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Amphetamine-Induced Displacement of [^{18}F] Fallypride in Striatum and Extrastriatal Regions in Humans

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This study examined D-amphetamine (D-AMPH)-induced displacements of [^{18}F] fallypride in striatal and extrastriatal regions and the correlations of these displacements with cognition, affect, and sensation-seeking behavior. In all, 14 normal subjects, six females and eight males (ages 21–32, mean age 25.9 years), underwent positron emission tomography (PET) with [^{18}F]fallypride before and 3 h after a 0.43 mg/kg oral dose of D-AMPH. Levels of dopamine (DA) D_2 receptor density were calculated with the reference region method of Lammerstma. Percent displacements in striatal and extrastriatal regions were calculated for the caudate, putamen, ventral striatum, medial thalamus, amygdala, substantia nigra, and temporal cortex. Correlations of changes in cognition, affect, and sensation seeking with parametric images of D-AMPH-induced DA release were computed. Significant displacements were seen in the caudate, putamen, ventral striatum substantia nigra, and temporal cortex with a trend level change in the amygdala. Greatest displacements were seen in striatal subdivisions—5.6% in caudate, 11.2% in putamen, 7.2% in ventral striatum, and 6.6% in substantia nigra. Lesser decrements were seen in amygdala—4.4%, temporal cortex—3.7%, and thalamus—2.8%. Significant clusters of correlations of regional DA release with cognition and sensation-seeking behavior were observed. The current study demonstrates that [^{18}F]fallypride PET studies using oral D-AMPH (0.43 mg/kg) can be used to study D-AMPH-induced DA release in the striatal and extrastriatal regions in humans, and their relationship with cognition and sensation-seeking behavior.
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INTRODUCTION

Several brain imaging studies have investigated D-amphetamine (D-AMPH)-induced dopamine (DA) release in the striatum (Laruelle *et al*, 1995; Kegeles *et al*, 1999; Drevets *et al*, 2001; Singer *et al*, 2002; Piccini *et al*, 2003; Martinez *et al*, 2003; Volkow *et al*, 1994, 2004). However, dopaminergic neurotransmission in cortex, thalamus, and limbic regions is believed to be significantly involved in psychosis, cognitive function, and psychostimulant drug abuse (Weinberger *et al*, 2001; Stevens, 1991; Kerwin and Murray, 1992; Goldman-Rakic, 1998; Yasuno *et al*, 2004; Koob and Le Moal, 2001). Most, but not all, recent brain-imaging studies suggest that extrastriatal DA D_2 receptors are the site of antipsychotic drug actions (Farde *et al*, 1997; Pilowsky *et al*, 1997; Bigliani *et al*, 2000; Xiberas *et al*, 2001a, b; Kessler *et al*, 2002; Bressan *et al*, 2003; Talvik *et al*, 2001). Extrastriatal dopaminergic neurotransmission is an important area of research in neuropsychiatric disorders (Kaasinen *et al*, 2001; Suhara *et al*, 2002).

The affinity of currently used DA D_2 radioligands such as [^{11}C]raclopride, 1.2 nM (Hall *et al*, 1989), and [^{123}I]IBZM, 0.4 nM (Kung *et al*, 1989), permits accurate measurement of DA D_2 receptor levels only in the striatum, which has the highest DA D_2 receptor levels in brain (Kessler *et al*, 1993b; Laruelle *et al*, 1995; Drevets *et al*, 2001). With the development of high-affinity radioligands, such as [^{11}C]FLB 457, [^{123}I]epidepride, and [^{18}F]fallypride, it has been possible to visualize and quantitate levels of striatal and extrastriatal DA D_2/D_3 receptors (Kessler *et al*, 1991, 1992, 1993a; Halldin *et al*, 1995; Mukherjee *et al*, 1995). The striatal uptakes of [^{11}C]FLB 457 and [^{123}I]epidepride are prolonged (Farde *et al*, 1997; Olsson *et al*, 1999; Fujita *et al*, 1999), making estimation of striatal DA D_2/D_3 receptor levels difficult. [^{18}F]fallypride is a benzamide with very high-affinity for DA D_2/D_3 receptors, which has been used to visualize and quantify levels of striatal and extrastriatal DA D_2/D_3 receptors using positron emission tomography

