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Family history of alcoholism is related to increased D2/D3 receptor binding potential: a marker of resilience or risk?

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Abstract

Background—The aim of this study was to examine the relationship between family history of alcohol use disorder and striatal dopamine using positron emission tomography (PET) imaging.

Methods—Participants were 84 healthy, 18–30 year old, social drinkers recruited via fliers and newspaper advertisements. At assessment, participants completed measures of lifetime personal and family substance use and psychiatric symptoms. Participants underwent two consecutive PET scans using the D2/D3 dopamine (DA) receptor radioligand [^{11}C]raclopride. Scans were preceded by intravenous saline and amphetamine 0.3mg/kg, providing measures of baseline [^{11}C]raclopride

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Author Contributions:

MM and GW were responsible for the study concept and design. AA completed preliminary analyses and wrote the initial manuscript draft. XX completed data analyses. MM, GW, HK and DW provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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binding potential (BP_{ND}) and change in [^{11}C]raclopride (ΔBP_{ND}). Subjective ratings of stimulant drug effects were collected during scans. Subjects were classified as family history positive (FHP) if they reported any first degree relative with alcohol use disorder (AUD) and family history negative (FHN) if no first degree relatives had history of AUD.

Results—Participants were predominantly White (69.0%) and male (62.1%). Baseline [^{11}C]raclopride BP_{ND} was generally higher in FHP compared with FHN subjects across striatal subdivisions. There were no differences in ΔBP_{ND} across regions. Negative subjective drug effects were more pronounced in FHP than FHN subjects. While FHN subjects evidenced the expected positive relationship between ΔBP_{ND} and positive subjective drug effects, this relationship was disrupted in FHP subjects.

Conclusion—There are key differences in DA status and subjective stimulant drug experiences as a function of family AUD history. These findings have important implications for understanding risk for AUD development in FHP offspring.

Keywords

family history; mesolimbic dopamine; positron emission tomography (PET); alcohol use disorder; amphetamine; dopamine release

Introduction

Alcohol use disorders (AUD) are common and contribute substantially to global disease burden (Hasin et al., 2007, Rehm et al., 2009). A family history of alcoholism is associated with increased likelihood of AUD development in offspring, with genetic factors conferring 50–60% of risk (McGue, 1999, Schuckit, 2009). Yet, exact mechanisms underlying this increased risk are complex, multifactorial and largely undetermined.

Preclinical and human studies have demonstrated that psychoactive substances, including alcohol, stimulants and opioids, increase dopamine concentrations in the striatum (Chiara and Imperato, 1988, Leshner and Koob, 1999, Boileau et al., 2003, Martinez et al., 2003, Volkow et al., 2004, Pierce and Kumaresan, 2006, Constantinescu et al., 2008, Spreckelmeyer et al., 2011), a key factor in rewarding effects of abused substances. Moreover, the dorsal striatum provides circuitry that consolidates habit-based learning, a form of cognition often more pronounced in persons with substance use disorders (Smith and Graybiel, 2014). In healthy young adults, baseline dopamine (DA) D2 receptor availability in the nucleus accumbens was positively correlated with subjective scores of intoxication following alcohol administration (Yoder et al., 2005). In alcohol dependent persons compared to healthy controls, multiple studies have demonstrated lower levels of dopamine receptor availability and dopamine release (Hietala et al., 1994, Volkow et al., 1996, Heinz et al., 2004, Martinez et al., 2005), changes that persist following detoxification (Volkow et al., 2002b, Volkow et al., 2007).

These differences in baseline dopamine receptor availability and release may predate development of alcohol misuse, and contribute to risk for AUD development. Genetic studies have identified associations between dopamine receptor D2 gene polymorphisms and alcohol dependence. The Taq1A polymorphism is among the most widely studied. While

there is inconsistency in individual studies, meta-analyses have confirmed a modest increased risk of alcohol dependence (OR 1.20 −1.38) associated with the A1 allele (Munafo et al., 2007, Smith et al., 2008, Le Foll et al., 2009).

Yet, findings on the relationship between family history of alcoholism and DA D2 receptor levels are inconsistent. Using positron emission tomography (PET) imaging with [^{11}C]raclopride, Volkow and colleagues (Volkow et al., 2006) found higher levels of baseline DA D2 receptors in caudate and ventral striatum of nonalcoholic participants with a high density of alcoholism in their families (i.e., father and at least two second-degree relatives) compared to subjects with no first or second degree alcoholic relatives. In contrast, using similar PET procedures, Munro and colleagues (Munro et al., 2006a) found no association between family history and baseline DA D2 binding potential or amphetamine-induced change in dopamine receptor binding potential (ΔBP_{ND}) on PET imaging; however, family history status was more variable in this study. Recently, using PET imaging with [^{11}C]raclopride, Casey and colleagues reported decreased amphetamine-induced ΔBP_{ND} in multigenerational family history positive (FHP) young adults with extensive personal histories of alcohol and drug use compared to both drug naïve and drug exposed family history negative (FHN) controls (Casey et al., 2013).

