the timing of alcohol exposure is likely to affect the timing of dopamine release. We have shown that if the timing of DA release is not held constant, then the outcome measure of [^{11}C]RAC binding potential could be confounded (Yoder et al., 2004). The PBPK model was therefore used to specify individual alcohol infusion profiles based on each subject's height, weight, and gender. Profiles were calculated such that an IV infusion of alcohol (6% vol/vol in lactated Ringer's) would achieve a breath alcohol concentration (BrAC) of 80 mg% (0.08) for both scans involving alcohol infusion. This infusion profile was also used for the Ringer's lactate infusion during Scan 1. For alcohol infusion following the CUES condition (scan 2), infusion began immediately after PET image acquisition was completed, continued for 15 minutes (the time at which BrAC was calculated to reach the 80 mg% target), and then stopped. For scan 3 (EtOH), alcohol infusion began 4 minutes after RAC injection, ascended over 15 minutes to the target based on model calculations, and was then clamped to maintain the 80 mg% target throughout the remaining 25 minutes of image acquisition (Fig. 1). Following imaging in scans 2 and 3, a BrAC sample was taken using a Dräger Alcotest® 7410 handheld breath meter to determine the subject's actual breath alcohol level. Subjects were thoroughly debriefed following scan 3 about the need for the experimental deception.

Subjective Impressions. Subjects were assessed for desire to drink (craving) using the Alcohol Urge Questionnaire (AUQ; Bohn et al., 1995) before scanning. After scanning, subjects completed a second AUQ, with the items modified to refer retrospectively to how they felt "while in the scanner, and while seeing and smelling the items on the table."

During scanning, subjects rated how "high" (up, stimulated, feeling good) and how "intoxicated" (drunk, inebriated, tipsy) they felt during imaging, using a modified Subjective High Assessment Scale (SHAS; Schuckit and Gold, 1988). In our modified version, subjects spoke a number ranging from 0 (same as before infusion) to 100 (most high or intoxicated ever experienced). Subjects were prompted for responses every 10 minutes during imaging. Subjects were informed that they would be assessed for their feelings of "high" and "intoxication" throughout all 3 scan sessions, regardless of the kind of infusion (alcohol or saline) they received.

Subject Expectations. After each scan, subjects were asked to rank their subjective expectations about what they believed would occur during scanning. Subjects rated 2 statements ("It was clear that I was about to get drunk" and "I knew that I was *not* about to get drunk") on a visual-analog scale anchored by 1 (strongly disagree) to 7 (strongly agree).

Image Processing

Image processing procedures were as previously described (Yoder et al., 2007) . MRI and PET images were converted to Analyze format using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). All subsequent data processing steps were performed with SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/). For each scan, a summed image was created from the first 10 minutes of dynamic [^{11}C]RAC data using the Realign function in SPM2. These summed images contained a mixture of blood flow and specific striatal D_2/D_3 binding, permitting accurate registration of all time frames to a single image. The summed image was co-registered to the individual subject's MRI scan using SPM2. Motion correction was achieved by coregistering individual PET frames to the coregistered, summed PET image. Each subject's MRI was normalized into Montreal Neurological Institute (MNI) stereotactic space using SPM2's default normalization parameters. The transformation matrix obtained from this normalization step was applied to the motion-corrected, coregistered PET images from each subject, thus placing all dynamic PET data in MNI stereotactic space.

Parametric Binding Potential Images

The binding potential of RAC is an index of the number of DA D_2/D_3 receptors that are available for binding, and is operationally

defined as B_{avail}/K_D. Binding potential will be denoted herein as BP_{ND}, that is, binding potential calculated as bound tracer concentration relative to nondisplaceable tracer concentration (Innis et al., 2007). Changes in BP_{ND} can be used as indices of change in [DA] (Innis et al., 2007; Laruelle, 2000). If RAC BP_{ND} values from an experimental scan condition are different from baseline BP_{ND} values, the changes in BP_{ND} are presumed to be caused by changes in endogenous [DA] (Dewey et al., 1992, 1993; Seeman et al., 1989; Young et al., 1991). Increases in BP_{ND} relative to baseline indicate decreases in [DA], and decreases in BP_{ND} relative to the baseline BP_{ND} indicate increases in [DA].