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(PET) (Mukherjee *et al*, 1999, 2002; Rieck *et al*, 2004). Although [^{18}F]fallypride has an *in vitro* K_D for the DA D_2/D_3 receptors similar to that of [^{123}I]epidepride and [^{11}C]FLB 457, it has considerably more rapid washout from striatum, allowing estimation of DA D_2/D_3 receptor levels in both striatal and exrtastriatal regions (Mukherjee *et al*, 1997; Kessler *et al*, 1991; Olsson *et al*, 1999, 2004; Christian *et al*, 2004).

SPECT and PET studies of DA D_2/D_3 receptors performed before and after a D-AMPH challenge have been used to study striatal DA release. The decrement in striatal binding potential (b.p.) or V_3'' for benzamide DA D_2/D_3 radioligands following D-AMPH administration in primates has been shown to be linearly related to the level of D-AMPH-induced DA release (Laruelle *et al*, 1997; Breier *et al*, 1997). In humans, PET and SPECT studies using either [^{11}C]raclopride or [^{123}I]IBZM have demonstrated D-AMPH (0.3 mg/kg intravenous)-induced decrements of 7.1–16.1% in striatal b.p. or V_3'' (Abi-Dargham *et al*, 1998; Laruelle *et al*, 1995; Drevets *et al*, 2001; Martinez *et al*, 2003). Recently, Cardenas, using [^{11}C]raclopride PET, reported that an oral dose of 30 mg of D-AMPH produced a decrease in striatal b.p. of 13–18% in humans (Cardenas *et al*, 2004). Epidepride with an affinity of 24 pM for the DA D_2 receptor shows virtually no displacement after a 1 mg/kg dose of D-AMPH (Kessler *et al*, 1993c; al-Tikriti *et al*, 1994). Studies of [^{11}C]FLB 457 with a reported affinity of 20 pM for the DA D_2 receptor (Olsson *et al*, 1999) have produced conflicting results regarding its sensitivity to extracellular DA levels (Chou *et al*, 2000; Okauchi *et al*, 2001). Primate studies of [^{18}F]fallypride, with an affinity of 33 pM for the DA D_2 receptor and 31 pM for the DA D_3, have reported D-AMPH-induced decreases in b.p. of 12–36% in the thalamus, hippocampus, amygdala, and ventral striatum following 0.3–1.0 mg/kg intravenous doses of D-AMPH (Mukherjee *et al*, 1997, 2002; Slifstein *et al*, 2004).

No PET or SPECT studies of D-AMPH-induced DA release in extrastriatal regions have been reported in humans although, as discussed above, such studies have been reported in nonhuman primates (Mukherjee *et al*, 1997, 2002; Slifstein *et al*, 2004). The aim of this study was to assess whether [^{18}F]fallypride can be used to estimate D-AMPH-induced DA release in striatal and extrastriatal regions in humans following a 0.43 mg/kg oral dose of D-AMPH. An oral dose of 0.43 mg/kg of D-AMPH in comparison to an intravenous dose of 0.2–0.3 mg/kg produces lesser side effects such as elevated blood pressure, but similar plasma levels and displacement of [^{11}C]raclopride in striatum (Angrist *et al*, 1987; Breier *et al*, 1997; Cardenas *et al*, 2004).

