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Variability in paralimbic dopamine signaling correlates with subjective responses to d-amphetamine

Christopher T. Smith [a, *], Linh C. Dang [a], Ronald L. Cowan [a, b], Robert M. Kessler [c], David H. Zald [a, b]

[a] Department of Psychology, PMB 407817, Vanderbilt University, 2301 Vanderbilt Place, Nashville, TN 37240-7817, United States
[b] Department of Psychiatry, Vanderbilt University School of Medicine, 1601 23rd Ave South, Suite 3057, Nashville, TN 37212, United States
[c] Department of Radiology, UAB School of Medicine, United States

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ABSTRACT

Subjective responses to psychostimulants vary, the basis of which is poorly understood, especially in relation to possible cortical contributions. Here, we tested for relationships between participants' positive subjective responses to oral d-amphetamine (dAMPH) versus placebo and variability in striatal and extrastriatal dopamine (DA) receptor availability and release, measured via positron emission tomography (PET) with the radiotracer ^{18}F-fallypride. Analyses focused on 35 healthy adult participants showing positive subjective effects to dAMPH measured via the Drug Effects Questionnaire (DEQ) Feel, Like, High, and Want More subscales (Responders), and were repeated after inclusion of 11 subjects who lacked subjective responses. Associations between peak DEQ subscale ratings and both baseline ^{18}F-fallypride binding potential (BPnd; an index of D2/D3 receptor availability) and the percentage change in BPnd post dAMPH (%ΔBPnd; a measure of DA release) were assessed. Baseline BPnd in ventromedial prefrontal cortex (vmPFC) predicted the peak level of High reported following dAMPH. Furthermore, %ΔBPnd in vmPFC positively correlated with DEQ Want More ratings. DEQ Want More was also positively correlated with %ΔBPnd in right ventral striatum and left insula. This work indicates that characteristics of DA functioning in vmPFC, a cortical area implicated in subjective valuation, are associated with both subjective high and incentive (wanting) responses. The observation that insula %ΔBPnd was associated with drug wanting converges with evidence suggesting its role in drug craving. These findings highlight the importance of variability in DA signaling in specific paralimbic cortical regions in dAMPH's subjective response, which may confer risk for abusing psychostimulants.

1. Introduction

Significant individual variability exists in subjective responses to oral d-amphetamine (dAMPH) in humans (Brauer et al., 1996; Brown et al., 1978; de Wit et al., 1986; Dommisse et al., 1984). While some subjects report strong experiences of liking, high, and euphoria, others are unable to discriminate between drug and placebo (Chait et al., 1985, 1989). Understanding individual differences in these positive subjective responses is important as their magnitude after early drug exposure have been linked to drugs' abuse potential (Lambert et al., 2006). Thus, they may serve as risk factors for repeated drug use, leading to addiction (de Wit and Phillips, 2012; Haertzen et al., 1983). Despite their importance, the neural and neurochemical events that contribute to subjective response differences to dAMPH have yet to be fully elucidated.

Given that dAMPH causes the release of the neurotransmitter dopamine (DA) primarily via blockade and reversal of the dopamine transporter (DAT) (Jones et al., 1998) and animal work has linked DA release in nodes of the mesocorticolimbic system with reward processes (Wise and Rompre, 1989), researchers have proposed that DA release in this system may be directly or indirectly responsible for dAMPH's euphoric effect in humans. Indeed, previous work has found that dAMPH-induced DA release measured in the striatum with ^{123}I-IBZM SPECT is associated with a positive reinforcement factor (Abi-Dargham et al., 2003). PET studies using ^{11}C-raclopride have, more specifically, implicated ventral striatum (VS) dAMPH-induced DA release with self-reported dAMPH-induced euphoria (Drevets et al., 2001) or drug wanting (Leyton

* Corresponding author.
E-mail address: christopher.t.smith@vanderbilt.edu (C.T. Smith).

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et al., 2002). Furthermore, an analysis using an earlier sample of the participants included in this study found a positive relationship between DA release in striatum measured with ^{18}F-fallypride PET and "Want More" drug ratings on the Drug Effects Questionnaire, DEQ (de Wit et al., 1986; Morean et al., 2013), after oral dAMPH (Buckholtz et al., 2010). Whether differences in dopaminergic functioning in other nodes of the mesocorticolimbic DA system impact subjective responses to dAMPH is currently unknown. However, data suggest functional connections between the VS and paralimbic cortical areas (Haber and Knutson, 2010; Lee et al., 1999) and there is evidence that paralimbic areas are involved in addiction relevant processes such as value coding in the medial prefrontal cortex (mPFC) and neighboring orbitofrontal cortex (OFC) (Bartra et al., 2013; Clithero and Rangel, 2014; Diekhof et al., 2012; First et al., 1997) and drug craving in the insula (Kilts et al., 2001; Naqvi et al., 2014).

