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ORIGINAL INVESTIGATION

Lack of consistent sex differences in D-amphetamine-induced dopamine release measured with [^{18}F]fallypride PET

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Abstract

Rationale Sex differences in the dopaminergic response to psychostimulants could have implications for drug abuse risk and other psychopathology involving the dopamine system, but human data are limited and mixed.

Objectives Here, we sought to investigate sex differences in dopamine release after oral D-amphetamine administration.

Methods We used [^{18}F]fallypride positron emission tomography (PET) to measure the change in dopamine D2/3 receptor availability ($\%\Delta BP_{ND}$, an index of dopamine release) between placebo and D-amphetamine sessions in two independent datasets containing a total of 39 females (on either hormonal birth control $n = 18$, postmenopausal $n = 10$, or studied in the first 10 days of their menstrual cycle $n = 11$) and 37 males.

Results Using both a priori anatomical regions of interest based on previous findings and voxelwise analyses, we failed to consistently detect broad sex differences in D-amphetamine-induced dopamine release. Nevertheless, there was limited evidence for greater right ventral striatal dopamine release in young adult males relative to similarly aged females, but this was not consistently observed across samples. Plasma estradiol did not correlate with dopamine release and this measure did not differ in females on and off hormonal birth control.

Conclusions While our finding in young adults from one dataset of greater $\%\Delta BP_{ND}$ in males is partially consistent with a previously published study on sex differences in D-amphetamine-induced dopamine release, our data do not support the presence of consistent widespread sex differences in this measure of dopamine release.

Keywords (up to 10): Sex differences · Dopamine · PET · D2/3 receptor availability · Dopamine release · D-amphetamine

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Introduction

Women and men differ in the symptom expression, onset, and prevalence of psychopathology (Dohrenwend and Dohrenwend 1976; Earls 1987; Seeman 1997). In the context of addiction, differences have been observed in female versus male responses to psychostimulants and drug-associated cues. Female rats acquire cocaine self-administration more readily (Lynch and Carroll 1999) and display increased motivation (higher breakpoints on a progressive ratio schedule) to self-administer intravenous cocaine than males (Lynch 2008; Roberts et al. 1989). Furthermore, cocaine self-administration varies across the estrous cycle in female rodents (Lynch et al. 2000). Serum estradiol correlates with the amount of cocaine self-administered (Lynch 2008), and estradiol increases both cocaine self-administration (Jackson et al. 2006; Lynch et al. 2001) and extracellular dopamine levels (Cummings et al. 2014) in ovariectomized female rats (Jackson et al. 2006; Lynch et al. 2001).

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Furthermore, estradiol has been shown to increase striatal dopamine synthesis (Pasqualini et al. 1995), levels of tyrosine hydroxylase (Ivanova and Beyer 2003), and basal dopamine neuron activity in the ventral tegmental area (VTA) (Calipari et al. 2017). A recent study by Calipari et al. also found that estradiol increases post translational modifications of the dopamine transporter (DAT) which ultimately increase cocaine's ability to inhibit DAT's function (Calipari et al. 2017). The authors go on to demonstrate that these estradiol-mediated modification of DAT lead to increased cocaine-conditioned place preference (Calipari et al. 2017).

These preclinical data suggest that sex differences may exist in response to psychostimulant drugs (which act on DAT) in humans. Indeed, although overall rates of addiction are higher in men, cocaine-dependent women have been shown to have more severe drug-related problems at intake (Griffin et al. 1989; Kosten et al. 1993) and greater drug craving to cocaine cues than men (Robbins et al. 1999). Furthermore, estrogen and progesterone have been shown to affect the subjective responses of euphoria to, liking of, and wanting of oral D-amphetamine (dAMPH) in human subjects (Justice and de Wit 1999; White et al. 2002). In addition, subjective ratings of cocaine in cocaine-smoking women vary over the menstrual cycle (Evans et al. 2002).

Amphetamine-induced dopamine release is also potentiated by estradiol in rodents (Becker 1990, 1999). Two human PET studies have investigated differences in dAMPH-induced dopamine release as a function of participant sex (Munro et al. 2006; Riccardi et al. 2006). Munro et al. (2006) found that young adult (aged 18–29) men ($n = 28$) displayed heightened striatal dopamine release measured with [^{11}C] raclopride compared to women ($n = 15$). Using [^{18}F]fallypride, Riccardi et al. (2006) found young adult women ($n = 6$; aged 21–29) displayed greater dopamine release in right globus pallidus and inferior frontal gyrus compared to men ($n = 7$). Given the small sample sizes in these PET studies, it is critical to evaluate potential sex differences with larger sample sizes, especially when existing findings from smaller sample studies have conflicted.

Here, we assessed sex differences in dAMPH-induced dopamine release across two separate studies using [^{18}F]fallypride PET to evaluate the reliability of potential sex effects in independent datasets.

Materials and methods

Participants and procedure

All participants were recruited from the Nashville, TN, metropolitan area using a combination of print, radio, and online advertisements and completed written informed consent approved by the Vanderbilt University Institutional Review Board. Exclusion criteria included any axis-1 psychiatric disorder, use of psychoactive drugs, illicit drug use, and alcohol consumption greater than ~ 5 standard alcoholic drinks/week. Furthermore, > 3 lifetime stimulant use episodes was exclusionary for study inclusion. All participants underwent a structured clinical interview (First et al. 2002) for these exclusionary criteria in addition to a medical physical (with EKG), a complete blood count panel, and structural MR scans (T1 and T2-FLAIR weighted) to exclude pathology. All female participants were either postmenopausal (dataset 2: $n = 10$), on hormonal birth control (dataset 1: $n = 11$; dataset 2: $n = 6$ young adults, 4 on birth control pill, 2 on Mirena IUD; $n = 1$ middle-aged adult using birth control as hormone replacement therapy) or naturally cycling (dataset 1: $n = 7$; dataset 2: $n = 4$ young adults), in which case, they completed both PET scans within the first 10 days of their menstrual cycle.