Parametric BP_{ND} images were generated as described previously (Yoder et al., 2007), using a multilinear reformulation of the Logan reference region graphical analysis (Ichise et al., 2002; Logan et al., 1996). The parametric whole brain BP_{ND} images were smoothed with an 8 mm Gaussian kernel (Costes et al., 2005; Picard et al., 2006; Ziolko et al., 2006). We restricted the search area for the voxel-wise paired *t*-tests to the striatum, as (1) our sole focus was the striatum, and (2) the striatum has the highest density of D_2/D_3 receptors in the brain, and is the only brain structure with high enough signal-to-noise ratio to support quantification of D_2/D_3 receptor availability with [^{11}C]RAC. A bilateral striatal binary mask (created from basal ganglia ROIs from MARINA http://www.bion.de/index.php?title=MARINA&lang=eng) was applied to the whole brain parametric images to create striatal parametric images. The striatal parametric images were used for SPM analysis.

Dopamine responses, which include increases and decreases in [DA], can be indexed by change in BP_{ND} (ΔBP_{ND}), defined here as $(BP_{ND1}-BP_{ND2})/BP_{ND1}$. BP_{ND1} refers to the BL scan, and BP_{ND2} refers either to the CUES or EtOH condition. Positive ΔBP_{ND} values indicate increases in [DA], and negative ΔBP_{ND} values reflect decreases in DA levels. Striatal ΔBP_{ND} maps were created from the parametric BP_{ND} images using the ImCalc function in SPM2 for each subject. These maps of changes in [DA] were used as the dependent measures for the CUES and EtOH conditions.

Voxel-Wise Statistics. To test for effects of CUES and EtOH conditions on [DA] via changes in BP_{ND}, one-sample voxel-wise *t*-tests were conducted on the striatal ΔBP_{ND} maps in SPM2 to test the null hypothesis that $\Delta BP_{ND} = 0$ at each voxel.

Other Statistics. Repeated-measures analysis of variance (ANOVA) was used to test for: (1) changes in pre-scan and postscan AUQ, (2) changes in SHAS scores during the respective scanning periods, and (3) changes in subject expectations. One-way ANOVA was used to test for differences between scan conditions in mCi injected and mass dose injected. Pearson's correlation coefficient was used to test for exploratory relationships among variables. Statistical significance was set at $p < 0.05$.

RESULTS

Cue Paradigm Validity

To test the validity of the behavioral paradigm, we tested for differences in pre- and postscan AUQ craving scores across all scan sessions using a repeated-measures ANOVA. The omnibus test revealed significant differences across all time points ($F_{5,35} = 17.90$, $p < 0.001$). A planned contrast showed a significant difference in AUQ scores between measurements made before and after the CUES scan ($F_{1,7} = 33.67$, $p = 0.001$, Fig. 2), in which the visual and olfactory stimuli signified impending alcohol infusion. This result suggests that the multi-sensory paradigm was successful in evoking a significant desire for alcohol. The cues also successfully directed subjects' expectations in the direction intended by the cues, with significant changes across scans for the questions: "It was clear that I was about to get drunk" ($F_{2,14} = 9.38$, $p = 0.003$) and "I knew that I was *not* about to get drunk" ($F_{2,14} = 7.81$, $p = 0.005$). For each question, planned comparisons showed that expectations at baseline and during EtOH (both of which involved neutral cues) were significantly different than during the CUES scan, which involved the alcohol cues (*p*'s < 0.05; Fig. 3).