Here, we sought to characterize the relationship between the subjective effects of dAMPH assessed with DEQ High, Like, Feel and Want More ratings and ^{18}F-fallypride measures of DA D2/3 receptor availability and dAMPH-induced DA release in a sample of healthy young adults. Until now, work focused on assessing a potential relationship between extrastriatal DA characteristics and subjective responses has been limited due to ^{11}C-raclopride and ^{123}I-IBZM's inability to reliably estimate DRD2/3 availability (measured as binding potential, BPnd) outside the striatum. The radiotracer ^{18}F-fallypride, however, is able to estimate DRD2/3 BPnd in PFC, temporal lobes, and the insula in addition to the striatum (Mukherjee et al., 2002; Riccardi et al., 2008) and can index DA release after d-amphetamine (dAMPH) administration, measured as %ΔBPnd from baseline (Riccardi et al., 2006a; Slifstein et al., 2010). We were particularly interested in using fallypride to test whether DA functions in paralimbic cortical areas, specifically the mPFC/OFC, related to subjective responses to dAMPH given past evidence that activity in these areas are increased in response to psychostimulants in drug naïve individuals (Vollm et al., 2004) and correlate with their self-reported euphoric effects (Udo de Haes et al., 2007).

2. Methods and materials

2.1. Subjects

Forty-six (23 men; ages 18–35, mean = 22 ± 2.86) healthy individuals participated in the study. Participants had no known past or present neurological or psychiatric diagnoses, no history of substance use disorders, and no current use of psychoactive medications or substances as assessed by Structured Clinical Interview for DSM Disorders I (First et al., 1997) administered at screening. On interview, none of the subjects reported having ever used amphetamine or cocaine. In terms of other psychostimulants, three subjects acknowledged past use: Dexatrim for a few days in one case, ephedrine 4 times in one case, and ephedrine once daily for three months in a final case. Data were reanalyzed excluding the case with the more extensive ephedrine exposure, but this did not produce any marked change in the results. Women were tested during the follicular phase of their cycle. Participants gave written informed consent, as approved by the Vanderbilt University Institutional Review Board.

It should be noted that 30 of our subjects were included in an earlier report by Buckholtz et al. (2010) with the other 2 subjects from that study not included here as they lacked full DEQ measures at both placebo and dAMPH sessions. The remaining 16 subjects in our sample were collected after completion of analyses for Buckholtz et al. (2010). Although that report focused on correlations with impulsivity, it did note a relation between striatal DA release and drug wanting as part of a secondary analysis aimed at understanding the functional link between impulsivity and striatal response to amphetamine. However, it did not explore the pattern of correlations with the different DEQ scales, and critically did not test for relations between subjective responses and cortical DA indices.

We performed analyses with both the entire sample and limited to the 35 participants (22 male; age: 21.9 ± 2.72) who demonstrated at least some evidence of a subjective response to dAMPH versus placebo (DEQ Responders). The rationale for performing initial analyses excluding participants who lack a subjective response to dAMPH is that they might be qualitatively different, for instance due to atypical DAT functions. Inclusion of such participants in analyses related to subjective responses may hide real relations. However, we also report the results of our key analyses when the 11 Nonresponders were included in order to capture the full range of subjective responses and for comparability to prior studies of dAMPH that typically include Nonresponders in analyses.

2.2. Drug administration

Participants, themselves blind to drug administration order, received placebo for their first experimental PET session and a target dose of 0.43 mg/kg oral dAMPH during their second PET session (separated by a minimum of 24 h). The actual administered dose of dAMPH was rounded to the nearest 2.5 mg (mean actual dose: 30.5 mg, range: 20–42.5 mg) based on individual participants' weight to achieve the targeted 0.43 mg/kg dose. We note that because our primary interest in the study was the relation between individual differences in DA measures and subjective responses, we used a standardized administration order instead of a counter-balanced design. This standardized administration order avoids the potential introduction of systematic variance across subjects caused by some subjects receiving dAMPH first, and others receiving it second (order effects). If order effects do exist (which is a reasonable possibility for a study with psychostimulants), the avoidance of this source of systematic variance makes the standardized administration order design more efficient for detecting relations among variables across subjects. Having the placebo occur first also avoided any lingering effect of the dAMPH across sessions.

2.3. Procedure

Participants were tested for pregnancy before each PET session. They were instructed not to eat for 3 h before the sessions to standardize drug absorption. Subjects completed the Drug Effects Questionnaire (DEQ; see below) 60, 120, 180, 270, and 345 min after ingesting the capsule. Plasma samples were obtained 60, 120, 180, and 270 min after capsule ingestion.

2.4. Drug effects questionnaire

Individuals rated each term on 100 mm labeled magnitude scale (Lishner et al., 2008); 1) feel any substance effect(s) ("Feel"), 2) feel high ("High"), 3) like the effects ("Like"), 4) want more of the substance ("Want More") from NOT AT ALL (0 mm) to MOST IMAGINABLE (100 mm). The Drug Effects Questionnaire (DEQ) has good psychometric properties (Morean et al., 2013) and is sensitive to the effect of dAMPH (Brauer et al., 1996; de Wit et al., 1986). DEQ values were recorded as proportions of the 100 mm scale (values range from 0 to 1). Each DEQ rating post dAMPH was subtracted from the placebo rating taken at that same timepoint such that all analyzed ratings reflect responses to dAMPH relative to placebo. We defined Nonresponders as having a max average DEQ rating (across all 4 subscales; DEQ_{All}) <0.10 (>1 standard deviation below mean DEQ_{All} across all subjects). Across the dataset as a whole, DEQ

subscale ratings were highly correlated with one another (min $\rho = 0.64$ (between High and Like), max $\rho = 0.84$ (between Want More and Like); all $p < 0.001$) suggesting consistency in DEQ_{All} measure. One Nonresponder subject, however, did show a divergence in DEQ High/Feel (positive) and DEQ Like/Want More (negative) to dAMPH resulting in a low DEQ_{All} score despite modestly positive High and Feel ratings (>0.10). As Nonresponders were included only in follow-up analyses this one case of divergence in DEQ ratings did not affect the clusters identified in our DEQ/PET regression analyses in Responders.

