

Striatal Dopamine Release and Family History of Alcoholism

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Background: The offspring of alcohol-dependent individuals are at increased risk for alcoholism. The present study was designed to determine whether mesolimbic dopamine binding potential (BP), dopamine release, stress hormones, and subjective responses to intravenous amphetamine are different in nonalcoholic offspring from families with a history of alcohol dependence [family history positive (FHP)] than in nonalcoholic offspring without a family history of alcohol dependence [family history negative (FHN)].

Methods: Participants were 41 healthy men and women (11 FHP, 30 FHN; age range 18–29). After completing baseline psychiatric symptom and personality measures, striatal D₂/D₃ dopamine BP and dopamine release in response to an amphetamine challenge were measured with positron emission tomography (PET) using the D₂/D₃ dopamine (DA) receptor radioligand [¹¹C]raclopride. Binding potential was defined as B_{\max}/KD , percent change in BP from baseline defined dopamine release. During the scans, subjects rated the degree to which they were experiencing each of 10 possible drug effects. Plasma cortisol and growth hormone (GH) were also measured at scheduled intervals during the scans.

Results: Neither baseline BP nor dopamine release differed by family history. Similarly, subjective responses to amphetamine did not differ by a family history of alcoholism. Although both cortisol and GH increased following administration of amphetamine, these increases did not differ between family history groups.

Conclusions: Using amphetamine to provoke mesolimbic dopamine, we did not show significant differences in dopamine release, subjective responses, or stress hormone measures as a function of family history of alcoholism.

Key Words: Alcoholism, Family History, PET, Dopamine, Amphetamine.

THERE IS CLEAR evidence that a family history of alcoholism is a significant risk factor for the development of alcohol and other drug use disorders. Twin studies (Cloninger, 1988; Hrubec and Omenn, 1981; Kendler et al., 1992), adoption and cross-fostering studies (Cloninger, 1988; Merikangas, 1990), and pedigree analyses (Foroud et al., 2000; Leal and Heath, 1999) indicate that genetic factors exert a moderate to strong influence on the development of alcohol dependence for both men and

women. The awareness of genetic determinants for alcoholism stimulated a search for hormonal, neurobiological, and genetic markers that might identify individuals at increased risk for alcohol dependence (Begleiter et al., 1984; Hill et al., 1988; Schuckit and Smith, 1996; Wand et al., 1998). The family history of alcoholism research strategy compares nonalcoholic offspring from families with a high density of alcoholism (referred to as family history positive or FHP) with offspring from families with no history of alcoholism (family history negative or FHN). A variety of psychological and biological variables have been studied in sober FHP subjects, including body sway, perceptual-motor functioning, personality measures, school performance, verbal abilities, abstraction/conceptual reasoning, neurological, and biochemical measures.

Many people have tried alcohol or drugs at least once, but few develop addiction. Alcohol and drugs of abuse require a special vulnerable substrate to develop their abuse potential. Numerous studies have emphasized the interplay of genetic and environmental determinants in establishing this vulnerable substrate. Considerable evidence has emerged from preclinical studies suggesting that drugs of abuse act through mechanisms involving

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mesocorticolimbic dopamine pathways. A region in the ventral striatum, the nucleus accumbens, appears to be the key zone involved in the rewarding effects of drugs. Findings from preclinical studies have shown that psychostimulants, opioids, and alcohol all increase synaptic dopamine accumulation within this important brain region (Bonci et al., 2003; Doyon et al., 2003; Koob, 1992, 2003; Spanagel and Weiss, 1999; Wise, 1998). Preclinical studies have also shown that drug reward can be reduced or attenuated by pharmacological or genetic manipulations that alter mesolimbic dopamine neurotransmission (Liu and Weiss, 2002; Phillips et al., 1998; Samson and Hodge, 1993).

Positron emission tomography (PET) imaging has permitted observations originally made in rodent models to be translated to the human condition. A substantial body of evidence has accumulated in humans, indicating that drugs of abuse alter mesolimbic dopaminergic activity. With PET imaging, we and others have measured the effects of amphetamine, methylphenidate, and cocaine on dopamine neurotransmission (Oswald et al., 2005; Volkow et al., 1999). These studies have shown that mesolimbic dopamine release is correlated with positive subjective effects for the drug triggering dopamine release.

The aim of the present PET study was to determine whether there are differences in the striatal dopamine system between nonalcoholic offspring from families with alcohol-dependent individuals compared with nonalcoholic subjects without a family history of alcohol dependence.