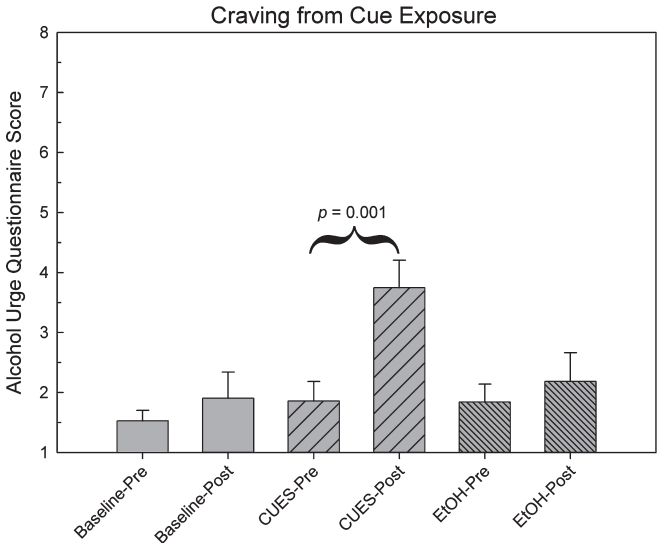

Fig. 2. Alcohol Urge Questionnaire (AUQ) scores before and after each scan condition. Alcohol-related cues significantly increased the postscan AUQ score.

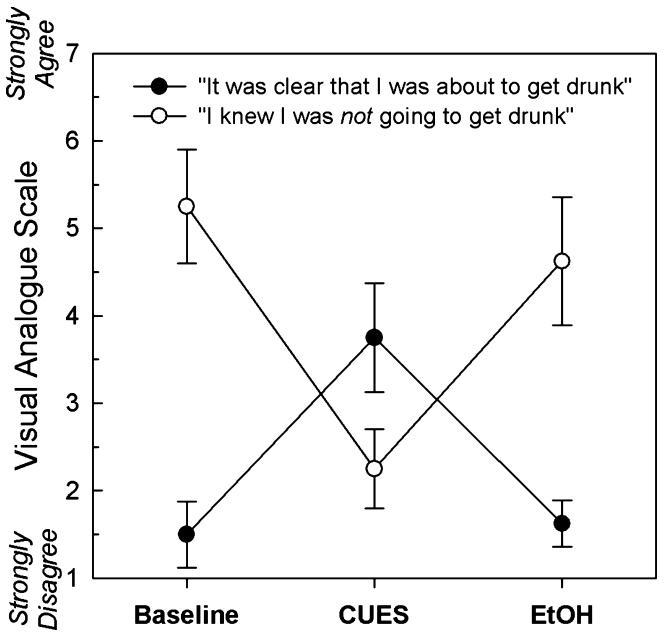

Fig. 3. Subject expectations after cue presentation.

Subjective Effects of Alcohol

Following alcohol infusion during scan 3, the actual mean BrAC as measured was 79 ± 11 mg%, which compares favorably with the pharmacokinetic model target of 80 mg%. SHAS data for perceived "High" and "Intoxication" were analyzed separately for each scan with a 2(SHAS) × 6(Time) repeated-measures ANOVA, using polynomial contrasts to test for linear trends across the duration of the scan (see Fig. 4). There were no significant changes in subjective impressions of the effects of alcohol during the course of BL image acquisition. While there were some significant changes in perceived effects during the course of the CUES scan (omnibus $F_{1,7} = 7.56$, $p < 0.05$, Greenhouse-Geisser correction), the changes were not highly linear over time ($p = 0.1$). During the EtOH scan, there were significant changes in subjective ratings over time (omnibus $F_{5,35} = 4.96$, $p < 0.005$), as well as a significant interaction between "High" and "Intoxication" ($F_{5,7} = 5.18$, $p = 0.001$), with "Intoxication" showing a more distinct linear trend over time ($F_{1,7} = 7.53$, $p < 0.05$). "High" showed a borderline level of omnibus significance ($p = 0.051$), but did not exhibit a significant linear trend ($p = 0.14$).