This study used [^{11}C]raclopride to explore the relationship between family history of AUD and striatal dopamine at baseline and following amphetamine administration in FHP compared with FHN young adults, with very limited alcohol and drug exposure. Our sample includes participants from the 2006 Munro study, but the current sample more than doubles the original report. This expanded sample allows us to refine the definition of FHP, provides increased power to detect differences as well as the opportunity to explore potential associations between striatal dopamine and subjective responses to amphetamine.

Materials and Methods

Participants

Participants were 84 healthy young adults, ages 18–30, recruited via fliers and newspaper advertisements in the Baltimore area. Study exclusion criteria included: a current Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) axis I disorder (American Psychiatric Association, 2000); drinking greater than 30 standard alcohol drinks per month; past 30-day illicit drug use; positive urine drug screen or alcohol breathalyzer at time of initial assessment or day of study procedures; reported maternal alcoholism; a medical condition prohibiting completion of study procedures; use of any medications in the past 30 days; or past 6-month treatment with antidepressant, appetite suppressant, dopamine, glucocorticoid, estrogen, neuroleptic, opiate or sedative hypnotic medications. Additionally, women who were pregnant, lactating, or using hormonal birth control or hormone replacement medications were excluded. The study was approved by the Johns Hopkins University Institutional Review Board; all participants provided written informed consent.

Assessments

Participants were screened by telephone for preliminary study inclusion criteria and subsequently scheduled for an in-person assessment, including medical history, physical examination and collection of standard laboratory and diagnostic studies. Master's-level interviewers administered The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; (Bucholz et al., 1994)) to determine the absence or presence of DSM IV axis I disorders in the proband. Participants also completed the Perceived Stress Scale (Cohen et al., 1983) as part of the assessment battery.

Family history of AUD in 1st and 2nd degree relatives was first assessed using the Family Tree Questionnaire (FTQ (Mann et al., 1985)). For all first or second degree relatives scored 3 (suspected) or 4 (definite) on the FTQ, the proband provided additional information on specific alcohol-related problems using the Family History Assessment Module (FHAM) for alcohol (Rice et al., 1995). FHAM responses were used to classify relatives for alcohol abuse and or dependence.

Participants were classified as family history positive (FHP, N=24) if they reported an AUD history (abuse and/or dependence) in at least one first degree relative (father or sibling). Of these, 21 (87.5%) had a father with an AUD, with a mean number of affected first degree relatives of 1.3 (SD 1.27). Though they did not contribute to the classification of FHP, we also examined the number of affected second degree relatives (grandparents, aunts and uncles). Amongst the 24 participants, there was a total of 45 2nd degree relatives with an AUD, with a mean of 1.9 (SD 1.45). Overall, the mean number of 1st and 2nd degree relatives with an AUD in the FHP group was 3.1 (SD 1.39).

All other participants were classified as FHN (N=60); thus, FHN participants could report an AUD in a 2 degree relative. We also conducted sensitivity analyses examining only those FHN subjects with no first or second degree affected family members (N=30).

Procedures

MRI Magnetic Resonance Image Assessment and Mask Fitting, PET Scanning Procedures, Data Acquisition and Volumes of Interest—Detailed magnetic resonance image (MRI) assessment and mask fitting, PET scanning and data acquisition procedures have been described previously (Oswald et al., 2005, Munro et al., 2006a) and are provided in Supplement 1. Briefly, MRI images were obtained using a spoiled gradient sequence (SPGR) for anatomical identification of brain structures. Participants were instructed not to ingest alcohol, drugs or over-the-counter medications for 48 hours prior to admission and were admitted the day before PET procedures. After a calorie-controlled, caffeine-free breakfast, PET images were acquired on the 3D GE Advance whole-body PET scanner (GE Medical Systems, Waukesha, WI). After a 10-minute attenuation scan employing a rotating germanium-68 source, participants underwent 2 consecutive 90-minute PET scans with [^{11}C]raclopride, a benzamide antagonist at the DA D2 and D3 receptors, which has previously been shown to be sensitive to stimulant-induced changes in brain dopamine concentration (Volkow et al., 1994, Endres et al., 1997, Laruelle, 2000). The first scan was preceded at −5 minutes by an intravenous saline injection; the second scan was

preceded at −5 minutes by 0.3 mg/kg amphetamine 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 5 minutes in length over the 90-minute period. Participants were under continuous cardiovascular monitoring during scans.