METHODS

Forty-one healthy men and women, aged 18 to 29 years, were recruited for participation by newspaper advertisements and fliers posted in Baltimore-area communities. All participants provided written informed consent under the oversight of the Johns Hopkins School of Medicine Institutional Review Board. Subject assessment included a medical history and physical exam performed by a physician, complete blood count, comprehensive metabolic panel (including renal and hepatic function tests), electrocardiogram, urinalysis, alcohol breathalyzer test, and urine toxicology screen. Master's-level interviewers administered the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) to identify DSM-IV axis I psychiatric diagnoses, including past or current diagnoses of alcohol and drug abuse or dependence. Except for 1 subject who had a history of major depression (this subject was FHN), none of the subjects had a history of axis I disorder. Two subjects reported having tried various illicit drugs, but neither had ever met criteria for abuse or dependence. Three former cigarette smokers were included in the study: 2 of them last smoked 4 years before participation in the study, and the remaining subject last smoked 3 years before participation.

Subjects determined to be free of current axis I disorder were administered the Family History Assessment Module (FHAM; Rice et al., 1995). This module determines the number of first-, second-, and third-degree relatives who have demonstrated symptoms of selected psychiatric disorders and alcohol or drug abuse or dependence. Subjects designated as FHP reported their father and possibly other first/second-degree relatives as meeting criteria for alcohol dependence. In our sample, 11 individuals met this criterion; all had fathers who met criteria for alcoholism, and no subject reported a

history of alcoholism in their mother. Of the FHP subjects, 1 subject reported no other relative besides the father as meeting criteria for alcoholism. Of the remaining 10 FHP subjects, 4 had a single second-degree relative, 2 had 2 second-degree relatives, 1 had 3 second-degree relatives, 2 had 4 second-degree relatives, and 1 had 5 second-degree relatives in addition to their fathers. Subjects were categorized as FHN if no first-degree relative was reported to be alcohol dependent. Based on these criteria, 30 subjects were designated as FHN. Of these, 9 reported a history of alcoholism in only 1 second-degree relative. The remaining FHN subjects reported no family history of alcoholism in any first-degree or second-degree relatives. Analyses were conducted with and without the 9 subjects.

Alcohol use was assessed using the timeline follow-back method (Sobell and Sobell, 1992) for the 3 months before the screening interview. The average number of episodes of drinking per week and the average number of drinks per drinking episode were the variables of interest.

Exclusionary criteria included the following: (1) presence of DSM-IV axis I disorder; (2) treatment in the past 6 months with antidepressants, neuroleptics, sedative hypnotics, glucocorticoids, appetite suppressants, estrogens, or opiate or dopamine medications; (3) use of any medications within the past 30 days; (4) women currently using a hormonal method of birth control or hormone replacement therapy or currently pregnant or lactating; (5) medical conditions that might contraindicate the subject undergoing the study procedure, including history of seizure disorder or closed head trauma; (6) unable to provide clean urine drug screens at intake or during study participation; (7) report of drinking more than 30 alcoholic drinks per month or illicit drug use within the 30 days before participation; or (8) current smokers. Following screening procedures, eligible subjects were scheduled for admission to the Johns Hopkins General Clinical Research Center (GCRC) to complete the study.

Behavioral Measures

Baseline Measures. Measures of psychiatric symptoms, perceived stress, and personality dimensions were administered during the initial assessment interview to establish that the 2 study groups did not differ on variables that might be related to outcome measures. Measures that differed between the FHP and FHN groups were entered as covariates in subsequent analyses. These measures included the *State-Trait Anxiety Inventory* (STAI; Spielberger, 1983), *Brief Depression Inventory*, 2nd Edition (BDI-II; Beck et al., 1996), *Brief Symptom Inventory* (BSI; Derogotis and Melisaratos, 1993), *NEO-PI-R* (Costa and McCrae, 1992), *Perceived Stress Scale* (Cohen et al., 1983), *Life Experiences Survey* (LES; Sarason et al., 1978), and the *Combined Hassles and Uplifts Scale* (Lazarus and Folkman, 1989).

Subjective Drug Responses. At scheduled intervals—5 minutes before and 3, 6, 10, 15, 25, 55, and 85 minutes during the placebo and amphetamine PET scans—subjects rated verbally, on a 5-point scale (0 = least, 4 = most), the degree to which they were experiencing each of 10 possible drug effects. Positive effects included “high,” “rush,” “good effects,” “liking,” and “desire for drug.” Negative effects included “fidgety,” “anxious,” “dizziness,” “dry mouth,” and “distrust” (Bigelow and Walsh, 1998).

Magnetic Resonance Image Assessment and Mask Fitting

The magnetic resonance images (MRIs) were acquired with a spoiled gradient sequence (SPGR) with 1.5-mm-thick slices for anatomical identification of brain structures (see Volumes of Interest below) and a double echo (proton density and T2 weighted, 5-mm-thick slices) sequence used as a diagnostic scan. To minimize head motion during MRI acquisition and PET scanning, a thermoplastic facemask was molded for each subject before admission to GCRC.