2.5. Peripheral amphetamine absorption measure

Plasma amphetamine levels were analyzed via a selegiline + metabolites assay conducted by NMS Laboratories.

2.6. Fallypride 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. Data were collected on one of two GE Discovery PET scanners located at Vanderbilt University Medical Center, with the first twelve subjects collected on a Discovery LS model and the remainder (n = 34) on a Discovery STE system. Both scanners possess similar in plane resolution, but the Discovery STE has thinner axial slices (3.27 vs. 4.25 mm). All subjects received both their placebo and dAMPH scan on the same scanner system, and no differences were observed in BPnd measures across scanners (Buckholtz et al., 2010). Approximately 3 h after placebo or dAMPH administration, serial scan acquisition was started simultaneously with a 5.0 mCi slow bolus injection 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, which together lasted approximately 3.5 h with two breaks for subject comfort. With the PET scanner upgrade to the STE system that occurred after the first 12 subjects, the PET acquisition time protocol for the first dynamic run was slightly altered (see Supplemental Table S1). However, including PET scanner/acquisition type as a covariate did not alter any of the BPnd and %ΔBPnd relationships we report below.

2.7. Fallypride 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 region 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 reference region 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 fallypride binding potential (BPnd, a ratio of specifically bound fallypride to its free concentration). Specifically PMOD's PXMOD tool was used to estimate BPnd voxel-wise using a published basis function fitting approach (Gunn et al., 1997). The cerebellum served as the reference region due to its relative lack of D2/3 receptors (Camps et al., 1989). The resulting BPnd maps for placebo/baseline and dAMPH days were linearly registered to one another (FLIRT, 6 degrees of freedom) and the difference in BPnd maps (%ΔBPnd) after dAMPH was calculated as:

$$\%\Delta BPnd = (\text{baseline BPnd} - \text{dAMPH BPnd})/(\text{baseline BPnd}) \times 100\%$$

Thus, an increase in %ΔBPnd corresponded to an increase in synaptic DA release. Subject-specific baseline BPnd and %ΔBPnd images were then warped to MNI space using the saved FSL transforms to create MNI-normalized BPnd and %ΔBPnd 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 their relation to subjective responses to dAMPH.

2.8. Data analysis

Taking a whole-brain approach, we regressed MNI-normalized placebo/baseline fallypride BPnd and %ΔBPnd data against max DEQ ratings from each subscale separately using SPM8. Cluster-level significance was set at $p < 0.05$ family-wise error (FWE) corrected. For clusters showing a significant relationship between fallypride measures and max DEQ ratings, we extracted mean BPnd or %ΔBPnd data using Marsbar (Brett et al., 2002) and subjected these values to a bootstrapped Pearson correlation (to identify 95% confidence intervals, *CI*) and multiple regression analyses (to test for the impact of potential confounds on BPnd) in SPSS. We covaried for potential confounds of plasma amphetamine levels, effective dAMPH dose, sex (known to impact DA signaling (Pohjalainen et al., 1998; Riccardi et al., 2006b)), and subject age (found to negatively correlate with BPnd (Mukherjee et al., 2002; Narendran et al., 2011)) in these follow-up regression analyses.

3. Results

3.1. DEQ ratings, dAMPH responders, and sex distributions

Readers are directed to Smith et al., 2016 (Smith et al., 2016) and Table S2 for details of DEQ ratings by Responder Group. While the proportion of males and females varied across Responder groups ($\chi^2 = 9.68$, $p = 0.002$), we note our female Responders did not differ from male Responders in their max DEQ ratings or in any of the PET relationships we report below. Also, the addition of sex as a predictor in our fallypride-DEQ regressions did not remove the relationships we observed.

3.2. Baseline DRD2/3 availability and DEQ ratings: relationship between vmPFC BPnd and DEQ_{High}

Regressing our placebo fallypride BPnd data on each max DEQ rating in our 35 DEQ Responders, we identified a large cluster (k = 388) in vmPFC (MNI coordinates of max T value: −10, 40, −2; $T = 4.53$; $p_{FWE} = 0.039$) showing a positive correlation with max DEQ High ratings (DEQ_{High}; $r = 0.57$, $p < 0.001$; *CI*: 0.34, 0.75; Fig. 1). We observed no areas showing a negative relationship between BPnd and DEQ_{High}. No area showed a positive or negative relationship between BPnd and the other DEQ ratings (Feel, Like, and Want More). To rule out possible confounds, we tested whether BPnd in the identified vmPFC cluster remained predictive after controlling for PET scanner type and timing differences (length of overall placebo PET acquisition time; see Methods, Table S1), peak plasma-amphetamine level, effective dAMPH dose, sex, and subject age. After controlling for these variables, there was no decline in the