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. PET frames were coregistered to the frame taken at 20 minutes by means of the mutual information theory as implemented in SPM2 (Maes et al., 1997, Friston and Penny, 2003) to reduce head motions between frames.

For statistical analyses, we defined six volumes of interest (VOIs): anterior and posterior putamen (aPU and pPU), anterior and posterior caudate nucleus (aCN and pCN), right and left ventral striatum (RtvS and LtvS). Based on prior research showing left and right striatal asymmetry (Larisch et al., 1998), separate analyses were conducted for the right and left hemispheres of the ventral striatum. Binding potential (BP_{ND}) and change in binding potential (ΔBP_{ND}) were measured in each VOI.

Modeling of PET Outcome Measures—BP_{ND} (Innis et al., 2007) was estimated via the simplified reference tissue model with 2 parameters (SRTM2) (Lammertsma and Hume, 1996, Wu and Carson, 2002) and the multilinear reference tissue method (MRTM2) (Ichise et al., 2003) using cerebellum as the reference tissue (Lammertsma and Hume, 1996). Specific binding of [^{11}C]raclopride is thought to be negligible in the cerebellum because the cerebellum is nearly devoid of DA D2/D3 receptors (Breier et al., 1997). The VOIs defined on MRI were transferred to PET images to obtain time-activity curves of regions. ΔBP_{ND} was estimated as the percent change in BP from the placebo scan to the amphetamine scan ($[(BP_{placebo}-BP_{amphetamine})/BP_{placebo}] \times 100$), with lower BP values during the amphetamine scan indicating greater levels of endogenous dopamine. Although release of endogenous dopamine is thought to be the biggest factor contributing to amphetamine-induced changes in [^{11}C]raclopride BP, “dopamine release,” the term typically used in the PET literature, probably results from several different mechanisms, which also include 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). Therefore, we use the term ΔBP_{ND}.

Drug Assays and Subjective Drug Effects—In a subset of participants, blood was collected for amphetamine measurement at 15, 25, 55, 85 and 90 minutes following amphetamine injection. Plasma amphetamine levels were assessed by gas chromatography mass spectroscopy (Quest Diagnostics Lyndhurst, NJ).

On a 5-point visual analog scale (VAS; 0=least and 4=most), participants verbally rated the extent to which they were experiencing each of 10 stimulant drug effects. VAS ratings were collected 5 minutes before and 3, 6, 10, 15, 25, 55, and 85 minutes during the placebo and amphetamine PET scans. First, each participant’s peak value across time points was identified for each item. Then a factor analysis on peak scores was performed to reduce the dimension of the data and to uncover underlying causes or factors. Using the iterated

principal factor method, the analysis based on 9 items yielded a positive (high, rush, good effect, liking, desire for drug) and negative factor (anxious, dizziness, dry mouth, distrust); the item fidgety did not clearly load on either factor and was excluded. Factor scores are a latent continuum ranging from approximately −3 to +3. In our sample, the calculated factor scores ranged from −2.1 to 2.8.

Statistical Analyses

Demographic and baseline characteristics of FHP and FHN subjects were compared using chi-square or Fisher's exact tests for categorical variables and t-tests or a non-parametric equivalent method for continuous variables. For the six selected VOIs, separate ANCOVA models were constructed to examine the relationship between AUD family history and placebo BP_{ND} and ΔBP_{ND}. We have previously reported significant sex effects on ΔBP_{ND} (Munro et al., 2006b), and so included sex as a covariate in analyses. Past 90-day binge drinking status (binge vs. no binge; binge defined as > 3 standard drinks for female and > 4 standard drinks for male subjects) also was added to the model as a covariate as there was a trend of a higher likelihood of baseline binge drinking in FHP vs FHN subjects. Adaptive Holm procedure (Q) was used to correct p values for multiple comparisons over the six VOIs (Hochberg and Benjamini, 1990). Finally, we conducted sensitivity analyses and repeated the models using a more stringent definition of FHN in which no first or second degree relative was classified with AUD (N=30).

We also examined subjective drug effects as a function of family history status. We compared positive and negative factor scores for FHN and FHP participants using ANCOVA models. Again sex and baseline binge status were added to the models as covariates, and the adaptive Holm procedure was used for multiple comparison correction.