METHODS

In all, 14 normal subjects, six females and eight males (ages 21–32 years, mean age of 25.9 years), were recruited by advertisement. All subjects were right hand dominant and none were smokers. Exclusion criteria included a history of psychiatric or neurological condition, a history of severe concomitant or past medical illness, borderline elevated blood pressure (135/90), any psychotropic medication usage for the last 6 months, a history of substance abuse and dependence, inability to provide informed consent, an IQ less than 80, and pregnancy or lactation. After an initial assessment, the study was explained to subjects and informed consent was obtained. The consent form included a recommendation for all participants to use adequate birth control measures during the study. All female subjects capable of childbearing had pregnancy tests performed 6 h or less prior to each PET study. All subjects received a physical and neurological examination, SCID (Williams *et al*, 1992), blood chemistries, urine analysis and urine drug screen, EKG and MRI study. Subjects additionally completed the Sensation Seeking Scale-Form (Zuckerman *et al*, 1978). MRI scans were performed using a GE 1.5 T scanner with echospeed gradients. Thin-section, high-resolution, T1-weighted coronal and sagittal IR SPGR sequences were obtained (TE = 3.6, TR = 18.9, TI = 400, slice thickness of 1.2–1.4 mm) and an axial T2-weighted sequence (TE = 106, TR = 5000, slice thickness of 3 mm) was obtained as well. Subjects who met the study criteria were scheduled for PET studies which were performed using a GE Discovery LS PET scanner; 3-D emission acquisitions and transmission attenuation correction scans were performed following a 5.0 mCi slow bolus injection of [^{18}F]fallypride (specific activity greater than 3000 Ci/mmol) prior to and 3 h following a 0.43 mg/kg oral dose of D-AMPH. Serial scans were initiated simultaneously with the bolus injection of [^{18}F]fallypride and were obtained for approximately 3.5 h. The initial scan sequence was started coincident with the start of the [^{18}F]fallypride injection and included the following frames: 8 for 15 s, 6 for 30 s, 5 for 1 min, 2 for 2.5 min, 3 for 5 min, and 3 for 10 min. After the initial scan sequence, a 10-min transmission scan was obtained and the subject given a break. At approximately 85–90 min, a second scan sequence of two frames of 25 min each followed by a second transmission scan were obtained. The subject was then allowed a second scan break, and at approximately 165–170 min, a 40-min emission scan followed by a third transmission scan was obtained. For the post-D-AMPH study, subjects were instructed to have a light breakfast on the day of the scan, that is, a single cup of coffee, cold cereal, and/or bread, which was ingested approximately 4 h prior to D-AMPH administration. Physiological measures (blood pressure, heart rate, temperature, and respirations) were monitored throughout the study and a brief neurological examination performed.

Blood samples were collected for determination of plasma levels of D-AMPH at 1, 3, and 5 h following D-AMPH administration. The plasma samples were analyzed using a modification of the method of Campins-Falco *et al*, 1996. Briefly, 1.0 ml plasma samples, following addition of the internal standard B-phenylethylamine, were made basic and the amines isolated and derivatized on Waters Sep-Pak C-18 cartridge using 1,2-naphthoquinone-4-sulphate (NQS) as described by Campins-Falco. Following washing, the derivatized amines were eluted with acetonotrile : water (1 : 1), the volume reduced under vacuum, and the eluate analyzed by HPLC. The peaks corresponding to derivatized amphetamine and NQS were separated using a 7×53 mm Hypersil BDS 'Rocket' column (Alltech Assoc.) and quantitated by UV analysis at 450 nM.

Serial PET scans and thin-section T1-weighted MRI scans were coregistered to each other using a mutual information

rigid body algorithm (Pluim *et al*, 2001). Regions of interest were delineated for the right and left caudate, putamen, ventral striatum, amygdala, substantia nigra, the medial thalami, and temporal cortex on MRI scans of the brain (see Figures 1 and 2) by a neuroradiologist experienced in PET data analysis (RMK) and automatically transferred to both the pre- and post-D-AMPH PET studies. The ventral striatum was defined according to criteria of Mawlawi *et al*, 2001. The substantia nigra was delineated based on landmarks from the Schaltenbrand atlas (Schaltenbrand and Wahren, 1977); the substantia nigra is located in the ventral midbrain posteromedial to the cerebral peduncles from the superior aspect of the interpeduncular fossa approximately 9 mm below the ACPC line to 16 mm below the ACPC line. These regions of interest were transferred to the coregistered PET scans and regional DA D_2 receptor b.p.'s were calculated using the reference region method (Lammertsma *et al*, 1996). Percent displacements were calculated for each region of interest. Parametric images of DA D_2/D_3 receptor density and percent displacement were calculated on a pixel-by-pixel basis using the reference region method. Images were coregistered across subjects using an elastic deformation algorithm (Rohde *et al*, 2003). Approximately 60 min after D-AMPH administration (and at the equivalent point in time on non-drug administration days), subjects began a 75-min neuropsychological battery. The battery included measures of attention—Stroop task (Stoelting Co., 2000), information-processing speed—Digit Symbol Coding and Symbol Search (Wechsler, 1997), spatial working memory (Park *et al*, 1999), and affect—Positive Affect Negative Affect Scale (Watson *et al*, 1988). In order to minimize the practice effects, all tests were either presented using parallel forms, or utilized random order presentation of stimuli. One male subject was color-blind; although he completed all tests, he was excluded from analysis of the Stroop task that requires color processing. A second male subject had a disrupted spatial working memory trial during the baseline study and he was excluded from the working memory analysis.