PET Procedures and Data Acquisition

Subjects were admitted to the GCRC the day before the PET procedures. They were instructed not to ingest any alcohol, drugs, or over-the-counter medications for 48 hours before admission. Laboratory studies upon admission included a urine toxicology screen, alcohol breathalyzer test, hematocrit, electrolyte panel, and urine pregnancy screen for women. A calorie-controlled, caffeine-free breakfast was provided to subjects before the PET procedures. Beginning at 08:30 AM, subjects underwent 2 consecutive 90-minute PET scans with [¹¹C]raclopride. This radioligand is a benzamide antagonist at the D2 and D3 receptors, previously shown to be sensitive to stimulant-induced changes in brain dopamine concentration (Endres et al., 1997; Laruelle, 2000; Volkow et al., 1994).

A high-specific-activity intravenous bolus injection of approximately 18 mCi [¹¹C]raclopride was administered at the beginning of each scan. Subjects lay supine on the scanner table in a nonspecific baseline condition with their heads restricted with the thermoplastic mask. The first scan was preceded at -5 minutes by an intravenous injection of saline; the second scan was preceded at -5 minutes by 0.3 mg/kg amphetamine, each delivered over 3 minutes. The scanning image protocol consisted of up to 30 scan acquisitions in 3-D mode, starting from a 15-second duration and increasing to 6 minutes in length over a 90-minute period. Subjects were instructed to rest with their eyes closed during the scans. They were permitted to arise briefly after the first scan and were repositioned on the scanner table for the second. They were under continuous cardiovascular monitoring during the scans. All images, acquired on the 3D GE Advance whole-body PET scanner (GE Medical Systems, Waukesha, WI), were preceded by a 10-minute attenuation scan employing a rotating germanium-68 source. Each PET frame was reconstructed to 35 transaxial images of 128 × 128 matrices by a back-projection algorithm using the manufacturer-provided software and correcting for attenuation, scatter, and dead time. Positron emission tomography frames were coregistered to the frame taken at 20 minutes by means of the mutual information theory as implemented in SPM2 (Friston, 2002; Maes et al., 1997) to reduce head motions between frames (Martinez et al., 2003). Subjects were escorted back to the GCRC following the scans. They were evaluated by a physician before discharge from the unit.

Definition of Volumes of Interest

For statistical analyses, we defined 5 volumes of interest (VOIs): anterior putamen, posterior putamen, anterior caudate nucleus, posterior caudate nucleus, and ventral striatum (VS). The VOIs were defined for individual subjects on SPGR MRI volumes for the caudate nucleus and putamen bilaterally, and for the cerebellum using interactive segmentation software developed locally by one of the coauthors (H.K.). The software allowed users to select upper and lower MRI intensity thresholds to delineate the structure of interest such that manual drawing was required only to limit spatial boundaries of the structure when there was continuation of the within-threshold voxels to other structures. The software also allowed users to define VOIs in any of three orthogonal planes facilitating the inclusion of the whole structure in a VOI. The VS, which was indistinguishable on SPGR MRI volumes, was separated from the caudate and putamen VOIs using published anatomical guidelines (Baumann et al., 1999). The automated implementation of the guidelines has been previously reported (Oswald et al., 2005). To transfer VOIs that were defined on MRI space to PET space, MRI volumes were spatially aligned to the baseline and postamphetamine binding potential (BP) images, respectively, using information theory (Ashburner and Friston, 1997; Collignon et al., 1995; Kuwabara et al., 2004) as implemented in SPM2 software (Friston, 2002; <http://www.fil.ion.ucl.ac.uk/spm/software/SPM2/>). The individual transformation parameters were applied to transfer VOIs from MRI

space to spaces of baseline and postamphetamine BP volumes. The cutoff level of VOIs in PET spaces was set at 0.5 where the value of VOI voxels in the MRI spaces was set to 1 and for the remaining voxels was set to 0.