Dataset 1 consisted of previously published dopamine release data (Buckholtz et al. 2010; Samanez-Larkin et al. 2013; Smith et al. 2016a) from 18 females (age = 22.9 ± 3.0) and 16 males (age = 21.8 ± 3.2). Dataset 1 scan order was fixed as (1) placebo, (2) dAMPH, with participants blind to drug administration order. Dataset 2 consists of data from a current study investigating adult age effects on dopamine signaling, recruiting participants aged 20–30 (young adults, YA) and 50–65 (middle-aged adults, MA). The analyzed data consisted of 21 females (10 YA, 11 MA; age = 40.2 ± 3.3) and 21 males (10 YA, 11 MA) age = 42.48 ± 3.4). In dataset 2, drug order was randomized with participants blind to administration on each visit; 42.9% of males and 52.4% of females received dAMPH on their first visit. Drug (or placebo) was administered orally (dAMPH dose, 0.43 mg/kg) 3 h prior to the [^{18}F]fallypride PET scan in both datasets. We have previously shown that blood levels of amphetamine peak by 3-h post oral dAMPH (Smith et al. 2016b) administration and remain elevated for several hours after reaching peak. Blood draws for female hormone (estradiol) analysis were performed on both placebo and dAMPH day in dataset 1 and only on dAMPH day in dataset 2. These blood draws were taken just prior to the placebo or dAMPH administration.

PET data acquisition

[^{18}F]fallypride ((S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3[^{18}F]fluoropropyl)-2,3-dimethoxybenzamide) was produced in the radiochemistry laboratory attached to the PET unit, following synthesis and quality control procedures described in US Food and Drug Administration IND 47,245.

Serial scan acquisition was started simultaneously with a 5.0 mCi (185 MBq) slow bolus injection (duration ~ 10 s) of DA D2/3 tracer [^{18}F]fallypride (specific activity > 3000 Ci/mmol). CT scans were collected for attenuation correction prior to each of the three emission scans (of lengths 68.5 min, 50 min, and 60 min), which together lasted

approximately 3.5 h, including time for two breaks between each scan for subject comfort. The specific acquisition timing of the dynamic data for each dataset can be found in Supplementary Table 1. The only difference in data acquisition across datasets was the number of frames acquired in the last two emission scans (which were the same total duration across datasets): second emission scan lasted 3000 s (with 2 1500-s length frames in dataset 1 and 4 750-s length frames in dataset 2) followed by a second break and then a third emission scan acquisition lasting 3600 s (with 2 1800-s length frames in dataset 1 and 3 900-s length frames in dataset 2). [^{18}F]fallypride PET signal reliably reaches equilibrium in the striatum within 3 h (Vernaleken et al. 2011), making our acquisition parameters more than sufficient to capture this equilibrium state, a key requirement for estimating BP_{ND}. Importantly, PET data reported from both studies were collected on the same GE Discovery STE scanner.

PET data processing

After decay correction and attenuation correction, PET scan frames were corrected for motion using SPM8 (Friston et al. 1995) with the last dynamic image frame of the first series serving as the reference image. The mean PET image created from the realignment was then registered to each subject's high-resolution T1 MRI image (FLIRT, 6 degrees of freedom), which was nonlinearly registered to MNI space (FNIRT) in FSL (Smith et al. 2004). Putamen and cerebellum reference regions of interest (ROIs) were created from the WFU Pickatlas (Maldjian et al. 2003) with the cerebellum modified such that the anterior ¼ of the ROI along with voxels within 5 mm of cortex were excluded to prevent contamination of the PET signal from nearby areas such as midbrain or occipital cortex. These ROIs were then warped to each subject's PET space using the FLIRT and FNIRT FSL transform matrices (MNI → T1 → PET) and used in a simplified reference tissue model (SRTM (Lammertsma and Hume 1996)) performed in PMOD software (PMOD Technologies, Zurich Switzerland) to estimate [^{18}F]fallypride binding potential (BP_{ND}, a ratio of specifically bound [^{18}F]fallypride to its non-displaceable concentration). Specifically, PMOD's PXMOD tool was used to estimate BP_{ND} voxel-wise using a published basis function fitting approach (Gunn et al. 1997). PXMOD uses time-activity curves extracted from the putamen and cerebellum from each subject to optimize the initial conditions for estimation of BP_{ND} with SRTM. The cerebellum data served as the input function to the model.

The resulting BP_{ND} maps for placebo and dAMPH days were then warped to MNI space using the saved FSL transforms to create MNI-normalized BP_{ND} images (resampled to 2 mm isotropic voxels). We also created $\%\Delta BP_{ND}$ images by linearly registering the placebo and dAMPH BP_{ND} maps to one another (FLIRT, 6 degrees of freedom) and the difference in BP_{ND} maps ($\%\Delta BP_{ND}$) after dAMPH was calculated as:

$$\%\Delta BP_{ND} = (\text{placebo}BP_{ND} - \text{dAMPH}BP_{ND})/(\text{placebo}BP_{ND}) \times 100\%$$

Thus, an increase in $\%\Delta BP_{ND}$ corresponded to an increase in synaptic DA release. Subject-specific $\%\Delta BP_{ND}$ images were also warped to MNI space using the saved FSL transforms to create MNI-normalized $\%\Delta BP_{ND}$ images (resampled to 2-mm isotropic voxels). These MNI-normalized images were then analyzed (using an explicit MNI brain mask) in SPM8 to test for sex differences in drug effects on BP_{ND}.