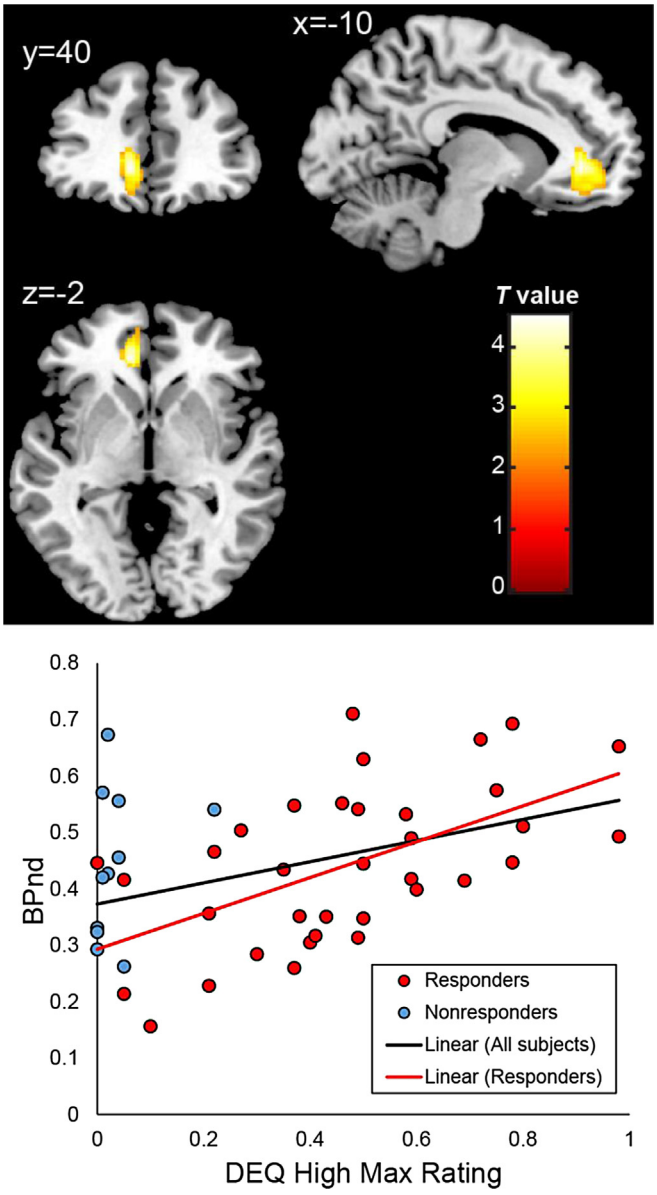

Fig. 1. Baseline DRD2/3 BPnd in a large cluster in vmPFC positively correlates with maximum DEQ High Ratings. Figure displays the significant vmPFC cluster from the baseline BPnd and DEQ High Max Rating regression ran on DEQ Responders in SPM8 surviving a cluster-level p, family-wise error correction of $p < 0.05$, overlaid on a MNI template brain (coordinates are in MNI space). A scatter plot of the relationship between mean BPnd in this cluster and DEQ High Max Rating across individuals shows a positive relationship between these variables across all subjects ($r = 0.39$, $p = 0.007$) and DEQ Responders only ($r = 0.57$, $p < 0.001$).

relationship between vmPFC BPnd and DEQ_{High} ($r = 0.76$: *F*-change 20.57, $p < 0.001$).

Reanalysis of the BPnd/DEQ_{High} relationship in this cluster including Nonresponders' data still resulted in a significant, albeit more modest, relationship ($r = 0.39$, $p = 0.007$; *CI*: 0.14, 0.61). Controlling for the variables mentioned previously did not remove the predictive relationship between vmPFC BPnd and DEQ_{High} across all subjects ($r = 0.56$: *F*-change 7.14, $p = 0.011$). Interestingly, we observed no difference in average placebo vmPFC BPnd among our DEQ Nonresponders (0.44 ± 0.132) and Responders (0.44 ± 0.140, $t_{44} = -0.013$, $p = 0.99$). Thus, while placebo BPnd in vmPFC is generally related to DEQ_{High} post dAMPH, it does not distinguish Responders from Nonresponders.

3.3. dAMPH-induced DA release

Testing for areas showing significant dAMPH-induced DA displacement of [^{18}F]-fallypride, we performed a one-way T-test in SPM8 on the %ΔBPnd data. Confirming previous work (Cropley et al., 2008; Riccardi et al., 2006a; Slifstein et al., 2010), we identified a large cluster (k = 4874) comprised of bilateral striatum that also encompassed the midbrain that displayed significant DA release (Fig. S1) in addition to areas in the temporal cortices and bilateral insula (Table S3).