To test the effects of D-AMPH on [^{18}F]fallypride binding, we performed a repeated-measures ANOVA implemented in the General Linear Model module of SPSS 11.5 (SPSS Inc., IL). The model used had three within-subject factors, condition (baseline, D-AMPH), region, and laterality. Paired two-tailed *t*-tests and Wilcoxon signed-rank tests were performed to delineate the source of significant differences on the ANOVA. Bonferroni correction for multiple comparisons were performed. Correlations of changes in cognition, affect, and sensation seeking with parametric images of [^{18}F]fallypride displacement were made using a Pearson

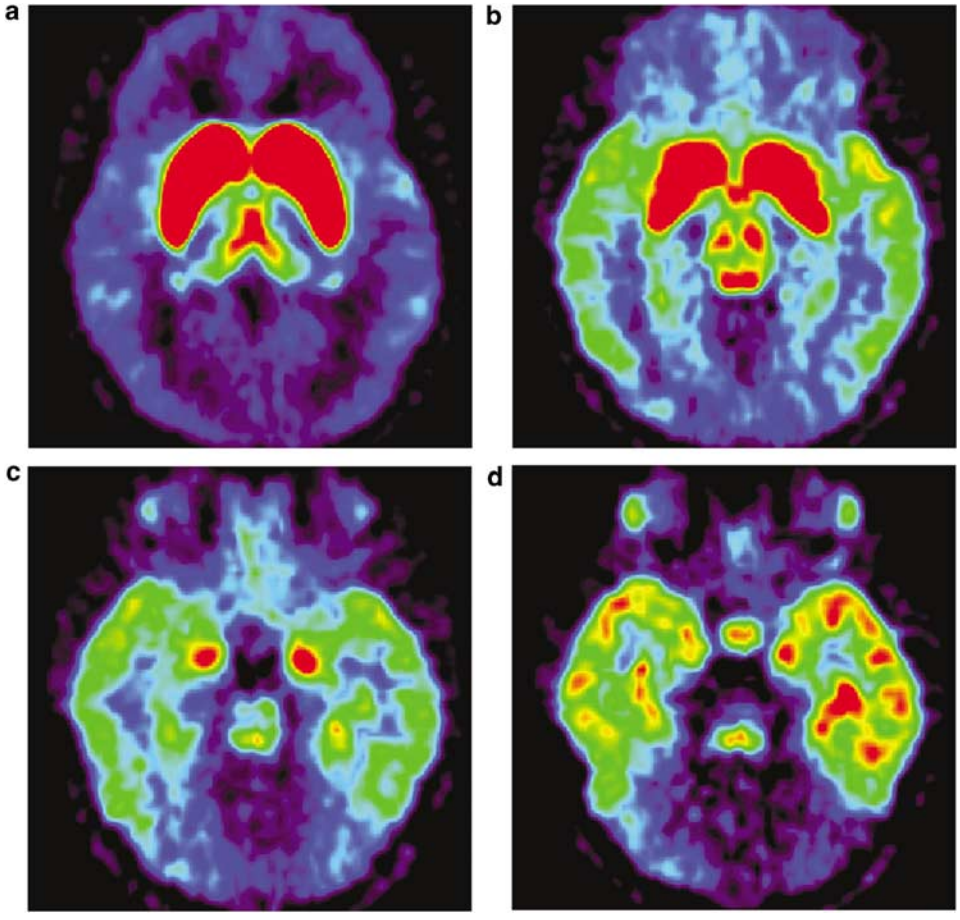

Figure 1 [^{18}F]fallypride PET scans obtained at baseline in a normal subject at (a) the level of the thalamus showing highest uptake in medial thalamus; (b) at the level of the midbrain showing uptake in the substantia nigra in the ventral midbrain and in the colliculi dorsally in the midbrain, (c) at the level of the uncus showing uptake in the amygdala, and (d) through the inferior temporal cortex showing high uptake in the pituitary and temporal cortex.