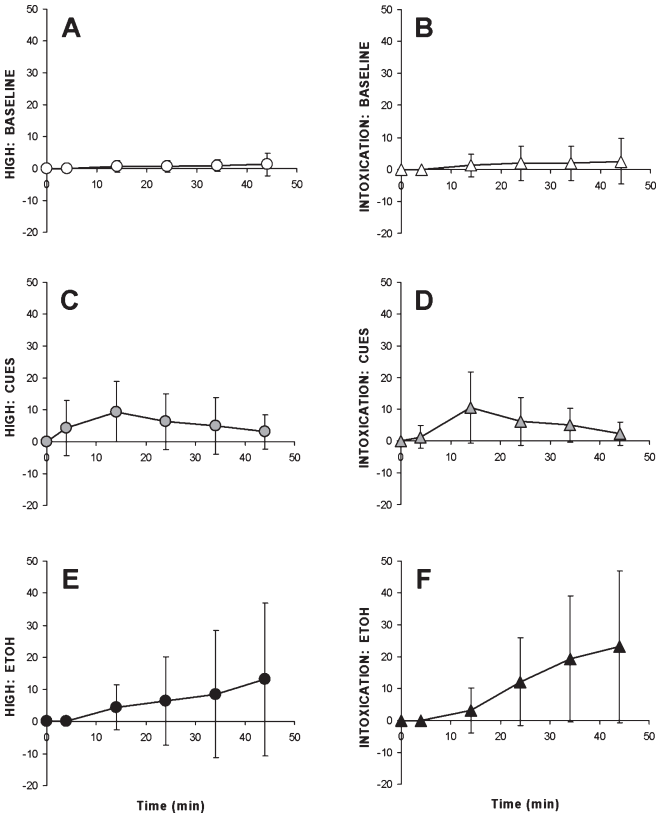

Fig. 4. Subjective High Assessment Score (SHAS) scores (mean ± SD) for high (circles, left panels) and intoxication (triangles, right panels) during the 3 scan conditions. For all scans, cue presentation began 2 minutes after [^{11}C]raclopride injection. Ringer's infusion (Baseline) or alcohol infusion (ETOH) began 4 minutes after [^{11}C]raclopride injection. (Panels **A**, **B)** Baseline. (**C, D**) CUES. (**E**, **F)** EtOH.

Imaging Results

There were no differences in either mCi injected or mass dose injected between scan conditions. mCi injected for baseline, CUES, and ETOH was 13.9 ± 1.30, 14.4 ± 0.64, and 14.1 ± 1.00, respectively. Mass dose injected (nmol/subject) was 14.6 ± 4.20, 14.5 ± 6.78, and 16.4 ± 6.33 for baseline, CUES, and ETOH conditions, respectively.

Contrary to the hypotheses, striatal DA concentration did not increase during the CUES condition relative to BL. Instead, the voxel-wise analysis showed a cluster of voxels in the right ventral striatum where ΔBP_{ND} was significantly negative (Fig. 5, top), reflecting a decrease in DA concentration. The average ΔBP_{ND} value of the voxels in this cluster was −0.20 ± 0.13 (i.e., a 20% increase in BP_{ND}).

The voxel-wise *t*-test of the unexpected EtOH ΔBP_{ND} map showed a cluster of voxels in the left NAc with significantly positive ΔBP_{ND} values, indicating an increase in DA concentration (Fig. 5, bottom). The average ΔBP_{ND} value of the voxels in this cluster was 0.12 ± 0.08 (i.e., a 12% decrease in BP_{ND}).

The average BP_{ND} values from the significant clusters are presented in Table 2.

Effects of Subject-Specific Variables

Subjects classified as "hazardous drinkers" (AUDIT scores > 8, $n = 5$) did not differ significantly from social drinkers ($n = 3$) in the average ΔBP from significant clusters in either experimental condition. Neither SHAS nor AUDIT score were significantly correlated with the average ΔBP from the CUES or ETOH clusters.