Modeling of PET Outcome Measures

[¹¹C]Raclopride D2-like receptor-specific binding was measured by $BP = B_{max}/KD$ (Wong, 2002). Binding potential was estimated via a simplified reference tissue model, using cerebellum as the reference tissue (Lammertsma and Hume, 1996). Because the cerebellum is nearly devoid of D2 and D3 receptors (Breier et al., 1997), specific binding of [¹¹C]raclopride is thought to be negligible in the cerebellum. Arterial blood was not sampled due to safety reasons and because it has been repeatedly demonstrated that amphetamine has no effect on radioactivity in the cerebellum for [¹¹C]raclopride (Breier et al., 1997; Martinez et al., 2003), even though amphetamine increases the blood-brain clearance of [¹¹C]raclopride (Price et al., 2002). Parametric BP images were generated after linear regression with a spatial constraint algorithm was used to fit the simplified reference tissue model to measure voxel kinetics (Zhou et al., 2003). The VOIs defined on MRI were transferred to PET images to obtain VOI BP values. The percent change in BP from baseline (i.e., the placebo scan) to the amphetamine scan was used to estimate dopamine release as $[(BP_{placebo} - BP_{amphetamine})/BP_{placebo}] \times 100$, with lower BP values during the amphetamine scan indicating greater levels of endogenous dopamine. It should be noted that although "dopamine release" is the term that is often used in the PET literature to describe amphetamine-induced changes in [¹¹C]raclopride BP, increases in dopamine concentrations that occur following amphetamine administration probably result from several different mechanisms, including dopamine reuptake blockade, reverse transport of dopamine through the dopamine transporter (Schmitz et al., 2001), as well as possible actions on endogenous opioid systems (Schad et al., 2002). Our use of the term "dopamine release," therefore, does not convey a full description of the mechanisms by which amphetamine can alter dopamine concentration.

Hormone Assays

Plasma concentrations of cortisol and growth hormone (GH) were obtained at baseline (-25 and -5 minutes) and at scheduled intervals (+15, +35, +55, and +75 minutes) during the scans. Cortisol concentrations were measured by radioimmunoassay (Diagnostic Products Corporation, Inc., Los Angeles, CA). Intraassay and interassay coefficients of variation were less than 10%. Plasma concentrations of GH were assayed by a 2-site IRMA (Nichols immunoradiometric assay). The intraassay coefficient of variation was 9.9%. Blood was collected for amphetamine measurement at 10, 20, 45, 55, and 85 minutes following injection of amphetamine. Plasma amphetamine levels were assessed by gas chromatography mass spectroscopy (Quest Diagnostics Lyndhurst, NJ).

Statistical Analysis

Demographic characteristics of FHP and FHN subjects were compared using *t*-tests or chi-square tests, as appropriate. Psychological symptom measures administered at baseline were compared using a series of *t*-tests, and differences between groups on these measures were entered as covariates in subsequent analyses. Multivariate analyses of covariance (MANCOVAs) were used to examine BP and dopamine release, with family history as the independent variable, BP or dopamine release in the 5 VOIs as the dependent variables, and baseline differences between the groups entered as covariates. Analog ratings of drug effect were examined by first identifying each subject's highest (peak) rating for each scale under the placebo condition and then under the amphetamine condition. To

adjust for nonnormal distribution, all peak values were square root transformed. Each peak value under the placebo condition was subtracted from the peak value under the amphetamine condition to obtain a "response." The 5 positive scales were highly correlated; therefore, a single "positive" score was derived by computing the mean of the 5 positive effects, and this measure was used in the analyses. The 5 negative scales were also highly correlated; a "negative" scale was thus calculated by computing the mean of the 5 negative scale responses. Multivariate analysis of covariance was used to compare FHP and FHN responses on the "positive" and "negative" scales. To further explore subjective responses, the "positive" and "negative" scales were correlated with dopamine release in the ventral striatum using Pearson correlations. Cortisol and GH were compared by subtracting the hormone level under the placebo condition at each time point from the hormone level in the amphetamine condition at each time point. The resulting "response" values were then compared in a MANOVA for repeated measures.

RESULTS

Demographics

Table 1 presents the means and standard deviations for the demographic characteristics of the sample. Although the overall sample was mixed in race and sex, FHP and FHN subjects did not differ significantly in age, sex distribution, race, body mass, or education. Further, the age range of the FHN group (18–29 years) and the FHP group (18–28 years) did not differ. FHP subjects drank more alcohol per drinking episode than FHN subjects.

Psychological Measures

Mean scores and standard deviations of mood assessments and measures of distress are shown in Table 2. FHP subjects scored higher on a measure of state anxiety (STAI). There was also a trend toward greater trait anxiety (STAI), symptoms of depression (BDI), and distress related to psychiatric symptoms (BSI) among FHP subjects compared with FHN subjects.