A priori anatomical regions of interest

Based on previous findings of sex differences in dAMPH-induced DA release (Munro et al. 2006; Riccardi et al. 2006), we focused on 5 anatomical ROIs. For each subject, we extracted each ROI's BP_{ND} value as the average value from the subject's PXMOD-generated SRTM BP_{ND} map, warped to MNI standard space. The a priori ROIs from which we extracted data included the right AAL atlas (Tzourio-Mazoyer et al. 2002) pallidum and inferior (opercular) frontal gyrus (IFG). In addition, we investigated bilateral striatal ROIs [ventral striatum (VS), caudate, and putamen] as defined in Mawlawi et al. (2001) and used previously in our research group (Smith et al. 2017). These ROIs are depicted on a template MNI brain in Supplementary Figure 1.

Data analysis

Taking a whole-brain approach, our main voxelwise analyses focused on testing for a dAMPH effect and then a sex x dAMPH effect on BP_{ND} via flexible factorial design implemented in SPM8. Within each dataset in SPM8, we first modeled the effect of sex group and drug type (placebo, dAMPH), while controlling for age and drug administration order (for dataset 2 only). We then added a sex group × drug type interaction to each flexible factorial model in SPM8 and tested for the presence of this interaction. We conducted *T* tests between BP_{ND} from each drug session (placebo>dAMPH) as well as testing for the interaction with sex: females (placebo>dAMPH)>males (placebo>dAMPH). We also conducted separate *T* tests on male and female $\%\Delta BP_{ND}$ to assess differences in drug effects on BP_{ND} by sex. In dataset 1, we controlled for age while in dataset 2, we controlled for age and drug administration order. Unthresholded statistical maps are available at: https://neurovault.org/collections/4040/ (dataset 1) and https://neurovault.org/collections/4041/ (dataset 2). For

our ROI data, we compared placebo and dAMPH BP_{ND} by sex using a repeated measures ANOVA, controlling for age and drug administration order (dataset 2), as needed. We also conducted *T* tests on our ROI data, comparing males to females on $\%\Delta BP_{ND}$. For the voxelwise analyses, visualization *p* was set at < 0.001 (voxel extent threshold = 20) and only voxels meeting pFDR < 0.05 at the cluster and/or peak level were considered significant. The raw participant data containing BP_{ND} values (from placebo and dAMPH session and calculated $\%\Delta BP_{ND}$) from our a priori ROIs (including bilateral and unilateral striatal ROIs), dataset label, birth control and menopausal status of female subjects, age, sex, plasma estradiol levels, and subjective response ratings (feel, like, high, want more) to the dAMPH are available on OSF: https://osf.io/24zxk/.

Results

First, we tested whether males and females from both datasets were well matched in terms of age, personality, ethnic distribution, injected dose of [^{18}F]fallypride (mCi, volume (ml) injected) for each visit, and dAMPH dosage received. Impulsivity (Barratt Impulsiveness Scale) and novelty seeking (Tridimensional Personality Inventory—novelty seeking) were well matched across males and females in both datasets. Though dataset 2 participants (mean age, 41.36 ± 15.13) were older than dataset 1 (mean age, 22.38 ± 3.10; $t(74) = 7.18$, $p < 0.001$), males and females within each dataset were well matched on age. Average age and ethnic distribution between males and females was similar within datasets (see Table 1). There were no differences in dAMPH dose by sex in either dataset 1 ($t(32) = 0.28$, $p = 0.78$) or dataset 2 ($t(40) = 1.81$, $p = 0.08$). Across both datasets, the average dAMPH dose was 0.438 ± 0.015 mg/kg for females and 0.433 ± 0.016 mg/kg for males. Also, we found no main effect of drug administration session or sex or drug session × sex interaction on injected dose of [^{18}F]fallypride in dataset 1 (max $F(1,32) = 3.37$, min $p = 0.076$, drug session effect on injected volume) nor dataset 2 (max $F(1,40) = 3.92$, min $p = 0.055$, sex group effect on injected volume). Supplementary Table 2 reports the average injected dose (in mCi) and volume (in ml) of [^{18}F]fallypride administered by dataset, sex group, and drug administration session.

Dopamine release

In our flexible factorial voxelwise analyses, we identified large areas of significant decrease in BP_{ND} on dAMPH relative to placebo with dataset 1 displaying a large striatal cluster ($k = 5004$, pFDR < 0.001, max $T = 10.32$) as well as a medial thalamic cluster ($k = 147$, pFDR = 0.001, max $T = 5.19$) and dataset 2 displaying a single large striatal cluster ($k = 1871$, pFDR < 0.001, max $T = 7.25$) where placebo > dAMPH BP_{ND} (Supplementary Fig. 2). However, we failed to detect a significant drug administration session × sex group effect on BP_{ND} in either dataset. Similar null results were observed when we tested for sex group differences in $\%\Delta BP_{ND}$ maps at a voxelwise level (see unthresholded SPM T-maps for dataset 1: https://neurovault.org/collections/3805/ and dataset 2: https://neurovault.org/collections/4124/). We also tested for a significant drug administration session × sex group effect on BP_{ND} only in the voxels found to display a drug effect on BP_{ND} within each dataset (masking within the drug effect voxels). There was still no significant drug administration session × sex group effect on BP_{ND} in either dataset using these more restrictive analyses