Finally, we examined the relationship between ΔBP_{ND} and subjective factor scores as a function of family history status, adjusting for sex and baseline binge drinking status. All analyses were performed using SAS 9.3.

Results

Baseline Characteristics

Overall, participants were in their early twenties (mean age 22.8 years, SD 3.14), predominantly White (69.0%), majority men (60.7%), and had greater than a high school education (mean years 14.8, SD 1.78) (see Table 1). There were no demographic differences between FHP and FHN participants. More than half of participants (58.3%) reported at least one episode of binge drinking in the previous 90 days. Three-quarters (75.0%) of the FHP participants reported at least one binge drinking episode during the past 90 days compared to 51.7% of FHN subjects; however, this difference just failed to achieve statistical significance (p=0.050). Seven of 84 participants (8.3%) reported smoking more than 100 cigarettes in their lifetime, of which five were FHN and two were FHP. The mean duration of smoking for these 7 participants was 22.7 months. Four of the seven (4.8% of the total sample), were current smokers; three FHN and 1 FHP. There were no family history differences in mean lifetime or current measures of smoking exposure. With respect to drug use, FHP were more

likely than FHN participants to report ever using marijuana (78.3% vs. 43.1%, p = 0.004). There was no family history difference in the number of subjects who reported > 21 episodes of marijuana use in the past year; mean use was 2.16 times for FHN and 0.57 for FHP subjects. There were no other differences in lifetime or past year drug use between FHP and FHN participants.

Dopamine Binding Potential (BP_{ND})

After confirming that SRTM2 and MRTM2 yielded essentially identical BP_{ND} values (SRTM2 = 1.0·MRTM2 − 0.009; R^2 >0.999; using data from all scans), BP_{ND} values given by MRTM2 were used in further analyses. In general, FHP participants had a higher mean BP_{ND} than FHN participants across VOIs (Table 2, upper section). The difference was statistically significant in the pCN (2.32 (0.077) vs. 2.14 (0.047), Q = 0.043) and the RtvS (2.35 (0.061) vs. 2.17 (0.037), Q = 0.017).

Using the more stringent definition of FHN in which no first or second degree family member was classified with AUD, results were similar. FHP participants had higher BP_{ND} across brain regions compared with FHN subjects. Differences were significant in the aPU (3.39 (0.064) vs. 3.21 (0.054), Q=0.039), and the RtvS (2.36 (0.067) vs. 2.12 (0.057), Q=0.012), and there was a trend in the pCN (2.31 (0.083) vs. 2.13 (0.070), Q=0.097). Stratified analyses by gender (not shown) for both the main and sensitivity analyses suggest that the significant findings were attributable to baseline differences in men rather than women.

Change in Dopamine Binding Potential (ΔBP_{ND})

Area under the amphetamine plasma curves were analyzed in a subset of participants and no difference was observed as a function of family history (FHP AUC M=2424, SD = 292; FHN AUC M=2327, SD=729; p=0.639). There were no significant family history differences for ΔBP_{ND} in any of the six striatal brain regions regardless of which definition of FHN was used for analyses (Table 2, lower section).

Subjective Effects of Amphetamine

Table 3 displays the results of participants' ratings of positive and negative drug effects. FHP subjects had higher peak negative drug effect ratings than FHN subjects (0.25 (0.108) vs −0.02 (0.064), Q = 0.038). Similar effects were obtained using the more stringent definition of FHN. No differences in positive drug effects were observed as a function of AUD family history. Similar to what we found with BP_{ND}, stratified analyses by gender (not shown) suggest that these differences in subjective effects are primarily explained by differences in men as opposed to women.

Correlation of Subjective Effects and BP_{ND} and ΔBP_{ND}

Figure 1 shows the relationship between positive drug effects factor scores and ΔBP_{ND} in FHP (left panels) and FHN subjects (right panels; defined as no first or second degree affected relatives). There was a significant positive relationship between positive subjective factor ratings and magnitude of ΔBP_{ND} in the aPU (Beta = 3.53, p=0.015) and the pCN (Beta = 5.15, p=0.039) in FHN subjects. In contrast, FHP subjects did not evidence this

relationship in either region (aPU Beta = −0.32, p=0.793; pCN Beta = −1.51, p=0.382). Table 4 shows the correlation results adjusted for sex and binge drinking. For the FHN subjects, positive drug ratings and ΔBP_{ND} were significantly correlated in both regions in the adjusted analyses. There continued to be no evidence of relationship in FHP subjects after adjustment. Neither positive nor negative subjective factor ratings were related to baseline BP_{ND} in FHP and FHN subjects. Analyses stratified by gender (not shown) revealed that men were responsible for this relationship between positive drug effects and $\Delta BP_{ND.}$ There were no significant relationships between positive drug effects and ΔBP_{ND} in women.