Table 1. Subject Demographics

	FHP	FHN	<i>t</i> or χ^2	<i>p</i>
Sample size	11	30		
Sex, M:F	7:4	20:10	0.033	0.856
Age (SD)	21.7 (2.8)	21.9 (3.1)	0.130	0.897
Race, no. (%)			4.007	0.405
Caucasian	7 (63.6)	18 (60.0)		
African American	4 (36.4)	5 (16.7)		
Asian	0 (0.0)	5 (16.7)		
Hispanic	0 (0.0)	1 (3.3)		
Other	0 (0.0)	1 (3.3)		
BMI, mean (SD) (kg/m ²)	24.8 (3.3)	24.1 (2.9)	−0.658	0.514
Education (SD) y	14.5 (1.8)	14.7 (1.9)	0.369	0.714
Drinking episodes per week (SD)	1.0 (0.7)	0.6 (0.6)	−1.705	0.100
Drinks per drinking episode (SD)	4.3 (1.8)	2.5 (2.2)	−2.404	0.021

FHP, family history positive; FHN, family history negative; BMI, body mass index.

Table 2. Mood and Personality Assessments

	FHP	FHN	<i>t</i>	<i>p</i>
Sample size	11	30		
Trait Anxiety (STAI)	34.9 (11.1)	28.9 (7.0)	−1.894	0.066
State Anxiety (STAI)	33.4 (7.8)	26.7 (6.6)	−2.467	0.018
Depression (BDI)	4.7 (4.9)	2.2 (3.0)	−1.878	0.068
Global Severity Index (BSI)	0.3 (0.3)	0.2 (0.2)	−1.983	0.054
NEO factor				
Neuroticism	49.3 (11.5)	42.8 (5.6)	−1.812	0.095
Extraversion	51.9 (6.0)	49.7 (7.2)	−0.872	0.389
Openness	55.2 (9.0)	54.3 (9.8)	−0.281	0.780
Agreeableness	45.7 (10.4)	48.9 (9.0)	0.972	0.337
Conscientiousness	49.0 (7.5)	54.4 (8.8)	1.806	0.079
Perceived Stress Scale (PSS)	12.4 (6.0)	12.1 (6.9)	−0.094	0.926
Hassles Frequency/Severity (H-U)				
Items	15.4 (4.5)	18.0 (8.5)	0.841	0.407
Mean	1.3 (0.3)	1.3 (0.4)	−0.290	0.774
Negative Events/Severity (LES)				
Items	2.3 (1.2)	2.9 (2.8)	0.853	0.400
Mean	1.5 (0.7)	1.4 (0.4)	−0.093	0.926

Note: Except for sample size, all variables are presented as mean (standard deviation). All degrees of freedom = 39.

FHP, family history positive; FHN, family history negative; STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; H-U, Combined Hassles and Uplifts Scale; LES, Life Experiences Survey.

Dopamine Binding and Release

Figure 1 illustrates D2 receptor availability during the placebo and amphetamine challenge. The mean volumes of striatal VOIs were 5.2 ± 0.8 , 5.5 ± 0.8 , 5.6 ± 0.9 , 1.5 ± 0.6 , and 1.8 ± 0.7 mL for anterior and posterior putamen, anterior and posterior caudate nucleus, and ventral striatum, respectively, for the FHN group and 5.1 ± 0.5 , 5.3 ± 0.7 , 5.8 ± 0.5 , 1.6 ± 0.3 , and 2.0 ± 0.9 mL for the FHP group in the respective subdivisions. There were no significant differences in VOI volumes between the 2 groups.

Mean BP and dopamine release in each of the 5 VOIs, along with standard deviations, are presented in Table 3. No significant family history differences in baseline BP ($F_{5,35} = 0.458$, $p = 0.804$) or dopamine release ($F_{5,35} = 0.584$, $p = 0.712$) in any of the 5 striatal brain regions were observed (Table 3). After controlling for family history differences on measures of anxiety (STAI), severity of distress related to psychiatric symptoms (BSI), and alcohol consumption, the results were unchanged for BP and dopamine release, respectively ($F_{5,32} = 0.273$, $p = 0.924$; $F_{5,32} = 0.584$, $p = 0.712$). To determine whether potential differences might have been obscured by some of the FHN subjects ($n = 9$) having alcoholism in a second-degree relative, the analyses were repeated without these subjects. The results did not change for BP ($F_{5,23} = 0.724$, $p = 0.612$) or for dopamine release ($F_{5,23} = 0.728$, $p = 0.610$). Plasma amphetamine concentrations obtained at 10, 20, 45, 55, and 85 minutes following the injection of amphetamine did not differ by family history.