Table 2 reports placebo and dAMPH BP_{ND} values by dataset and sex group across our a priori ROIs. In dataset 1, our ROI-based ANOVAs with drug administration as a within subject measure and sex group as a between subject measure found significant effects of drug (placebo > dAMPH BP_{ND}) on BP_{ND} in right pallidum ($F(1,32) = 24.374$, $p < 0.001$), bilateral VS ($F(1,32) = 24.374$, $p < 0.001$),

Table 1 Demographics of datasets 1 and 2 by sex. Males and females were well matched by age and impulsivity and novelty seeking personality traits. BIS-11, Barratt Impulsiveness Scale; TPQ-NS, Tridimensional Personality Questionnaire—novelty seeking

	M (std dev)	*M* (std dev)	*T*, p
Dataset 1	Males ($n = 16$)	Females ($n = 18$)	
Age	21.75 (3.24)	22.94 (2.96)	1.12, 0.27
BIS-11	58.06 (11.67)	57.50 (9.70)	− 0.83, 0.42
TPQ-NS	17.75 (4.96)	16.28 (5.38)	− 0.15, 0.88
Ethnicity (% Caucasian)	81.3	88.9	X^2=0.39, p=0.53
Dataset 2	Males ($n = 21$)	Females ($n = 21$)	
Age	42.48 (15.57)	40.24 (14.98)	− 0.48, 0.64
BIS-11	56.19 (9.23)	58.43 (8.39)	0.82, 0.42
TPQ-NS	12.67 (4.87)	13.33 (4.79)	0.45, 0.66
Ethnicity (% Caucasian)	90.0	61.9	X^2=1.87, p=0.17

Table 2 Effect of D-amphetamine on BP_{ND} signal relative to placebo across datasets and sex groups. Fallypride BP_{ND} after placebo (Plc) and dAMPH administration in males and females across the two datasets reveal consistent, significant BP_{ND} decline after dAMPH across datasets, regardless of participant sex

ROI	Plc BPnd *M* (std dev)	dAMPH BPnd *M* (std dev)	Plc > dAMPH *T*, *p*
Dataset 1 females ($n = 18$)			
R IFG	0.64 (0.16)	0.62 (0.14)	1.00, 0.33
R Pallidum	18.64 (2.96)	17.23 (2.25)	3.83, 0.001
VS	18.37 (2.33)	16.94 (1.61)	3.90, 0.001
Caudate	21.64 (2.21)	20.41 (1.58)	4.57, < 0.001
Putamen	24.92 (2.47)	22.23 (1.90)	8.24, < 0.001
Dataset 2 females ($n = 21$)			
R IFG	0.75 (0.37)	0.63 (0.28)	3.48, 0.002
R Pallidum	16.96 (3.15)	16.23 (3.10)	1.76, 0.095
VS	16.13 (2.41)	15.14 (2.67)	1.92, 0.07
Caudate	18.76 (3.40)	18.48 (2.95)	0.95, 0.35
Putamen	22.92 (3.52)	21.55 (3.09)	3.43, 0.003
Dataset 1 males ($n = 16$)			
R IFG	0.59 (0.14)	0.56 (0.11)	1.37, 0.19
R Pallidum	18.87 (3.01)	17.75 (3.45)	3.19, 0.006
VS	18.17 (1.98)	16.86 (2.21)	3.77, 0.002
Caudate	20.48 (2.03)	19.77 (2.35)	2.70, 0.017
Putamen	24.62 (1.92)	22.61 (2.58)	5.92, < 0.001
Dataset 2 males ($n = 21$)			
R IFG	0.61 (0.24)	0.54 (0.26)	3.05, 0.006
R Pallidum	16.98(2.99)	15.78 (2.11)	3.08, 0.006
VS	15.76 (2.55)	14.10 (1.94)	4.29, 0.001
Caudate	17.86 (3.17)	17.30 (2.72)	2.00, 0.059
Putamen	22.31 (2.91)	20.64 (2.87)	6.77, < 0.001

bilateral caudate ($F(1,32) = 26.331$, $p < 0.001$), and bilateral putamen ($F(1,32) = 99.215$, $p < 0.001$) with a smaller but non-significant effect in right IFG ($F(1,32) = 2.964$, $p = 0.095$). There was no significant main effect of sex nor a sex × drug interaction in any of the anatomically defined ROIs (max $F(1,32) = 2.014$, min $p = 0.166$ in bilateral putamen). In dataset 2, our ROI-based ANOVAs with drug administration as a within subject measure, sex group as a between subject measure and age and drug administration order as covariates found a significant main effect of drug (placebo > dAMPH BP_{ND}) in right pallidum ($F(1,38) = 5.98$, $p = 0.019$), bilateral VS ($F(1,38) = 4.75$, $p = 0.036$), and bilateral putamen ($F(1,38) = 8.19$, $p = 0.007$) with a smaller but non-significant effect in bilateral caudate ($F(1,38) = 2.84$, $p = 0.10$). There was no significant main effect of sex on BP_{ND} in the anatomically defined ROIs (max $F(1,38) = 1.81$, $p = 0.19$ in right IFG). Furthermore, no ROI displayed a significant Sex x drug interaction (max $F(1,38) = 1.28$, min $p = 0.27$ in bilateral VS) in dataset 2. Figure 1 displayes the lack of sex differences in dAMPH effects on calculated $\%\Delta BP_{ND}$ from the a priori ROIs, plotted by dataset and sex group.