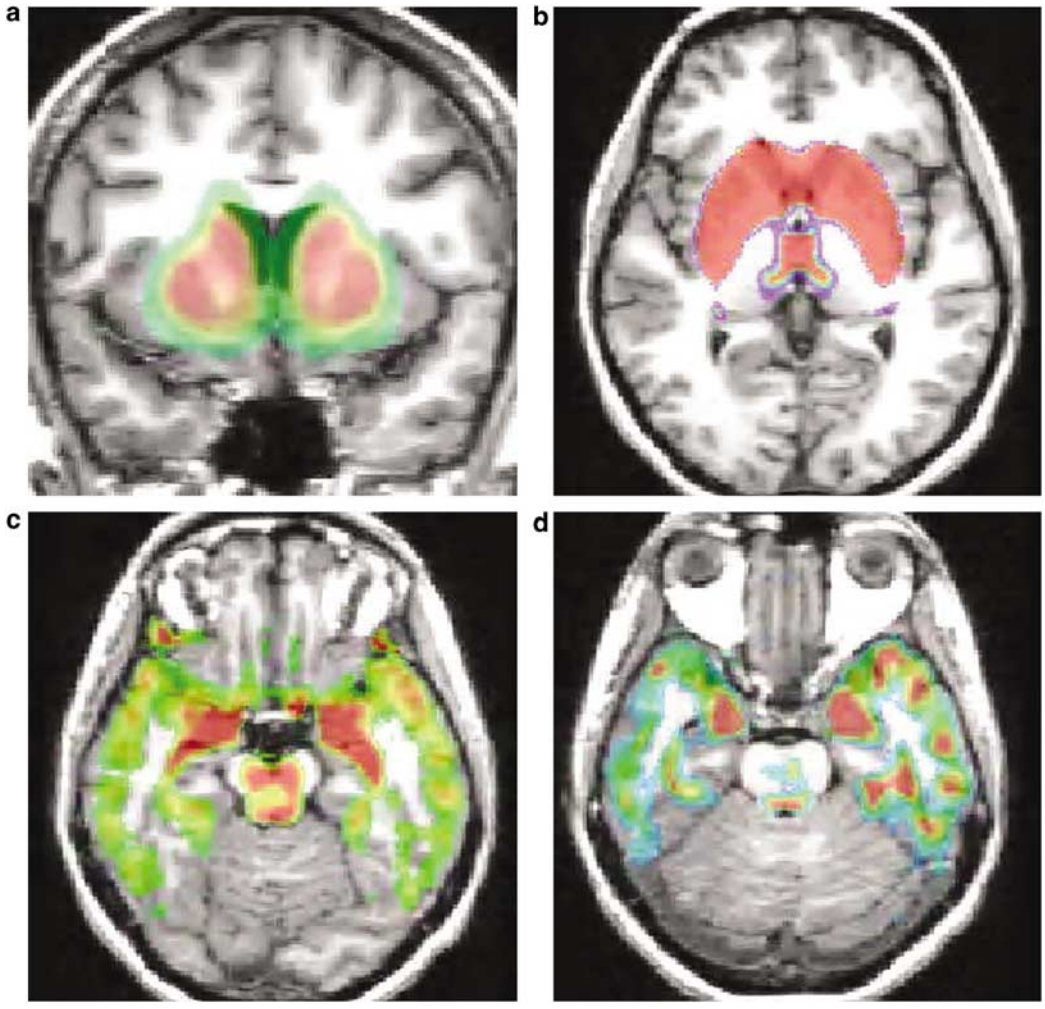

Figure 2 Parametric images of DA D2 receptor density coregistered with MRI images windowed to demonstrate [^{18}F]fallypride-b.p.'s in (a) the anterior and ventral striatum on a coronal image, (b) the medial thalamus on an axial image, (c) the substantia nigra, colliculi, and temporal cortex on an axial image through the midbrain, and (d) the amygdala and temporal cortex on an axial image through the uncus of the temporal lobes.