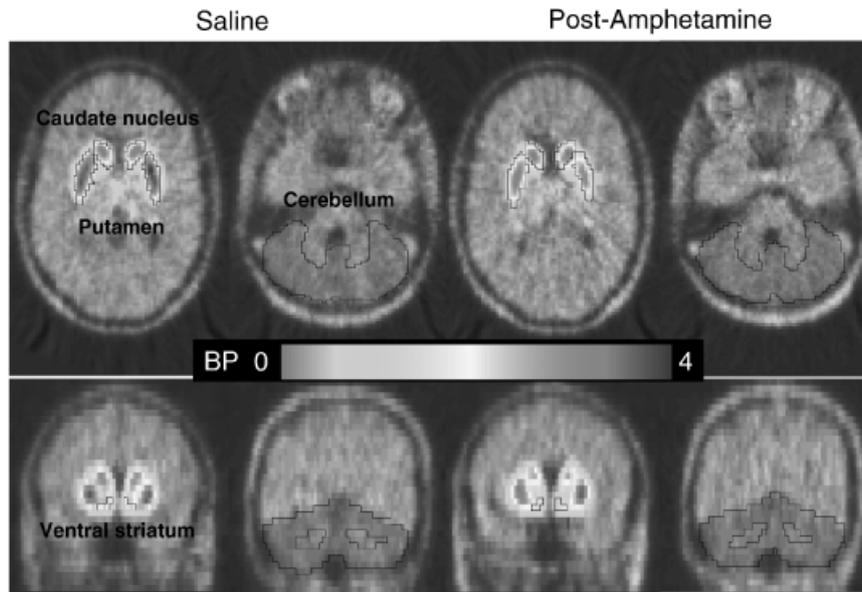


Fig. 1. Representative transaxial (*top row*) and coronal images (*bottom row*) of parametric binding potential (BP) volumes, baseline saline (*left panel*) and postamphetamine (*right panel*) scans taken from one subject. Outlines of volumes of interest for the caudate nucleus, putamen, and ventral striatum are shown. Color scale bar indicates voxel BP values that can assume negative values in cerebrospinal fluid space and outside the brain.

Subjective Drug Effects

Subjects’ verbal ratings of the degree to which they were experiencing positive and negative drug effects in response to amphetamine did not significantly differ by family history of alcoholism ($F_{5,38} = 1.415, p = 0.255$). As we have previously shown in a smaller sample (Oswald et al., 2005), there was a correlation between positive ($r = 0.362, p = 0.010$), but not negative ($r = 0.248, p = 0.059$), subjective effects and dopamine release in the ventral striatum. Examination of the individual positive scales revealed that subjects’ ratings of “good effects,” “liking,” and “desire for drug” correlated with dopamine release. Separating the sample by family history status revealed that this correlation was driven by participants without a family history of alcoholism. Specifically, for FHN subjects, three of the

positive scales, “rush” ($r = 0.401, p = 0.014$), “liking” ($r = 0.396, p = 0.015$), and “desire for drug” ($r = 0.474, p = 0.004$), were correlated with dopamine release in the ventral striatum, whereas for FHP subjects none of the scales correlated with dopamine release in the ventral striatum.

Cortisol and GH

Measurements of plasma cortisol and GH obtained at baseline and during the scans reflected a main effect of time, indicating an increase in both hormones following administration of amphetamine ($F_{5,175} = 15.365, p < 0.0001$ for cortisol; $F_{5,165} = 2.684, p = 0.023$ for GH). These increases did not, however, differ significantly between family history groups ($F_{1,35} = 0.087, p = 0.770$ for cortisol; $F_{1,33} = 2.444, p = 0.127$ for GH).

Table 3. Binding Potential and Dopamine Release for Each Brain Region by Family History

	FHP	FHN	F	p
Sample size	11	30		
Binding potential				
Anterior putamen	3.15 (0.29)	3.05 (0.31)	0.791	0.38
Posterior putamen	3.16 (0.31)	3.08 (0.40)	0.361	0.55
Anterior caudate nucleus	2.73 (0.27)	2.63 (0.30)	0.963	0.33
Posterior caudate nucleus	2.02 (0.42)	1.87 (0.34)	1.382	0.25
Ventral striatum	2.15 (0.32)	2.10 (0.27)	0.188	0.67
Dopamine release				
Anterior putamen	11.73 (4.89)	11.08 (6.32)	0.095	0.76
Posterior putamen	19.50 (3.49)	19.03 (6.85)	0.045	0.83
Anterior caudate nucleus	3.99 (4.10)	5.42 (6.00)	0.527	0.47
Posterior caudate nucleus	7.24 (4.37)	8.17 (7.74)	0.140	0.71
Ventral striatum	10.32 (5.90)	9.94 (5.75)	0.034	0.85

Note: Except for sample size, all variables are presented as mean (standard deviation).
FHP, family history positive; FHN, family history negative.