3.4. Relationship between dAMPH-induced DA release and maximum DEQ ratings

Multiple regression analysis on each DEQ subscale revealed 3 clusters showing positive relationships between %ΔBPnd and higher max DEQ Want More ratings (DEQ_{Want}; Table 1A; Fig. 2) at a cluster-corrected $p_{FWE}<0.05$. The 3 clusters localized to the right VS (extending ventrally into the area of the subcallosal gyrus and olfactory tubercle), the left insula and the vmPFC. Although we did not observe a significant association in the left VS in the voxelwise analysis, we note that a post-hoc ROI analysis using the left VS from the WFU PickAtlas revealed a statistically significant relationship with DEQ_{Want} in the same direction as the right VS ($r = 0.351$, $p = 0.039$, *CI*: 0.094, 0.556). Furthermore, we note that the vmPFC itself did not show statistically significant %ΔBPnd at the group level, though some subjects had positive %ΔBPnd here (Fig. S2). This was in contrast to the VS and left insula, where there was evidence of significant %ΔBPnd at the group level (Table S4). We observed no areas showing a negative relationship between %ΔBPnd and DEQ_{Want}. Importantly, as shown in Table 1B (also see Fig. S2), the inclusion of *all subjects* (including DEQ Nonresponders) in our DEQ_{Want} R0I analyses did not alter the statistical significance of correlations between %ΔBPnd and DEQ_{Want} ratings in the clusters from Table 1A. The addition of PET scanner type and minor differences in PET scan acquisition times between dAMPH and placebo sessions (Table S1), sex, age, dAMPH dose, and plasma amphetamine levels as predictors similarly did not alter these relationships.

3.5. Relationships to DEQ feel and like?

Using our *a priori* cluster-level threshold (see Methods), no areas were identified where either BPnd or %ΔBPnd related to max DEQ Feel and/or Like ratings. However, in a post-hoc follow-up analysis we observed that %ΔBPnd in the DEQ_{Want} vmPFC cluster correlated positively with all DEQ max ratings (DEQ_{High}: $r = 0.37$, $p = 0.01$, *CI*: 0.093–0.617; DEQ_{Like}: $r = 0.34$, $p = 0.021$, *CI*: 0.083–0.561; DEQ_{Feel}: $r = 0.30$, $p = 0.042$, *CI*: 0.019–0.543), suggesting that this may be a common area at which dAMPH's effects on DA transmission are associated with its subjective effects. The stronger relationship with DEQ_{Want} is evident, though, as vmPFC %ΔBPnd still showed a relation to DEQ_{Want} ($\beta = 0.59$, $R^2 = 0.28$) even after controlling for the other three DEQ ratings and no other DEQ rating is significantly associated with vmPFC %ΔBPnd when DEQ_{Want} is entered as the first predictor. Thus, although the vmPFC showed some modest associations with multiple ratings, %ΔBPnd change in vmPFC was more strongly associated with dAMPH wanting versus other subjective effects.

4. Discussion

4.1. vmPFC DA and subjective responses to dAMPH

Higher vmPFC D2/3 BPnd on placebo was associated with higher

Table 1
Brain areas showing significant positive relationships between %ΔBPnd and max DEQ Want More ratings.

Area (MNI coord at peak T value)	Cluster size (k)	Peak-level *T* value	pFWE-corrected	r, (95% CI)
A. DEQ Responders				
Right ventral striatum (4, 6, −8)	275	4.39	<0.001	0.59, (0.41, 0.76)
vmPFC (−4, 42, −6)	195	4.24	<0.001	0.68, (0.51, 0.81)
Left insula (−40, 2, −6)	215	3.95	<0.001	0.62, (0.39, 0.79)
Area	ROI Cluster size (k)			*r*, *p* (95% CI)
B. All subjects, ROI analyses				
Right ventral striatum	275			0.33, 0.024 (0.05, 0.59)
vmPFC	195			0.57, <0.001 (0.37, 0.71)
Left insula	215			0.50, <0.001 (0.31, 0.68)

A. Table reports areas identified via a positive regression analysis in SPM8. We report the MNI coordinates of the peak T value from the SPM as well as the cluster size and cluster-level significance from each area. In addition, we report the correlation value as well as 95% confidence interval between the mean %ΔBPnd in each cluster and max DEQ_{Want} ratings.
B. %ΔBPnd from the clusters identified in Responders were tested for relationships with max DEQ Want More ratings (DEQ_{Want}) in all subjects and the result of the correlations are reported along with 95% confidence intervals. Cluster size (k) is number of 2 mm isotropic voxels present in the cluster.