Discussion

Prior brain imaging research on the relationship between AUD family history and striatal dopamine binding potential has been equivocal, probably resulting from differences across studies in definitions of family history status, prior alcohol and drug exposure in the probands, inclusion of sex as a covariate in analyses, and typically small sample sizes (Wiesbeck et al., 1995). The present study represents the largest sample studied to date using PET imaging to examine baseline dopamine binding potential (BP_{ND}), amphetamine-induced change in dopamine binding potential (ΔBP_{ND}), and positive and negative subjective drug effects simultaneously, as a function of family history of alcoholism.

Similar to Volkow and colleagues (Volkow et al., 2006), we found that social drinkers with a positive family history of alcoholism but no personal history of excessive drinking or alcohol or drug-related problems had significantly higher baseline [^{11}C]raclopride BP_{ND}, consistent with higher DA D2/D3 receptor availability, compared with FHN social drinkers. Specifically, we noted significant differences in the right ventral striatum, a region associated with reward, drive and motivation, and in the posterior caudate and anterior putamen, striatal regions associated with cognition. As suggested by Volkow, higher DA D2/D3receptors in our sample with increased genetic and/or epigenetic risk for development of AUD but without evidence of current alcohol problems may be protective against AUD. This explanation is supported by preclinical studies demonstrating lower striatal DA D_2 levels in selectively bred alcohol-preferring rats compared to nonalcohol-preferring rats (Stefanini et al., 1992, McBride et al., 1993), increased administration of alcohol in alcohol-preferring rats in the presence of a DA D2 receptor antagonist (Levy et al., 1991), and substantial reductions in alcohol intake of alcohol preferring rats after artificially increasing DA D_2 receptor levels using an adenoviral vector (Thanos et al., 2001). These findings highlight the potentially critical role of baseline DA D2 receptor availability as a contributor to alcoholism risk and are consistent with this “protection” hypothesis.

We found significant differences in DA D2/D3 receptor availability in the right ventral striatum but not the left. This asymmetry is consistent with previous research demonstrating a preponderance of DA D2 receptors in the right compared to the left striatum (Larisch et al., 1998). Prior research suggests that right-sided neural pathways play a critical role in decision making (Bechara, 2005, Mohr et al., 2010). Right but not left ventral striatum ΔBP_{ND} has been associated with unpredictable monetary rewards in healthy controls (Martin-Soelch et al., 2011), gambling in both healthy controls and pathological gamblers

(Joutsa et al., 2012) and gambling severity in pathological gamblers (Joutsa et al., 2012). Recent brain imaging research has shown a relationship between high impulsivity, a personality factor with a well-established association with substance use disorders, and blunted right ventral striatum activity (Oswald et al., 2007, Beck et al., 2009). Of particular relevance to the current study, Casey and colleagues (2014) reported blunted amphetamine-induced ΔBP_{ND} in very high risk young adults with multigenerational FH of substance use disorders and personal current regular alcohol and drug use compared to FHN controls; no group differences were observed in baseline BP_{ND}. They also observed a relationship between age of first alcohol use, another well-known risk factor for AUD development, and magnitude of amphetamine-induced ΔBP_{ND}, such that earlier onset was associated with smaller ΔBP_{ND} response. Taken together it can be postulated that protection is conferred by baseline differences in DA D2/D3 receptors, particularly in the right ventral striatum, via neural mechanisms regulating reward and decision making. In contrast, risk, as measured by FH, impulsivity, age of drinking onset and current use, is associated with blunted dopamine activity. It is also important to consider the agent used to provoke ΔBP_{ND}. While the Casey et. al. paper demonstrated blunted ΔBP_{ND} in FHP subjects in response to amphetamine administration, Setiawan and colleagues (2014) observed increased ΔBP_{ND} in FHP participants when alcohol was used to stimulate the dopaminergic system.

In the present study, FHP and FHN subjects did not differ in magnitude of amphetamine-induced ΔBP_{ND}, yet we observed significant differences between FHP and FHN participants in patterns of subjective drug effect ratings following amphetamine administration. Specifically, FHP subjects rated negative drug effects significantly higher than FHN subjects, and there was a tendency for FHP subjects to rate positive drug effects lower than FHN subjects although this observation did not reach statistical significance. It is possible that observed differences in baseline DA D2/D3 receptor availability account for these findings. Previous studies have shown that DA D2/D3 receptor availability is inversely related to subjective liking of methylphenidate (Volkow et al., 2002a). Importantly, only FHN participants demonstrated the expected positive relationship between positive subjective drug effects and magnitude of amphetamine-induced ΔBP_{ND} (Drevets et al., 2001, Oswald et al., 2005). Indeed, this relationship was completely disrupted in FHP probands. Taken together, it appears that higher DA D2 receptor levels are associated with greater negative drug effects and a disruption of the positive relationship between ΔBP_{ND} magnitude and subjective drug reward.