product moment correlation and significance assessed using two tailed *t*-tests. Correction for multiple within-image comparisons was made using the method of Forman *et al* (1995) as implemented in the Alpha-Sim program of the AFNI analysis program. This was utilized as the image data violated the uniformity of variance assumption of SPM. After correction for multiple within-image comparisons, significant clusters were corrected for multiple behavioral tests using a Bonferroni correction.

RESULTS

Repeated-measures ANOVA using condition, region, and laterality as factors revealed significant effects of region ($F = 415.5$, $p < 0.00000008$) consistent with the large differences seen in regional b.p.'s (see Table 1, Figures 1 and 2), and a main effect of laterality ($F = 19$, $p < 0.001$) reflecting higher b.p.'s in the left temporal cortex, medial thalamus, and ventral striatum, but not caudate or putamen. There was a robust effect of condition due to a decrease in [^{18}F]fallypride b.p.'s following D-AMPH administration ($F = 48.5$, $p = 0.00001$) as well as a significant condition by region interaction consistent with varying decreases across regions ($F = 16.99$, $p = 0.0037$). In contrast, there were no significant interactions of condition by laterality ($F = 0.36$, $p > 0.1$) or condition by region by laterality ($F = 0.56$, $p > 0.1$). Given the lack of a laterality effect, regional displacements were averaged across the right and left regions of interest.

The greatest D-AMPH-induced displacements of [^{18}F]fallypride were seen in the striatum and substantia nigra, while lower levels of displacement were seen in the amygdala, temporal cortex, and thalamus (see Table 1). The mean displacement in the putamen was 11.22%, while the mean displacements in the ventral striatum and caudate were 7.23 and 5.57%, respectively. The mean displacement in the substantia nigra was 6.64% similar to that seen in caudate and ventral striatum. Lower levels of displacement were seen in the amygdala—4.36%, medial thalamus—2.84%, and temporal cortex—3.67%. Using paired two-tailed *t*-tests with a Bonferroni correction for multiple comparisons, displacements were significant in all regions except the medial thalamus which achieved a trend level ($p = 0.07$). The significance of regional displacements was also evaluated using the Wilcoxon signed ranks test (two-tailed)

Table 1 D-AMPH-Induced Decrements in Regional Binding Potentials (Means ± SD) and Levels of Significance Corrected for Multiple Comparisons Using Paired 2-Tailed *t*-Tests and Wilcoxon Signed-Rank Test in Parenthesis

Region	Baseline BP	Post-D-AMPH BP	Percent displacement	Significance level
Caudate	33.02 ± 2.09	31.17 ± 2.35	5.57 ± 4.60	0.005 (0.03)
Putamen	38.32 ± 2.64	33.98 ± 2.36	11.22 ± 4.34	0.000004 (0.007)
Ventral striatum	21.82 ± 2.07	20.19 ± 1.55	7.23 ± 5.29	0.002 (0.014)
Substantia nigra	2.57 ± 0.21	2.40 ± 0.22	6.64 ± 4.21	0.0004 (0.014)
Medial thalamus	4.58 ± 0.50	4.45 ± 0.46	2.84 ± 3.66	0.07 (0.23)
Amygdala	3.48 ± 0.44	3.32 ± 0.44	4.36 ± 3.40	0.008 (0.06)
Temporal cortex	1.64 ± 0.26	1.58 ± 0.26	3.67 ± 3.65	0.02 (0.03)