DISCUSSION

Considerable evidence has emerged from preclinical studies suggesting that drugs of abuse act through mechanisms involving mesocorticolimbic dopamine pathways. Human PET studies indicate that alcohol and psychostimulants alter dopaminergic activity in the ventral striatum and that the magnitude of dopamine release within this brain region correlates with subjective effects to the drug (Oswald et al., 2005; Volkow et al., 1999). The ventral striatum houses the nucleus accumbens, a proposed center of reward, reinforcement, and/or salience for many drugs of abuse (Goeders et al., 1984; Ikemoto et al., 1997; Kurumiya and Nakajima, 1988). It is important to know whether this neural substrate is different in individuals at increased risk for alcoholism before the onset of heavy

drinking. In support of this idea, studies in rodents have reported a decrease in D₂ receptor density in the caudate–putamen and nucleus accumbens of alcohol-preferring rats compared with non–alcohol-preferring rats (McBride et al., 1993). Furthermore, lower dopamine concentrations in the mesolimbic terminals have also been measured in alcohol-preferring compared with alcohol-nonpreferring rodents (Murphy et al., 1982). Previous imaging studies in alcohol-dependent human subjects have reported a decrease in D₂ receptor availability (Heinz et al., 2004) and in dopamine release (Martinez et al., 2005). However, no human study has assessed the mesolimbic dopamine system in high-risk individuals before the onset of heavy drinking.

Alcohol dependence is a complex behavioral disorder with polygenic and environmental determinants (Farren and Tipton, 1999). A family history of alcoholism is one of the more robust risk factors for the development of alcohol use disorders (Hesselbrock and Hesselbrock, 1992). In this study, we employed a well-validated PET imaging procedure to compare the striatal dopamine measures, subjective responses, and stress hormone responses to intravenous amphetamine in social drinking individuals with and without a family history of alcohol dependence. The study failed to show a significant effect of family history of alcoholism on striatal BP and amphetamine-induced dopamine release using the D₂/D₃ dopamine (DA) receptor radioligand [¹¹C]raclopride. Five striatal brain regions were studied, including the ventral striatum which houses the nucleus accumbens. We also failed to observe a family history effect on subjective responses to amphetamine or stress hormone levels. Furthermore, even when analyses were corrected for differences between subjects with and without a family history of alcoholism—number of alcoholic drinks per episode, state anxiety, and level of distress related to psychiatric symptoms—the results did not change.

Several factors may account for the negative findings reported here. It is possible that there are no significant family history differences in the particular measures of striatal dopamine assessed by this PET technique. This would not preclude the possibility that other dopaminergic measures of reinforcement *do* differ as a function of family history of alcoholism. It is also possible that to detect differences in dopamine measures by a family history of alcoholism it will require alcohol administration and not other medications that also provoke mesolimbic dopamine. Potential risk factors for alcohol use disorders include neurobiological substrates that are generally expressed and do not occur solely in the presence of alcohol (e.g., P300 wave; Begleiter et al., 1984; Hill et al., 1988; Steinhauer et al., 1987; Whipple et al., 1988). Conversely, risk factors may be specific to alcohol or other drugs and may come into play only when a drug has been ingested. For example, family history differences related to mesolimbic reward or reinforcement value of alcohol may not

necessarily generalize to other psychoactive drugs that also perturb mesolimbic dopamine.

Previous studies have revealed family history differences in subjective responses to the effects of alcohol (Evans and Levin, 2003; Lex et al., 1994; Schuckit et al., 2000). We hypothesized that subjective responses to amphetamine might likewise differentiate subjects with and without a family history of alcoholism. At least 1 study (Holdstock and deWit, 2001) found a correlation between the subjective effects of alcohol and amphetamine. Contrary to our prediction, we did not find any significant differences in the subjective effects of amphetamine in FHP compared with FHN subjects. A potential explanation for the lack of family history effect in our study might be the use of amphetamine rather than alcohol. Previous research supports this notion. Kouri et al. (2000) found no family history effect on subjective responses to cocaine. A study by McCaul et al. (1990) found that the effect of family history was reduced when subjects were given secobarbital rather than alcohol.

The influence of family history in subjective responses to alcohol compared with other drugs is complicated by findings of a sex difference in the effect of family history status on subjective responses to drugs other than alcohol. Whereas family history appears to confer a similar effect on subjective responses to alcohol in men and women (Eng et al., 2005; Schuckit et al., 2000), this finding might not generalize to amphetamine. A recent study by Gabbay (2005) found that although men who were FHP had greater subjective responses to amphetamine than those who were FHN, this effect of family history was not observed in women. That study, however, used oral administration of amphetamine; thus whether those results would apply to intravenous amphetamine is unclear. The present study was not designed to investigate the interaction between sex and family history and lacked the power to do so definitively. When we explored this issue by stratifying the sample by sex, we found that the family history groups did not differ in BP or dopamine release for men or women. Future studies with larger subjects will be able to examine this issue.