An alternative explanation for the elevated baseline [^{11}C]raclopride BP_{ND} is that it results from low tonic levels of endogenous synaptic dopamine in FHP participants. This dopamine deficiency model (Blum et al., 2000, Bowirrat and Oscar-Berman, 2005) hypothesizes that increased AUD risk results from the reduced ability of FHP persons to generate dopamine which results in reduced drug responsiveness. This would theoretically lead to increased consumption of alcohol/drugs to achieve comparable pleasurable effects as FHN persons. Unfortunately, findings derived from high-specific activity raclopride scans cannot differentiate whether high BP_{ND} is a reflection of a low dopamine state versus high D2/D3 receptor expression level. Future studies in FHP and FHN subjects could employ high- and low-specific activity raclopride scans, which would provide a comparison of B_{max} between the two groups.

Our study employed amphetamine to interrogate the dopamine system rather than alcohol, highlighting the breadth of drug use risk conferred by a positive family history of alcoholism. An earlier study by our group observed differences in self-reported rates of alcohol, marijuana, sedative and cocaine use in high density FHP compared with FHN subjects surveyed on local college campuses (McCaul et al., 1990). Interestingly, FHP respondents also reported a younger age at first marijuana use, experience with less commonly used drugs, and more personal drug-related problems. In our current study, FHP subjects were more likely to report experimenting with marijuana despite careful screening for drug use. There is strong evidence that genetic risk for substance use disorders is largely nonspecific and impacts across a wide range of drug classes (Kendler et al., 2003, Ystrom et al., 2014). Thus, our observation of low DA D2 in high-risk individuals may underpin risk across many different drug classes.

In addition to our large sample size, the current study has several important strengths. Our definition of FHP is consistent with Diagnostic Statistical Manual-5 (American Psychiatric Association, 2013), in that relatives were considered AUD positive if they met either alcohol abuse or dependence criteria. FHP subjects averaged over three AUD family members and therefore would be considered high density and highest risk. Also notably, our large sample size enabled examination of more and less stringent definitions of FHN. In the FHN sample (N=60) used in our primary analyses, half of our FHN subjects reported at least one 2nd degree AUD affected relative. It is striking that there were very few changes in overall findings when we conducted sensitivity analyses using the more stringent definition of FHN that ruled out both 1st and 2nd degree relatives. Future investigations should consider adoption of the more inclusive diagnostic system and family history classifications.

This is the first PET study of family history effects that has had a sufficient number of female subjects to allow stratified analyses by sex. Importantly, we observed FH differences in baseline BP_{ND} as well as amphetamine-induced subjective effects exclusively in male and not female subjects. These findings are in line with our own and others reports of sex differences in striatal dopamine function (Munro et al., 2006b, Riccardi et al., 2011) as well as sex differences in response to stimulant administration in FHP and FHN participants (Gabbay, 2005). There also is evidence of menstrual cycle effects on stimulant subjective drug effects (Evans et al., 2002, White et al., 2002), highlighting the importance of investigating menstrual cycle phase in future family history studies.

Despite study strengths, our findings should be interpreted in the context of several limitations. First, data related to family member's history of alcohol use was collected from the probands and was not corroborated via interviews with additional family members. However, this likely resulted in an underestimation of FHP participants, decreasing the likelihood of observing group differences. Additionally, while there were no differences in mean drinking frequency or intensity, FHP subjects tended to be more likely to report past 90-day binge drinking compared to FHN participants, despite our rigorous efforts to recruit FHP and FHN subjects with comparable demographic, alcohol and drug use, and psychological profiles. It is important to note that, although binge drinking rates were different as a function of FH status, rates were low and in line with those reported for young adults in this age range (Naimi et al., 2003).