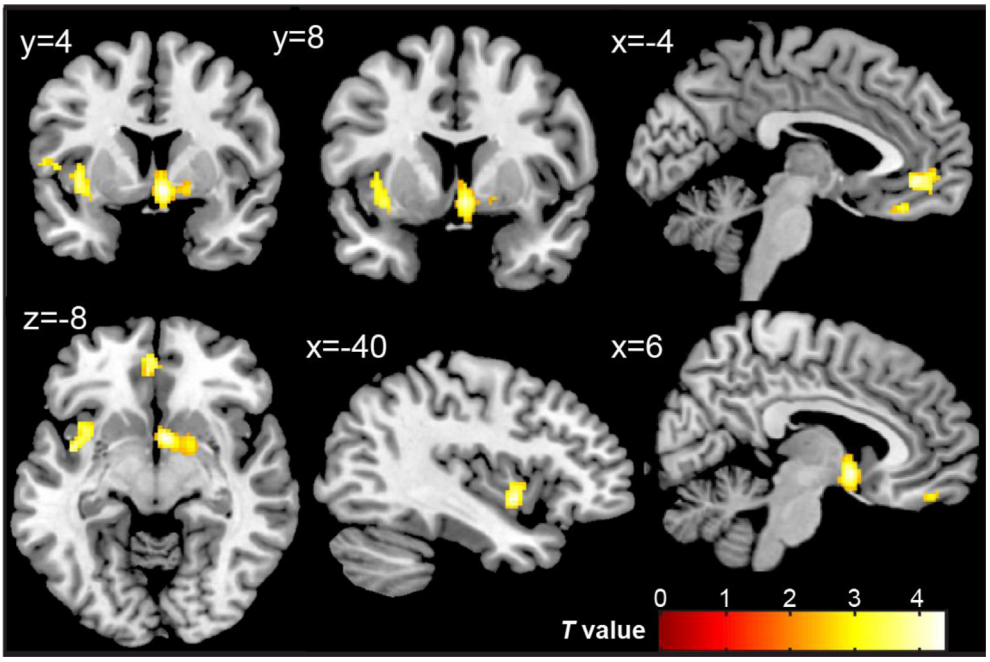

Fig. 2. %ΔBPnd is positively correlated with max DEQ Want More ratings in right ventral striatum, vmPFC, and left insula. Figure displays all significant clusters identified from DEQ_{Want} regression ran on Responders in SPM8 surviving a cluster-level p, family-wise error correction of $p < 0.05$, overlaid on a MNI template brain (coordinates are in MNI space). See Table 1A for MNI coordinates, voxel size, and peak T-values of these clusters. Note positive %ΔBPnd reflects DA release.

DEQ High ratings in response to oral dAMPH. To our knowledge, this is the first study suggesting that individual differences in subjective responses to psychostimulants are related to individual differences in dopaminergic functional characteristics in the vmPFC. Of note, the vmPFC area identified here extends into the anterior cingulate and subgenual cingulate cortices, whose activity have been implicated in psychostimulant response (Breiter et al., 1997; Udo de Haes et al., 2007; Vollm et al., 2004) and sympathetic arousal (Beissner et al., 2013), providing further support for its potential importance in mediating variation in dAMPH subjective responses. A potential issue arises in interpreting vmPFC D2/3 BPnd measured in a placebo condition, since it is possible that expectancy alters DA functioning. This is particularly relevant given recent evidence that cocaine cues can cause DA release in the vmPFC/medial orbitofrontal region (Milella et al., 2016). However, given the stability of cortical BPnd estimates (Dunn et al., 2013), the fact that subjects knew there was only a 50% chance of receiving amphetamine, and none had been exposed to dAMPH, it is reasonable to expect that most of the variance in vmPFC BPnd across subjects is driven by stable trait differences in DA functions in this region. As such, we strongly suspect that the present findings reflect trait differences that influence the sensitivity to experiencing subjective high in response to dAMPH.

It is notable that we only observed significant placebo BPnd relationships with stimulated DEQ_{High} and not the other DEQ measures. Although there are significant correlations among the different DEQ variables, they are not identical. Subjective High is a complex phenomenon that can encompass the perception of multiple cognitive, autonomic and mood experiences. As such it is not synonymous with euphoria or liking. Indeed, although DEQ_{High} & DEQ_{Like} ratings were correlated across the entire study population, the relationship between the variables is not particularly tight (among Responders high ratings were only related to euphoria/liking at a trend level: $\rho = 0.29$, $p = 0.093$).

4.2. vmPFC DA: individual differences without overall measurable DA release

Further evidence for the importance of the vmPFC to subjective responses comes from the changes in BPnd following dAMPH, where %ΔBPnd in vmPFC correlated with Want More ratings on dAMPH. Thus, high D2/3 receptor availability (BPnd) and greater changes in D2/3 binding (%ΔBPnd) in vmPFC were associated with multiple subjective responses to dAMPH with BPnd more related to drug "high" and %ΔBPnd related to drug "wanting". We note however that interpretation of the positive relationship between vmPFC %ΔBPnd and DEQ_{Want} must be treated with caution as no significant %ΔBPnd was detected here after dAMPH at the group level. Given that ^{18}F-fallypride is relatively weak at detecting small cortical changes in DA release, these apparent individual differences could reflect error in measurement. However, two pieces of data suggest otherwise. First, the BPnd estimates in the vmPFC showed reasonable stability across scan days: despite the fact that one scan had a drug manipulation, the placebo and dAMPH day BPnd data were as highly correlated in vmPFC ($r = 0.89$, $p < 0.001$) as they were in the right VS ($r = 0.91$, $p < 0.001$) and left insula ($r = 0.90$, $p < 0.001$) clusters across all subjects. Second, among Responders, vmPFC %ΔBPnd was also highly correlated with %ΔBPnd in VS: $r = 0.74$, $p < 0.001$ and insula: $r = 0.72$, $p < 0.001$, suggesting that common functional processes influence the %ΔBPnd response to dAMPH in these three regions (or, alternatively, a common unidentified methodological factor causes similar patterns across these striatal and extrastriatal regions).