DISCUSSION

Rodent studies suggest that conditioned cues or contexts that accompany or precede alcohol administration result in increased [DA] in the NAc (Gonzales and Weiss, 1998; Katner et al., 1996; Melendez et al., 2002; Weiss et al., 1993). However, in this human PET study, the sights and smells of subjects' preferred alcoholic drinks, intended to explicitly create anticipation of alcohol administration, did not cause any increases in [DA] in the NAc or other striatal areas. Instead, we found an effect in the opposite direction, such that alcohol-related cues *decreased* ventral striatal [DA]. This is consistent with microdialysis data from animals that were first trained to respond for alcohol and then subsequently underwent extinction training: Olfactory cues that reinstated operant responding for alcohol (without the alcohol delivery predicted by the cues) also decreased NAc [DA] (Katner and Weiss, 1999). Moreover, unexpected alcohol administration *increased* ventral striatal [DA]. This is similar to Boileau and colleagues (2003), but not to work from our laboratory (Yoder et al., 2005, 2007). In particular, we previously demonstrated that, in subjects who were aware that they would receive alcohol, intravenous alcohol administration did *not*

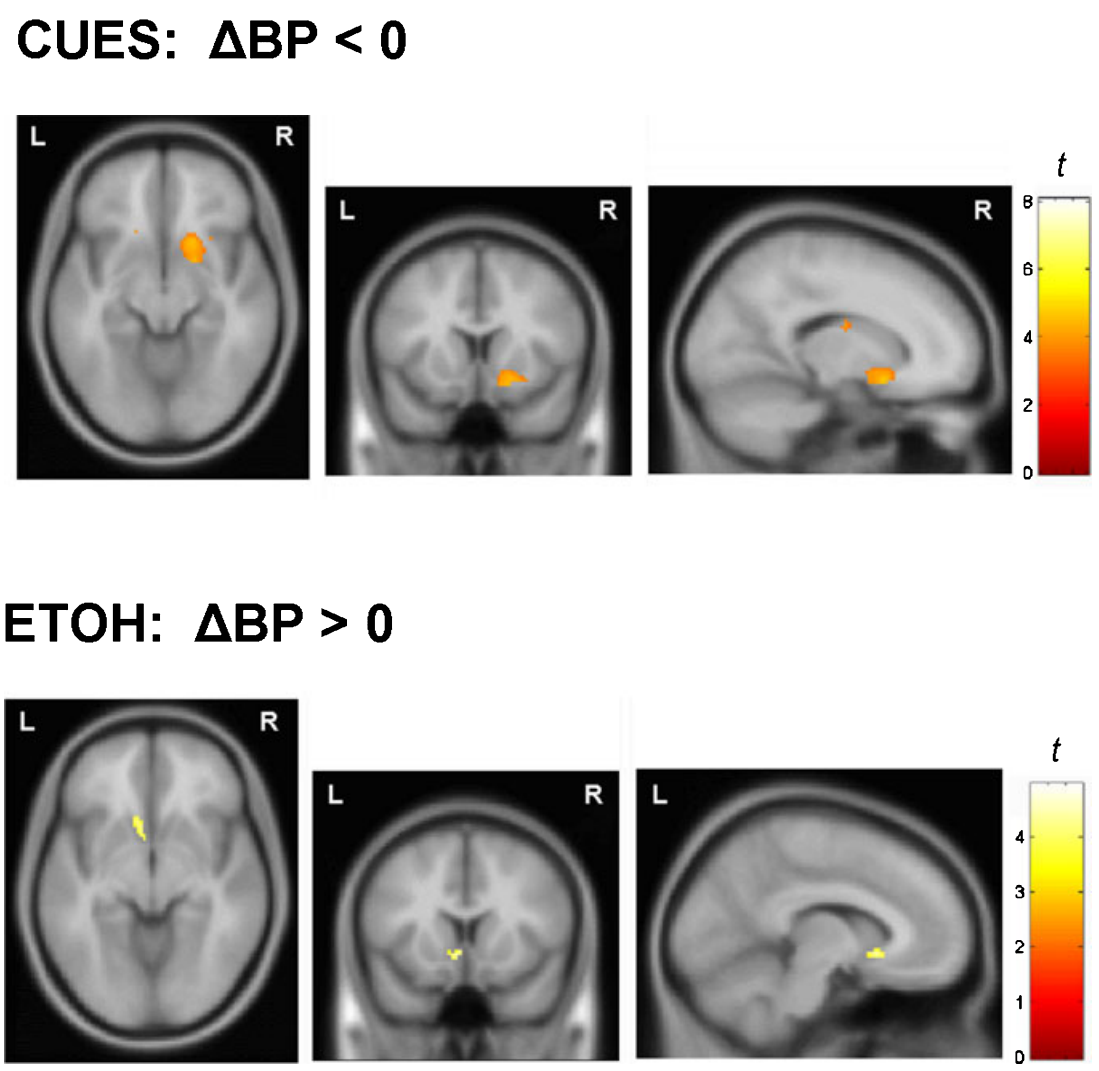

Fig. 5. Axial (left), coronal (middle), and sagittal (right) maps of *t*-values from voxel-wise statistical testing. Top: Voxel-wise 1-sample *t*-test to determine if ΔBP_{ND} at each voxel was significantly < 0. Dopamine levels were significantly lower during the alcohol-related cues (CUES) condition relative to the baseline (neutral cues) condition (display threshold $p < 0.005$). Bottom: Voxel-wise 1-sample *t*-test to determine if ΔBP_{ND} at each voxel was significantly > 0. Dopamine levels were significantly higher during the unanticipated alcohol (EtOH) condition compared with the baseline condition (display threshold $p < 0.005$).

cause detectable dopamine release (however, see Yoder et al., 2007, for alternative methods of analysis for quantifying EtOH-induced DA release).