The current findings provide important new insights into neural mechanisms of protective versus risk factors for substance use development. Our participants reported high-density AUD family histories but had no evidence of alcohol-related problems themselves. Although we cannot rule out development of problems in the future, our recruitment strategy may have resulted in highly resilient FHP participants, in whom high baseline DA D2/D3 receptor levels are associated with more negative drug effects and a disruption of the expected relationship between dopamine release and positive subjective drug effects. In contrast, much of the research on AUD risk factors, including FH, personal alcohol/drug use, impulsivity and age of onset, has found similar baseline DA D2/D3 receptor levels but blunted ΔBP_{ND} in at-risk subjects. Our results highlight the importance of studying persons across a range of current drinking patterns and problems to ensure a more complete understanding of the different mechanisms that may be involved in conferring risk and resilience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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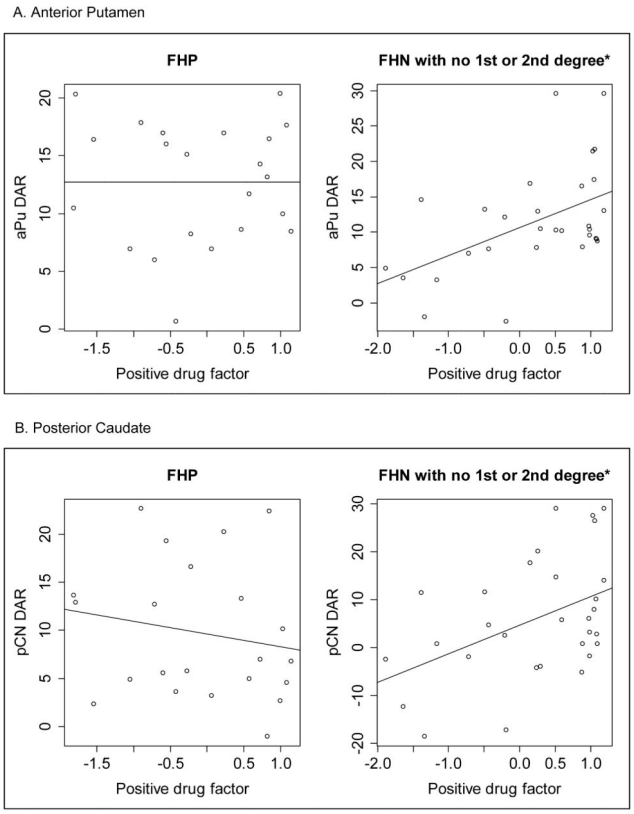

Figure 1.

Correlation of change in dopamine binding potential (ΔBP_{ND}) and subjective amphetamine-induced positive drug effects by family history of alcohol use disorder in A) the anterior putamen (aPU), and B) posterior caudate (pCN). Family history positive (FHP) subjects had at least one 1st degree family member with AUD and family history negative (FHN) subjects had no 1st or 2nd degree family members with AUD. * $p \leq 0.05$.

Table 1

Demographic and psychosocial characteristics of participants.

	Total	FHN[a]	FHP[b]	p value
Sample Size	84	60	24	
Age (Mean, SD)	22.8 (3.14)	22.7 (3.21)	23.1 (2.98)	.534
Race (n, %)				.456
% White	58 (69.0)	40 (66.7)	18 (75.0)	
% Non-White	26 (31.0)	20 (33.3)	6 (25.0)	
Sex				.437
Men	51 (60.7)	38 (63.3)	13 (54.2)	
Women	33 (39.3)	22 (36.7)	11 (45.8)	
Education (Mean years, SD)	14.8 (1.78)	14.7 (1.87)	15.0 (1.57)	.604
PSS[c] score (Mean, SD)	10.0 (5.76)	9.8 (5.61)	10.4 (6.24)	.714
Binge in last 90 days				.050
No Binges	35 (41.7)	29 (48.3)	6 (25.0)	
≥1 Binge	49 (58.3)	31 (51.7)	18 (75.0)	
Drinks per drinking episode (Mean, SD)	3.0 (2.02)	2.8 (2.16)	3.2 (1.65)	.710
Drinking episodes per week (Mean, SD)	2.4 (2.61)	2.1 (2.25)	3.3 (3.25)	.058
Smoked > 100 cigarettes lifetime				
Lifetime duration of smoking (Mean months, SD)	22.7 (9.78)	25.2 (10.73)	16.5 (2.21)	.330
Marijuana use ever (n, %)	43 (51.9)	25 (43.1)	18 (78.2)	.004
Marijuana use > 21 times in past year (n, %)	2 (2.4)	1 (1.7)	1 (4.2)	.063

[a] Family history negative

[b] Family history positive

[c] Perceived Stress Scale

Addict Biol. Author manuscript; available in PMC 2018 January 01.

Table 2

Mean (SEM) baseline binding potential and change in dopamine binding potential as a function of family history of alcohol use disorder (AUD).