We also tested for an interaction between age group (young adults, aged 20–30; middle-aged adults, aged 50–65), drug session, and sex on BP_{ND} in these ROIs in dataset 2. We found a significant drug × sex × age group interaction in bilateral VS ($F(1,37) = 9.10$, $p = 0.005$) and right pallidum ($F(1,37) = 8.34$, $p = 0.006$) with a smaller but non-significant drug x sex x age group interaction in right IFG BP_{ND} ($F(1,37) = 3.94$, $p = 0.055$). In both the bilateral VS and right pallidum, male young adults displayed significantly higher $\%\Delta BP_{ND}$ (VS 15.5 ± 8.7%; right pallidum 11.6 ± 6.1%) compared to female young adults (VS 0.02 ± 17.5%; right pallidum 1.3 ± 9.3%; $t(18) = 2.50$, $p = 0.022$ and $t(18) = 2.94$, $p = 0.009$, respectively). Female middle-aged adults showed non-significantly higher bilateral VS $\%\Delta BP_{ND}$ (10.7 ± 7.6%) relative to male middle-aged adults ($\%\Delta BP_{ND}$ = 4.3 ± 9.3%; $t(20) = 1.74$, $p = 0.097$) while the sex difference in right pallidum $\%\Delta BP_{ND}$ in the middle-aged group (females 5.9 ± 14.2%; males 0.73 ± 11.6%) was non-significant ($t(20) = 0.95$, $p = 0.36$). There was no drug × sex × age group

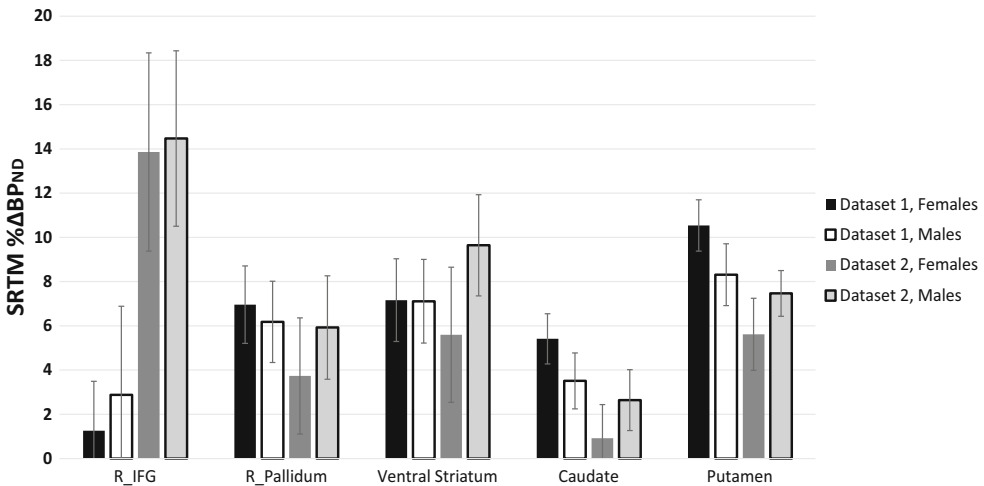

Fig. 1 $\%\Delta BP_{ND}$ does not vary by sex in a priori anatomical regions of interest. $\%\Delta BP_{ND}$ calculated from dAMPH and placebo BP_{ND} data from the five anatomical ROIs ($\%\Delta BP_{ND}$ = (placebo BP_{ND} − dAMPH BP_{ND})/(placebo BP_{ND}) × 100%) are plotted by Dataset and participant sex. We observed no significant differences in $\%\Delta BP_{ND}$ when comparing males to females in either Dataset. R, right; IFG, inferior frontal gyrus. Error bars represent standard error of the mean

interaction in bilateral caudate ($F(1,37) = 1.26$, $p = 0.27$) or putamen ($F(1,37) = 0.03$, $p = 0.87$).

Given the observed drug × sex × age group interaction in the ROI data for dataset 2, we reran the flexible factorial SPM analysis explicitly looking for drug × sex effects on BP_{ND} in the younger age group, which was the age group showing more evidence of a sex effect. In dataset 2 young adults, there were two distinct clusters showing a significant drug × sex effect on BP_{ND}: (1) a right ventral striatal/pallidum cluster (MNI coordinates 20, 2, − 2) showed significantly higher male (placebo > dAMPH BP_{ND}) effects relative to females ($T = 5.89$, k(cluster size) = 260, pFDR < 0.001 cluster level); (2) a narrow focus near the boundary of the dorsal striatum, insula and neighboring white matter (MNI coordinates 22, 16, 12) showed significantly higher female (placebo > dAMPH BP_{ND}) effects relative to males ($T = 4.14$, $k = 136$, pFDR = 0.003 cluster level; see unthresholded T-maps: https://neurovault.org/images/65821/).