One important methodological factor should be mentioned when interpreting the high incidence of positive *and negative* %ΔBPnd in the vmPFC. PET scanning was conducted during a period of relatively stable plasma amphetamine levels starting 3 h after drug administration, similar to previous oral dAMPH protocols with fallypride (Riccardi et al., 2006a). However, with scans continuing until over 6-h post dAMPH administration, these measurements may not only reflect initial DA release, but also compensatory or autoregulatory changes in DA, which could present as a seemingly paradoxical change in %ΔBPnd in some subjects. Importantly, there is precedent for dAMPH-induced increases and decreases in DA release in the vMPFC as this has been observed in rodent studies using microdialysis (Hedou et al., 2001). Interestingly, in that work the presence of increases or decreases appear dependent upon previous drug exposure, with decreases in DA occurring in drug naïve rats, and increases in animals who had undergone drug sensitization (reflected in greater psychomotor responses to the drug). While our exclusion criteria should have resulted in negligible prior sensitization to psychostimulants (only 3 subjects reported any previous dAMPH-like psychostimulant use (2 used ephedrine, 1 dexatrim) and removing the 1 subject with >4 previous psychostimulant uses did not alter any of our results), this animal work highlights the need to consider both increases and decreases in DA transmission in response to dAMPH, with those showing changes consistent with DA release possessing potentially greater behavioral effects to the drug.

4.3. VS DA release and dAMPH wanting

DA release in right VS positively correlated with DEQ_{Want}, suggesting that this region may be important in attributing incentive salience to dAMPH. Correlations between greater VS/striatal oral dAMPH-induced DA release and drug wanting have been seen previously (Buckholtz et al., 2010; Leyton et al., 2002), and this observation was expected given that the present sample included subjects from the Buckholtz et al. study (and therefore cannot be considered an independent replication). Nevertheless, these associations contrast with the work of Drevets where injected dAMPH-induced euphoria correlated with VS DA release (Drevets et al., 2001) and highlight an ongoing debate as to the relationship between DA and reward processes – whether DA conveys the hedonic value of rewarding stimuli themselves ("euphoria" (Wise and Rompre, 1989)) or motivates the pursuit of rewards by attributing incentive salience to reward-related stimuli ("wanting" (Berridge, 2007)). However, given the high correlation between our measure of dAMPH Want More with High ($\rho = 0.72$) and Liking ($\rho = 0.84$) and the absence of an assessment of drug wanting in the work by Drevets et al., it is possible that VS DA release in that study could have correlated with wanting as well. Despite the high correlation between DEQ Like and Want More ratings in our data, we found no evidence of a relationship between VS DA release and dAMPH "liking". Thus, our results are consistent with preclinical work showing that DA in the ventral striatum/nucleus accumbens attributes incentive salience to stimuli to promote "wanting" not "liking" (Berridge, 2007; Wyvell and Berridge, 2000). An important observation in our VS data however, is that DA release here was also high in DEQ Nonresponders (Table S4) suggesting that VS DA release occurs in most individuals after acute dAMPH but the degree to which this release relates to dAMPH wanting may differ across individuals via mechanisms not yet determined. Indeed the present data suggest that VS DA release and subjective response to dAMPH may be dissociated in the population of individuals who lack a subjective response to the oral administration of the drug. Further work is needed to understand how VS DA release could convey different subjective signals as part of larger functional circuits.

4.4. Insula DA release and dAMPH wanting

Despite a number of studies suggesting the insula's importance in drug craving (Naqvi et al., 2014) and the perpetuation of addiction (Gaznick et al., 2014; Naqvi et al., 2007), a link between psychostimulant-induced DA release in the insula and subjective drug "wanting" (incentive salience (Robinson and Berridge, 1993);) had not been shown previously. This is probably due to the inability for raclopride (the predominantly used PET ligand in dAMPH-DA release studies) to reliably measure DA release outside the striatum. The insula is thought to integrate interoceptive activity with other inputs to form a combined representation of homeostatically salient features of one's internal and external environment (Craig, 2011) and serves as an important hub of a stimulus salience network in the brain (Uddin, 2015). Given this previous work, DA release in the insula may serve to convey the incentive salience value of dAMPH to the rest of the brain, promoting increased dAMPH wanting.

We acknowledge that our insula finding could result from potential partial volume effects in our PET data. The proximity of this structure to the putamen, an area with high fallypride BPnd, raises the possibility that spillover from the putamen could bias insula fallypride signal. However, we note that we observed no relationship between DEQ Want More and %ΔBPnd in the left putamen in our voxelwise analysis, suggesting anatomical specificity of our left insula finding. Future PET work investigating DA signaling in the insula should be mindful of the possibility of partial volume effects in this structure and take care to address them in their analysis and interpretation of any insula finding.

4.5. Role of VS, insula, and vmPFC DA in drug seeking: a network conveying subjective value and incentive salience

Models of drug seeking behavior propose that the insula responds to interoceptive signals of drug administration and vmPFC

reflects the drug's relative/subjective value which are critical processes in determining the incentive value placed on the drug (Naqvi and Bechara, 2010; Naqvi et al., 2014). Projections from these structures to VS help to motivate continued drug use even in the face of negative consequences (Seif et al., 2013), a key hallmark of drug addiction. Our findings fit with this conceptualization and implicate DA release in these structures in initial wanting responses to dAMPH, supporting a role for these areas in the incentive motivational circuitry that promote drug seeking. Interestingly, placebo D2-receptor availability in these regions was not predictive of these wanting responses. Only placebo BPnd in the vmPFC predicted subjective experiences of drug-induced high. Thus, there is a partial dissociation between the impact of individual differences in vmPFC D2 receptors at placebo/baseline in predicting drug "High" versus the impact of differences in DA release in the vmPFC, VS, and insula in drug wanting. How the nodes we have identified here coordinate their activity to promote pleasurable and drug seeking effects will require further investigation with techniques that can measure the dynamics of neurochemical and neural activity over time.