We and others have previously reported a correlation between dopamine release in the ventral striatum and positive subjective responses to psychostimulants (Oswald et al., 2005; Volkow et al., 1999). In the current study, we again found that positive, but not negative, subjective responses were correlated with dopamine release in the ventral striatum. Further, we found this association in only the FHN subjects; no significant correlation between any of the positive subjective responses to amphetamine and dopamine release in the ventral striatum was observed in the FHP subjects. Whether this is due to a true family history difference, or simply due to the small number of FHP subjects, cannot be determined. Therefore, it is imperative that these findings be replicated and also to determine whether there is dissociation between dopamine

release and subjective responses to amphetamine in FHP subjects. If this were the case, it would be important to understand the mechanism underlying the effect and also to determine if the dissociated response is related to risk of substance abuse disorders.

The third finding in our study was no significant family history differences in the degree to which cortisol and GH responded to amphetamine. This finding is in contrast to previous studies that have shown a family history effect on cortisol responses to several activators of the hypothalamic–pituitary–adrenocortical (HPA) axis. Prior work has detected these differences with the use of opioid receptor antagonists (naloxone and naltrexone), alcohol, and psychological stressors rather than amphetamine (Gianoulakis et al., 1989; Hernandez-Avila et al., 2002; King et al., 2002; Schuckit et al., 1987; Uhart et al., 2004; Waltman et al., 1994; Zimmermann et al., 2004). Although amphetamine is a robust activator of the HPA axis, we did not observe any significant family history differences on cortisol or GH in response to amphetamine.

This study had several strengths. First, it represents one of the larger PET studies using the radioligand [^{11}C]raclopride to measure BP and dopamine release. Second, our participants were well characterized on psychological measures. Third, we examined 3 responses to amphetamine. Results derived from all 3 measures—dopaminergic, subjective, and hormonal—converged on the conclusion that a family history of alcoholism has no effect on response to amphetamine.

Despite its strengths, there are several limitations to this study. First, although the overall number of participants was large relative to other studies using PET, the number of subjects with a family history of alcoholism was small. It is possible that a larger number of FHP subjects will be required to detect an effect of family history in response to amphetamine. However, given the estimated effect size of 0.099 (Pillai's Trace) for the MANOVA concerning dopamine release, the number of subjects required to find a significant difference is quite large ($n = 1,328$). Thus, if this small effect size is accurate, the possibility for a type II error is remote. However, replication is required to be certain of our findings. Similarly, although subjects classified as FHP had moderately strong family histories of alcoholism, it is possible that individuals with multigenerational family histories of alcoholism would reveal a family history effect. Although a family history of alcoholism confers increased risk for alcohol use disorders, not all FHP individuals succumb to alcohol abuse/dependence. It is possible that our group of FHP persons was not enriched with subjects carrying the genetic burden for alcohol use disorders, thus minimizing the possibility of detecting differences in mesolimbic dopamine release as a function of family history. It might also be of significance that none of the FHP subjects had mothers with alcoholism. Whether we might have observed differences in dopamine release as a function of family history status

had we included subjects whose mothers were alcoholic is unknown. Second, FHP subjects consumed more alcohol per episode of drinking than those without a family history of alcoholism. Neither number of drinks per episode nor number of episodes of drinking per week correlated with any of the outcome measures, nor did the results change when drinking scores were entered into the model as a covariate. However, we cannot be certain that differences in the amount of alcohol consumed might have obscured potential differences between the groups. Third, due to the potential carryover effects of amphetamine on dopamine release, the placebo scan always preceded the amphetamine scan. It is therefore possible that order effects, such as the effect of novelty, on dopamine release might have obscured family history differences. Although it might be argued that order effects also concern the possibility that raclopride could alter dopamine transmission, the dose of raclopride used in this study is a nonpharmacological dose of less than 10 $\mu\text{g}/70$ kg of body weight. Used in this way as a tracer, rather than as a therapeutic agent, it would be very unlikely to affect dopaminergic transmission. Similarly, the environment of the PET scanner suite, where the scans occurred, might have altered the response to amphetamine such that family history differences were not apparent. Fourth, although caffeine intake was controlled by providing all subjects with a caffeine-free meal on the morning of the scan, we did not collect data on typical caffeine consumption. Therefore, the potential effects of caffeine withdrawal on the association between amphetamine and dopamine release could not be assessed.

In summary, this study found no significant effect of a family history of alcoholism on dopamine release, subjective effects, or hormone responses to intravenous amphetamine. Future studies including a larger number of subjects and/or those with stronger family histories of alcoholism will be important in determining if having a family history of alcoholism is related to an altered response to stimulant drugs.

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