When the data from the CUES and EtOH conditions are examined in a different context, they appear to match Schultz et al.'s work on dopamine neuron function in reward prediction error (Mirenowicz and Schultz, 1994; Schultz, 2002; Schultz et al., 1993): (A) If reward is expected but not delivered (negative prediction error), the activity of midbrain DA neurons is greatly reduced (Morris et al., 2004; Schultz et al., 2000). In our CUES condition, alcohol was promised but not delivered during scanning, with a resulting *decrease* in NAc [DA]. (B) The unexpected delivery of a reward (positive prediction error) increases DA neuronal activity (Mirenowicz and Schultz, 1994; Pan et al., 2005; Schultz et al., 2000). During our EtOH scan condition, alcohol was delivered unexpectedly, and [DA] consequently increased in the NAc. Given the strength of the midbrain dopaminergic innervation of the striatum, it seems likely that the firing rates of DA neurons would correspond to changes in striatal [DA]. We therefore suggest that our present *in vivo* human PET data are consistent with the aforementioned preclinical electrophysiological findings: (A) [DA] is reduced when alcohol was promised but

Table 2. Mean ± SD BP_{ND} Values From the Baseline and Challenge Scans (CUES or ETOH) for the Significant SPM Clusters (see Fig. 5)

	Scan	
Cluster	Baseline	Challenge
CUES-R	1.38 ± 0.46	1.59 ± 0.37
ETOH-L	1.23 ± 0.33	1.08 ± 0.30

CUES-R: voxel data from the right ventral striatal cluster in the CUES contrast ($\Delta BP_{ND} < 0$). ETOH-L: voxel data from the left ventral striatal cluster in the ETOH contrast ($\Delta BP_{ND} > 0$).

not delivered, (B) [DA] increased with unexpected alcohol administration.

Our results are consistent with and complementary to the work of other human neuroimaging investigations. Several fMRI studies have reported changes in striatal brain activity during conditions that involved prediction errors. Specifically, negative prediction errors resulted in lower ventral (Abler et al., 2006) and dorsal striatal (Davidson et al., 2004; McClure et al., 2003) activity, while unpredictable delivery of stimuli (positive prediction error) caused increased activity in the ventral striatum (Berns et al., 2001) and putamen (McClure et al., 2003). Although fMRI does not provide information about changes in specific neurotransmitter systems, these reported changes in local brain activity resulting from prediction errors parallel our data regarding the effects of prediction error on striatal dopamine activity. The data in the present work are also analogous to that of Pappata and colleagues (2002), who detected striatal DA release during unexpected monetary gain; however, this group did not detect any change in striatal [DA] in response to unexpected monetary loss.