Given the emergence of a lateralized effect in the above voxelwise analysis in young adults from dataset 2, we conducted exploratory ROI analyses using the right and left components of our caudate, putamen, and VS ROIs. We first tested for a sex × drug × age group interaction on BP_{ND} in dataset 2 in each of these 6 ROIs (Bonferonni corrected significance set at $p < 0.00833$), controlling for drug administration order. While we found sex × drug × age group effects in right caudate ($F(1, 37) = 7.804$, $p = 0.008$; $\eta^2 = 0.135$) and VS, only the right VS ($F(1, 37) = 23.768$, $p < 0.001$; $\eta^2 = 0.307$) interaction survived correction for multiple comparisons. A significant sex × drug × age group effect was also observed in the a priori right pallidum ROI ($F(1, 37) = 8.344$, $p = 0.006$; $\eta^2 = 0.142$). A closer examination found that dataset 2 young adult males had a larger change in BP_{ND} from placebo to dAMPH visits ($\%\Delta BP_{ND} = 23\%$; Cohen's d for drug effect on $BP_{ND} = 1.70$) relative to their female counterparts ($\%\Delta BP_{ND} = -0.039\%$; Cohen's d for drug effect on $BP_{ND} = -0.24$; sex × drug interaction: $F(1,17) = 17.58$, $p = 0.001$; $\eta^2 = 0.438$). By contrast, the sex × drug interaction was not significant in the left VS $F(1, 17) = 0.052$, $p = 0.82$; $\eta^2 = 0.003$). To test the reliability of the sex × drug effect observed in the right VS in dataset 2, we ran a follow-up test on this ROI in dataset 1 subjects who were similar in age to the young adults in dataset 2. However, we observed no significant sex × drug effect in right VS in dataset 1 ($F(1,32) = 0.122$, $p = 0.729$; $\eta^2 = 0.002$). In dataset 1, change in BP_{ND} from placebo to dAMPH visits was equivalent across males ($\%\Delta BP_{ND} = 6.49\%$; Cohen's d for drug effect on $BP_{ND} = 0.70$) and females ($\%\Delta BP_{ND} = 8.06\%$; Cohen's d for drug effect on $BP_{ND} = 0.82$).

Subjective effects

Previously, we found relationships between $\%\Delta BP_{ND}$ and the subjective effect of Wanting More dAMPH in vmPFC, left insula, and right VS in dataset 1 (Smith et al. 2016a). In dataset 1, females had lower Drug Effects Questionnaire (Morean et al. 2013) ratings (max FEEL, LIKE, HIGH, and WANT MORE dAMPH-placebo from one of five time points from 60 min to 345 min post drug) than males (all Ts < − 2.28, ps < 0.03; see Supplementary Table 3). To rule out the possibility that subjective effect differences by sex in dataset 1 obscured our ability to detect sex × drug effects on $\%\Delta BP_{ND}$, we reran the flexible factorial analysis in SPM8 controlling for WANT MORE max rating, given it was associated with $\%\Delta BP_{ND}$ in this dataset previously (Smith et al. 2016a). We still observed no significant clusters displaying a sex × drug effect on BP_{ND} in this voxelwise analysis.

We did not observe sex differences in DEQ subjective measures in either the full dataset 2 (max $T = 1.05$, min $p = 0.30$ (females > males) for max WANT MORE rating) or when restricting dataset 2 to young adults only (max $T = 2.10$, min $p = 0.05$ for max HIGH rating; all other ps > 0.20; Table S3). Interestingly, if we compare young adults from dataset 2 to dataset 1 individuals, males from dataset 1 showed enhance HIGH ratings (47.06 ± 24.52) relative to dataset 2 young adult males (20.40 ± 20.77; $t(24) = 2.85$, $p = 0.009$). In contrast, dataset 2 young adult females showed elevated WANT MORE ratings (55.30 ± 25.48) relative to dataset 1 females (19.00 ± 28.41, $t(26) = 3.36$, $p = 0.002$). It is unlikely that subjective effect differences across young adult females explain our finding a sex × drug effect in dataset 2 young adults but not dataset 1 given that the DEQ WANT MORE effect runs counter to our observed drug effect on right VS $\%\Delta BP_{ND}$. Previously, we had found a positive relationship between DEQ WANT MORE and right VS $\%\Delta BP_{ND}$ (Smith et al. 2016a). Females in dataset 1, however, showed less WANT MORE effects but displayed a modest effect of dAMPH on right VS BP_{ND} ($\%\Delta BP_{ND} = 8.06\%$; Cohen's d for drug effect on $BP_{ND} = 0.82$) which was not observed in dataset 2 young adult females ($\%\Delta BP_{ND} = -0.039\%$; Cohen's d for drug effect on $BP_{ND} = -0.24$) despite them showing higher WANT MORE ratings than dataset 1 females.

Hormone effects

Given past data on estradiol's effect on dAMPH-induced dopamine release in rodents (Becker 1990, 1999), we further examined whether there were any differences in our female subjects' response to dAMPH in relation to estradiol or birth control. In these data, women of childbearing potential were studied within the first 10 days of their menstrual cycle. In dataset 1 females, plasma estradiol levels were 25.76 ± 16.56 pg/ml (placebo visit) and 38.56 ± 31.47 pg/ml (dAMPH visit) and progesterone levels were 0.56 ± 0.38 ng/ml (placebo visit) and 0.96 ± 1.83 ng/ml (dAMPH visit). In dataset 2, plasma estradiol levels were 58.35 ± 46.37 pg/ml (dAMPH visit). Importantly, in dataset 1 estradiol

did not vary in women on hormonal birth control (21.90 ± 19.07 pg/ml) versus those that were naturally cycling (but studied within cycle days 1–10; 31.29 ± 11.19 pg/ml) during the placebo visit: $t(15) = 1.16$, $p = 0.26$. There was a significant but small difference in estradiol between the groups during their dAMPH visit: $t(16) = 2.47$, $p = 0.025$ (birth control group 25.74 ± 24.72 pg/ml; naturally cycling group 58.71 ± 31.83 pg/ml). In dataset 2 estradiol did not vary in women on hormonal birth control (60.40 ± 51.07 pg/ml) versus those that were naturally cycling (but studied within cycle days 1–10; 56.71 ± 46.86 pg/ml): $t(10) = -0.13$, $p = 0.90$ (data collected on dAMPH visit only).