4.6. Relationship to the D2/3 deficit model of addiction?

We observed no negative relationships between Fallypride BPnd and dAMPH responsivity. The D2 deficit model of addiction posits that lower levels of D2 receptors may lead individuals to self-administer drugs of abuse to compensate for low DA tone (Reward Deficiency Syndrome; Blum et al., 2000). This hypothesis is based on observations that low D2/3 receptor levels are associated with heightened cocaine self-administration in rats and monkeys (Dalley et al., 2007; Nader et al., 2006) and that increasing D2 receptor levels can lower levels of cocaine self-administration (Thanos et al., 2008). While cocaine dependence has been associated lower levels of D2/3 receptor availability (Martinez et al., 2004; Volkow et al, 1990, 1993) and dAMPH-induced DA release (Martinez et al., 2007) in the human striatum assessed with [^{11}C]-raclopride PET, the relationship between D2/3 levels and human psychostimulant addiction risk remains unknown. In the current study, one might have expected that dAMPH Responders or level of subjective response(s) to dAMPH would be associated with lower levels of baseline/placebo striatal BPnd or dAMPH-induced DA release here, if these are indeed measurable traits of psychostimulant addiction risk. This was not the case, however, and may be due to the fact that in all but 2 subjects (who had used ephedrine previously, see Methods) this was our participants' first exposure to a psychostimulant. It is possible that repeated dAMPH administrations are needed to alter D2/3 receptor levels to produce the commonly observed deficit in these receptors in human addicts. Alternatively, other aspects of DA signaling (beyond D2/3 receptor availability as measured with the D2/3 antagonists raclopride and fallypride) may be the key processes altered after psychostimulant exposure. For example, other PET work suggests that D2/3 agonist binding potential (and the post-synaptic D2/3 receptor levels it is thought to represent) is not different in cocaine dependent individuals when compared to controls (Narendran et al., 2011). Further work is needed to determine whether differences in D2 signaling are indeed risk factors for developing stimulant addiction and what particular components in DA signaling are altered with repeated stimulant use in human subjects.

4.7. Subjective dAMPH responders vs nonresponders

We are, to our knowledge, the first PET study investigating subjective effects of psychostimulants to look at Responders separately from Nonresponders. We note that previous work has not focused on such divisions despite substantial heterogeneity in the subjective responses reported (Drevets et al., 2001; Leyton et al., 2002). One important distinction between our DEQ Responders and Nonresponders was that Nonresponders were predominantly female (~91%) while Responders were more frequently male (~63%). We note that the only other study (outside our group) to associate dAMPH wanting with DA release examined males exclusively (Leyton et al., 2002). Thus, if males are more responsive to the positive subjective effects of dAMPH, this study was biased toward seeing a high proportion of Responders in their sample. Furthermore, the relationship between dAMPH-induced DA release and a variety of behavioral and personality measures have been shown to vary across the sexes (Riccardi et al, 2006b, 2011), suggesting dAMPH's effects may not be consistent across males and females. In our sample, though, the reason why ~43% of females were Nonresponders is not currently clear. Female Responders and Nonresponders did not differ in age, dAMPH dose, or peak plasma amphetamine levels nor in either placebo BPnd or %ΔBPnd from the clusters we identified in our DEQ regression analyses (max $t(21) = 1.36$, min $p = 0.19$). Furthermore, all females were tested in the early follicular phase of their menstrual cycle on both PET scan days and no hormone that we measured (plasma estrogen, estradiol, or progesterone) significantly differed between female Responders or Nonresponders on either PET scan day. Given literature suggesting a potential relationship between female hormones and DA signaling (Bazzett and Becker, 1994; Becker, 1990; Czoty et al., 2009; Di Paolo et al., 1988; McDermott et al., 1994; Nordstrom et al., 1998), though, the role of female hormone effects on PET measures of DA signaling should be investigated in future studies.

5. Conclusion

In conclusion, the data presented here suggest that variation in vmPFC DA signaling (baseline/placebo BPnd and %ΔBPnd) are related to the level of subjective effects reported after oral dAMPH. Specifically, higher vmPFC DA D2/3 receptor availability under placebo conditions is associated with greater self-reported High ratings after dAMPH *and* DA release post dAMPH in the vmPFC is related to higher Want More drug ratings. Furthermore, we confirm a role of dAMPH-induced DA release in VS in drug wanting and identify, for the first time, a role for the left insula in this process as well. Taken together, our results suggest dAMPH-induced DA release in a network of structures associated with value (vmPFC/VS) and interoceptive/affective (vmPFC/insula) processing may work together to convey incentive salience to dAMPH in drug-naïve individuals. Furthermore, differences in DA signaling in these regions may confer risk for abusing psychostimulants in the future.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.neuropharm.2016.05.004.

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