It is possible that our observed increase in [DA] during alcohol administration resulted from pharmacological effects of alcohol on dopaminergic neurons (Brodie and Appel, 2000; Brodie et al., 1999; Gessa et al., 1985) rather than prediction error, per se. Using the same radioligand as in the present work, Boileau and colleagues (2003) demonstrated that oral alcohol induced DA release in the ventral striatum of human subjects. However, when we used a similar analysis, our group could not show increased [DA] from IV alcohol administration (Yoder et al., 2005, 2007). Were the effect of alcohol on DA release strictly pharmacological, increased [DA] would be expected with either IV or oral alcohol. We instead propose that the discrepancy between the Yoder and colleagues (2005, 2007) and Boileau and colleagues (2003) studies stems from the *mode* of administration of alcohol (oral versus IV). In particular, IV alcohol administration does not provide conditioned gustatory and olfactory cues (which are present in oral administration), which may themselves induce DA release (Doyon et al., 2003, 2005).

Our present work also parallels an emerging view that the NAc DA release observed following investigator-administered alcohol was provoked by novelty, unexpectedness, and/or aversiveness of the administration (Bradberry, 2002; Gonzales et al., 2004; Heidbreder and De Witte, 1993; Imperato and Di Chiara, 1986; Joseph et al., 2003; Marinelli et al., 2003; Philpot and Kirstein, 1998; Yan, 1999; Yim et al., 1998, 2000; Yoshimoto et al., 1992). Although several studies have documented increases in NAc [DA] during oral self-administration of alcohol (Doyon et al., 2005; Gonzales and Weiss, 1998; Melendez et al., 2002; Weiss et al., 1992, 1993, 1996), Doyon and colleagues (2003, 2005) showed that increases in NAc [DA] were dissociated from changes in brain ethanol concentration: NAc DA levels peaked 5 minutes after the onset of oral alcohol self-administration, then gradually tapered off over the next 30 minutes as the animals continued to drink alcohol and brain ethanol levels continued to rise. These authors suggested that the sensory properties of alcohol (e.g., scent, taste, intraoral sensation) associated with subsequent alcohol administration/intoxication are the sources of increased accumbal DA levels seen at the beginning of alcohol consumption. Likewise, in the 2003 Boileau study, subjects began drinking alcohol 30 minutes prior to scanning, at which time they also became aware of the drink's contents. If the properties of oral alcohol cause effects in humans similar those observed in Doyon and colleagues' work, it may have been the case that the intraoral sensory properties of alcohol raised ventral striatal dopamine levels high enough and long enough to produce a measurable decrease in RAC binding. Even if NAc [DA] tapered off after drinking (Doyon et al., 2003, 2005) and before the start of the PET scan, modestly elevated DA levels at the time of RAC injection may have been sufficient to cause a measurable decrease in RAC binding potential relative to the control scan. This possibility is supported by the fact that the measure of BP_{ND} is especially sensitive to early perturbations of endogenous dopamine (Morris et al., 1996; Yoder et al., 2004). Future studies are needed to further explore and reconcile these findings.