In regression analyses, dAMPH session estradiol was not predictive of dAMPH-induced DA release ($\%\Delta BP_{ND}$) in any of the a priori anatomical ROIs (max $r = -0.29$, min $p = 0.13$ in right IFG, across all female participants but controlling for dataset). In dataset 1, percent change in estradiol from placebo to dAMPH session was not correlated with $\%\Delta BP_{ND}$ in any region (max $\rho = -0.37$, $p = 0.147$ in bilateral VS).

In addition, exploratory analyses were performed to examine whether dAMPH-induced DA release differed based on use of hormonal birth control. We found birth control use in young adult females (age < 50; total $n = 28$, 17 on birth control) did not lead to any significant differences in dAMPH-induced DA release in the a priori anatomical ROIs we tested here (max $F = 3.05$, min $p = 0.093$ in right IFG; controlling for subject age and dataset). In addition, we found no evidence of sex differences in dAMPH-induced DA release in the a priori anatomical ROIs when comparing males ($n = 26$) to females on or not on hormonal birth control (three groups, all age < 50; max $F = 1.58$, min $p = 0.22$ in bilateral putamen; controlling for subject age and dataset). Finally, rerunning our flexible factorial SPM voxelwise analyses in each dataset comparing males to females on and off birth control separately (datasets 1 and 2) or comparing postmenopausal females to age-matched males (dataset 2) did not lead to the identification of any significant clusters showing a sex × drug interaction on BP_{ND} (see unthresholded SPM T-maps for dataset 1: https://neurovault.org/collections/4040/ and dataset 2: https://neurovault.org/collections/4041/).

Discussion

Elucidation of sex differences in the responsivity of the DA system is important given that sex differences in addiction vulnerability have been previously speculated to reflect dopaminergic differences (Becker and Hu 2008). The present data indicate that to the extent healthy males and females show differences in d-AMPH-induced DA release, these differences appear subtle, regionally specific, and inconsistent across samples. In one of our two studies, we observed greater DA release in the right ventral striatum/ventral pallidum region, with young adult men showing greater release than females. This result is partially consistent with a prior study by Munro et al. (2006), who observed greater dAMPH-induced DA release in a bilateral VS ROI in men than women as measured with [^{11}C]raclopride (Munro et al. 2006). This is intriguing in that it would suggest an enhanced response in a region specifically associated with reward-motivational processes. However, although our results partially replicate the finding of Munro et al. (2006), caution is necessary in drawing conclusions about VS sex differences given that we did not see evidence of a similar effect in the left VS, or other striatal regions, and we failed to see evidence for a similar sex effect in the other dataset presented here. While there may be methodological variables that contribute to different findings across datasets and studies, the overall picture suggests that sex differences in DA release are subtle and are not robust enough to emerge consistently across typical, modestly-powered PET studies.

A clearer conclusion can be made regarding the possibility of a heightened DA response in women. While, the small preliminary study by Riccardi et al. (2006) suggested that women have a greater response to dAMPH than men in the pallidum and inferior frontal gyrus, this has not been replicated, and indeed across the two present studies, and the papers by Riccardi et al. (2006) and Munro et al. (2006), no studies have indicated a heightened striatal response in women relative to men within the striatum proper.

While the present data do not support a widespread difference in dAMPH-induced DA release based on sex, they also do not rule out the possibility that other features of the DA system may show sex differences. Indeed, there is at least some evidence of sex differences in other components of DA signaling. Females have been reported to show greater DA synthesis capacity, especially in caudate, measured with [^{18}F] fluorodopa PET relative to males (Laakso et al. 2002). Women have also been reported to have higher striatal DAT availability than men (Mozley et al. 2001) and this might be particularly pronounced in Parkinson's disease and age-related declines in DAT which have been suggested to be steeper in men (Lee et al. 2015). Furthermore, estradiol can inhibit DA uptake via the DAT in PC12 cells (Watson et al. 2006) while also being able to rapidly reverse DAT to increase extracellular DA levels (Alyea et al. 2008). In addition, a SPECT pilot study found that estrogen replacement therapy increased putamen DAT availability after 4–6 weeks of treatment (Gardiner et al. 2004). That said, our results suggest that those differences do not substantially impact the amount of DA release induced by oral dAMPH, at least as assessed with [^{18}F]fallypride PET.

In interpreting our effects, it is worth considering whether issues of menstrual phase, menopausal status, and reproductive hormone levels might influence the results. One possibility for our lack of widespread consistent sex effects could be

that differences in dAMPH-induced DA release are more related to female hormone levels than strict male and female differences per se. Returning to previous dAMPH-induced DA release PET studies, Munro et al. (2006) excluded women on hormonal birth control and measured plasma estradiol and progesterone levels in the 15 women in their study. They found no relationship between estradiol nor progesterone and baseline [^{11}C]raclopride BP_{ND} or DA release despite having nine women in the follicular phase (estradiol 59.63 ± 45.03 pg/ml; progesterone 0.83 ± 0.48 ng/ml) and six in the luteal phase (estradiol 118.41 ± 69.62 pg/ml; progesterone 10.18 ± 7.12 ng/ml) of their menstrual cycle. Riccardi et al. (2006) did not examine hormone levels in their participants.