	FHP[a] vs all FHN[b]			FHP[a] vs FHN[c] with no 1st or 2nd degree		
	FHP	**FHN**	**Q value[d]**	**FHP**	**FHN**	**Q value[d]**
Sample Size	24	60		24	30	
***Baseline Binding Potential*[e]**						
Anterior Putamen	3.38 (0.062)	3.27 (0.038)	0.113	3.39 (0.064)	3.21 (0.054)	***0.039***
Posterior Putamen	3.57 (0.078)	3.43 (0.047)	0.142	3.58 (0.078)	3.41 (0.066)	0.121
Anterior Caudate Nucleus	2.98 (0.056)	2.89 (0.034)	0.163	2.99 (0.06)	2.85 (0.051)	0.106
Posterior Caudate Nucleus	2.32 (0.077)	2.14 (0.047)	***0.043***	2.31 (0.083)	2.13 (0.07)	*0.097*
Left Ventral Striatum	2.36 (0.063)	2.25 (0.039)	0.162	2.36 (0.069)	2.21 (0.059)	0.105
Right Ventral Striatum	2.35 (0.061)	2.17 (0.037)	***0.017***	2.36 (0.067)	2.12 (0.057)	***0.012***
***Change in Dopamine Binding Potential*[d]**						
Anterior Putamen	13.07 (1.228)	11.37 (0.749)	0.953	13.42 (1.363)	11.23 (1.156)	0.469
Posterior Putamen	20.63 (1.455)	20.12 (0.888)	1	20.81 (1.599)	19.74 (1.357)	0.822
Anterior Caudate Nucleus	6.6 (1.175)	5.81 (0.717)	1	7.01 (1.299)	5.58 (1.102)	0.822
Posterior Caudate Nucleus	9.79 (2.075)	6.8 (1.266)	0.88	10.5 (2.254)	5.57 (1.913)	0.217
Left Ventral Striatum	13.59 (1.638)	11.64 (0.999)	1	13.73 (1.86)	11.52 (1.578)	0.758
Right Ventral Striatum	13.48 (1.754)	11.75 (1.07)	1	13.71 (1.858)	11.44 (1.577)	0.731

[a] Subjects classified as family history positive (FHP) had at least one 1st degree family member with AUD.

[b] Subjects classified as family history negative (FHN) had no 1st degree family members with AUD. May have had 2nd degree relatives with AUD.

[c] Subjects classified as FHN had no 1st or 2nd degree family members with AUD.

[d] Adaptive Holm procedure (Q) was used to correct the p values for multiple comparisons.

[e] Analyses adjusted for sex and binge drinking.

Table 3

Mean (SEM) positive and negative subjective factor scores as a function of family history of alcohol use disorder (AUD).

	FHP[a] vs all FHN[b]			FHP[a] vs FHN[c] with no 1st or 2nd degree		
	FHP	**FHN**	**Q value[d]**	**FHP**	**FHN**	**Q value[d]**
Positive drug effects factor[e]	−0.05 (0.110)	0.07 (0.065)	0.313	−0.06 (0.118)	0.19 (0.097)	0.115
Negative drug effects factor[e]	0.25 (0.108)	−0.02 (0.064)	***0.038***	0.26 (0.104)	−0.1 (0.086)	***0.010***

[a] Subjects classified as family history positive (FHP) had at least one 1st degree family member with AUD.

[b] Subjects classified as family history negative (FHN) had no 1st degree family members with AUD. May have had 2nd degree relatives with AUD.

[c] Subjects classified as FHN had no 1st or 2nd degree family members with AUD.

[d] Adaptive Holm procedure (Q) was used to correct the p values for multiple comparisons.

[e] Analyses adjusted for sex and binge drinking.

Table 4

Correlation of change in dopamine binding potential (ΔBP_{ND}) and subjective amphetamine-induced positive and negative drug effects by family history of alcohol use disorder, adjusted by sex and binge drinking

	FHP[a]				FHN[b] with no 1st or 2nd degree			
	Positive drug effects factor[c]		Negative drug effects facor[c]		Positive drug effects factor[c]		Negative drug effects factor[c]	
	Slope	P value	Slope	P value	Slope	P value	Slope	P value
Anterior Putamen	0.001	0.999	−1.509	0.171	3.529	**0.017**	0.592	0.809
Posterior Caudate Nucleus	−0.847	0.619	2.479	0.088	5.192	**0.041**	2.182	0.598

[a] Subjects classified as family history positive (FHP) had at least one 1st degree family member with AUD.

[b] Subjects classified as family history negative (FHN) had no 1st or 2nd degree family members with AUD.

[c] Analyses adjusted for sex and binge drinking.