We detected unilateral effects in each prediction error condition. Asymmetries in human neurotransmitters (including dopamine) were first documented several decades ago (Glick et al., 1982), and asymmetries in rodent dopaminergic systems can have functional relevance at molecular and behavioral levels (e.g., Adrover et al., 2007; Besson and Louilot, 1995; Louilot and Le Moal, 1994). Particularly relevant to the present work is a study suggesting that the NAc dopaminergic response to appetitive odors is differentially lateralized as a function of the animal's conditioning history (Besson and Louilot, 1995). There are also a growing number of human studies reporting that the left and right dopaminergic systems subserve qualitatively different aspects of cognitive functions (Badgaiyan et al., 2007; Cheesman et al., 2005; Tomer and Aharon-Peretz, 2004; Tomer et al., 2008). Tomer and colleagues (2008) recently reported that motivated behavior is related to higher DA receptor availability in the left putamen relative to the right. This same group found that novelty-seeking was decreased in Parkinson's Disease patients who had initial left-side dopaminergic loss, but not in PD subjects with initial right-side DA loss. Badgaiyan and colleagues (2007) hypothesized that the anterior left caudate was responsible for detecting rule changes during an implicit learning task. Further study is required to determine if positive and negative prediction errors recruit hemisphere-specific dopaminergic circuitry consistently across populations and paradigms.

Although very little work exists on prediction error and addiction, both positive and negative prediction errors could conceivably contribute to development of alcohol addiction. Berridge suggests that increases in DA code incentive salience, or "wanting," the component of reward that motivates seeking and consumption (Berridge, 2007). Equally interesting is the manner in which prediction errors may drive excessive alcohol consumption (Lapish et al., 2006). For example, early

drinking experiences may be more rewarding than initially thought, creating the equivalent of a positive prediction error. With repeated drinking, and with the transition from alcohol abuse to addiction, the perceived reward value of alcohol may diminish from factors such as tolerance, effectively creating a negative prediction error. In the latter case, the perceived effects of alcohol do not match the effects expected from earlier experiences, and more alcohol is consumed in an attempt to reproduce the desired (“expected”) effects (Lapish et al., 2006). It is therefore possible that alcoholics code alcohol-related “prediction errors” differently than social drinkers, and that the relative strength of these signals mediates the destructive drinking behavior in alcoholism. The dopaminergic responses to prediction errors may constitute potential biomarkers that represent components of the neurochemical basis for alcohol addiction, and may be predictive of how likely individuals are to respond to treatment. Further research in both addicted and nonaddicted populations would be required to test such hypotheses.

There is an important consideration that could temper our interpretation that the decrease in DA we observed during the CUES condition is indicative of a negative prediction error. Specifically, we did not assess subjects' beliefs as to whether they had actually received alcohol during scanning, and the group data suggests a transient (although highly variable) change in subjective effects at the third time point of measurement (~12 minutes after cue exposure). Thus, we cannot rule out the contribution of a “placebo” effect (i.e., the errant belief that alcohol was being administered). However, this interpretation of a placebo effect runs counter to reports that placebo administration *increases* striatal DA concentration (de la Fuente-Fernandez et al., 2001, 2002; Kaasinen et al., 2004)—an effect *opposite* to what we observed during the CUES condition. Nevertheless, further study is indicated to better dissociate these phenomena.

Although none of our subjects were dependent drinkers, our sample was heterogeneous with respect to recent drinking and family history of alcoholism. We did not find any effects of drinking history on our results. However, it is possible that a larger sample would reveal relationships between drinking and the dopamine response to prediction error. As only 2 subjects had an *unambiguous* positive family history of alcoholism (see Table 1), we were unable to assess the effects of family history. Given that family history-positive subjects without alcoholism may possess protective factors in the dopamine system (Volkow et al., 2006a; but see Munro et al., 2006), it will be important to understand how dopaminergic responses to prediction error may differ across alcoholic and nonalcoholic subjects who vary according to family history.

To the best of our knowledge, this is the first report to provide in vivo human evidence that striatal dopamine concentration varies bi-directionally as a function of violations of reward expectation. Our results can be explained in the context of preclinical electrophysiological data which show that the firing rates of midbrain dopamine neurons change during prediction errors—errors which themselves may play a role in addiction by heightening differences between original reward experiences and a tolerance-driven inability to recapture that original experience (Lapish et al., 2006). The results of this study provide further rationale for using PET to study the dopaminergic signals associated with alcohol-related stimulus processing and learning in humans.

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