In the two current datasets, women were either naturally cycling but studied in the first 10 days of their menstrual cycle (when estradiol and progesterone levels are low), on hormonal birth control, or postmenopausal (dataset 2). Calculation of plasma estradiol measurements in both datasets and progesterone (dataset 1) confirmed that hormone levels were relatively low in our female sample. Therefore, the relatively low level of female-associated hormones could have impacted the results. However, Munro et al. (2006) had a larger range in these hormone values in their female subjects and still observed no effect on dAMPH-induced DA release. Thus, at present, support that either estradiol or progesterone lead to a differential response is lacking.

The lack of consistently observable sex differences in dAMPH-induced DA release may be informed by the work of Alyea and Watson (Alyea et al. 2008; Alyea and Watson 2009; Watson et al. 2006) who demonstrate that estradiol at physiological levels can sequester DAT in intracellular compartments (Watson et al. 2006) in vitro where it would be inaccessible for dAMPH to act to release DA. Estradiol at physiological concentrations can also lead to DAT-specific DA efflux on its own (via actions at the estrogen receptor α, ERα) in the same in vitro preparation (Alyea et al. 2008). In fact, ERα been shown to associate with DAT on the plasma membrane (Alyea and Watson 2009). If these in vitro relationships hold in vivo, the presence and relative level of ERα in a brain region (Osterlund et al. 2000) along with the level of estradiol may affect DA concentration. dAMPH would presumably increase synaptic DA levels further but this may be limited by the relative surface availability of DAT, which has also been shown to be influenced by estradiol (Watson et al. 2006). As such, there may be a combination of sex differences in DAT functioning that are not captured by, or may even mask, observable dAMPH-induced DA release.

Limitations

First, we contrasted BP_{ND} following dAMPH versus placebo as the index of DA release. The use of placebo (where there was an expectation of potentially receiving dAMPH given that participants were blind to drug administration) rather than a true baseline state means that our measure of DA release could have been reduced by dopamine release occurring due to expectations on the placebo day (de la Fuente-Fernandez et al. 2001; Lidstone et al. 2010; Scott et al. 2008). However, the blind study design utilized here has advantages of limiting the impact of expectancies as opposed to actual drug effects.

While our findings are strengthened by the fact that we tested for sex effects in two independent datasets, the sample sizes in these studies, like prior studies, are individually relatively small. Unfortunately, the cost and complexity of a two-visit PET study limits the sample size that can be collected. In addition, there could be more subtle or time-limited sex differences in DA release in the brain. In order to estimate BP_{ND} and DA release, dynamic image acquisition is required over a time period through which the tracer reaches a pseudo-equilibrium state. In the case of [^{18}F]fallypride, this collection time is roughly 3.5 h. Thus, our PET measure of DA release may not capture short, transient increases in DA. Such temporally specific measures, however, can only be collected invasively in animals using techniques such as fast-scan cyclic voltammetry (Walker et al. 2000). There remains the possibility, then, that there are sex differences in more transient periods of DA release in humans.

In addition, it should be noted that although [^{11}C]raclopride and [^{18}F]fallypride are sensitive to dopamine release, the overall sensitivity is relatively modest, with [^{11}C]raclopride being somewhat more sensitive than [^{18}F]fallypride (Morris and Yoder 2007). However, the overall effect of dAMPH on [^{18}F]fallypride binding was statistically significant, especially in striatum (see Supplementary Figure 2) and has been shown to be sensitive enough to detect associations with other individual differences such as subjective responses to dAMPH (Smith et al. 2016a), effort-based decision making (Treadway et al. 2012), and the effects of dAMPH on task switching (Samanez-Larkin et al. 2013).

The complexity of studying sex effects and naturally fluctuating sex hormones is compounded by issues of birth control use and the postmenopausal transition with aging. Our datasets presented here contained women in these groups. While studying these women is more representative of the broader human population, the variability they could have introduced in our analyses may have hindered our ability to detect sex effects here. Importantly, however, we found no evidence for birth control use or menopausal status effecting dAMPH-induced DA release in our data. While, our statistical power was weak to detect the effects of birth control or menopausal status, the lack of observable birth control or menopausal status effects in the present samples indicates that these variables cannot easily explain why we observed no difference in male and female dAMPH-induced DA release.

Additionally, in the data presented here, females were always run within the first 10 days (follicular phase) of their

menstrual cycle when estradiol and progesterone are relatively low. It is possible that comparing females in the luteal phase of their menstrual cycle when hormone levels are higher would have led to the observation of sex differences. The work of Munro et al. (2006), however, found no effect of cycle phase on dAMPH-induced DA release, albeit with a limited sample size ($n = 9$ and 6 in follicular and luteal phase, respectively). This analysis was between and not within-subjects, however. Thus, there remains the possibility that dAMPH-induced DA release could vary across the menstrual cycle within individual women, especially given evidence that D2/3 receptor availability varies over the cycle in non-human primates (Czoty et al. 2009), but see (Nordstrom et al. 1998), which did not find effects in a small number of human females. Finally, there is evidence that female rats show greater and more rapid sensitization to the locomotor activating effects and demonstrate larger changes in striatal DA signaling in response to repeated amphetamine administration (Camp and Robinson 1988). While there is no experimental evidence confirming this in humans, there remains the possibility that females could show enhanced DA release after repeated dAMPH exposure when compared to males.

More work is needed to isolate precisely which aspects of DA functioning show sex differences in humans. However, the present findings indicate that these sex differences do not include a widespread, robust or generalizable difference in the level of DA release in response to dAMPH, at least within the early follicular phase, and possibly regardless of menstrual phase.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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