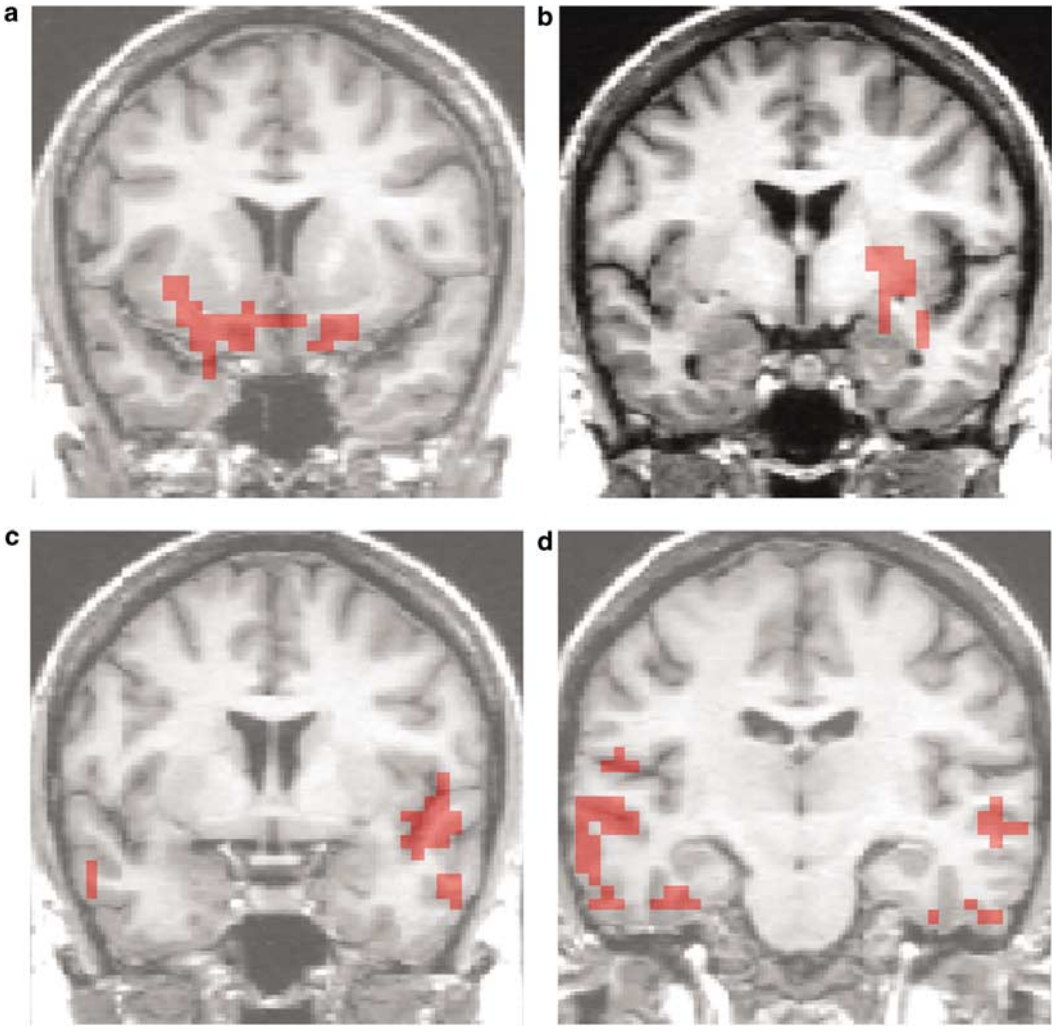

Figure 3 Significant clusters of correlations between D-AMPH-induced DA release and (a) digit symbol coding (ventral striatum and basal forebrain), (b) symbol search (left ventral putamen), and (c, d) stroop task (left temporal and insular cortex, right temporal cortex).

with a Bonferroni correction; displacements remained significant in the caudate ($p < 0.03$), putamen ($p = 0.007$), ventral striatum ($p < 0.014$), substantia nigra ($p = 0.014$), and temporal cortex ($p < 0.03$), but fell to a trend level in the amygdala ($p = 0.06$).

Correlations of changes in cognition with parametric images of DA release following D-AMPH administration showed a number of significant clusters of correlations with measures of attention and speed of cognitive processing (see Figures 3 and 4). Changes in performance on the Digit Symbol Coding, a test of attention, and speed of cognitive processing, were significantly correlated with a cluster centered in the right ventral striatum, but involving the right and left ventral striatum and basal forebrain ($p < 0.006$, corrected for multiple-image comparisons and behavioral tests) due to significant negative correlations

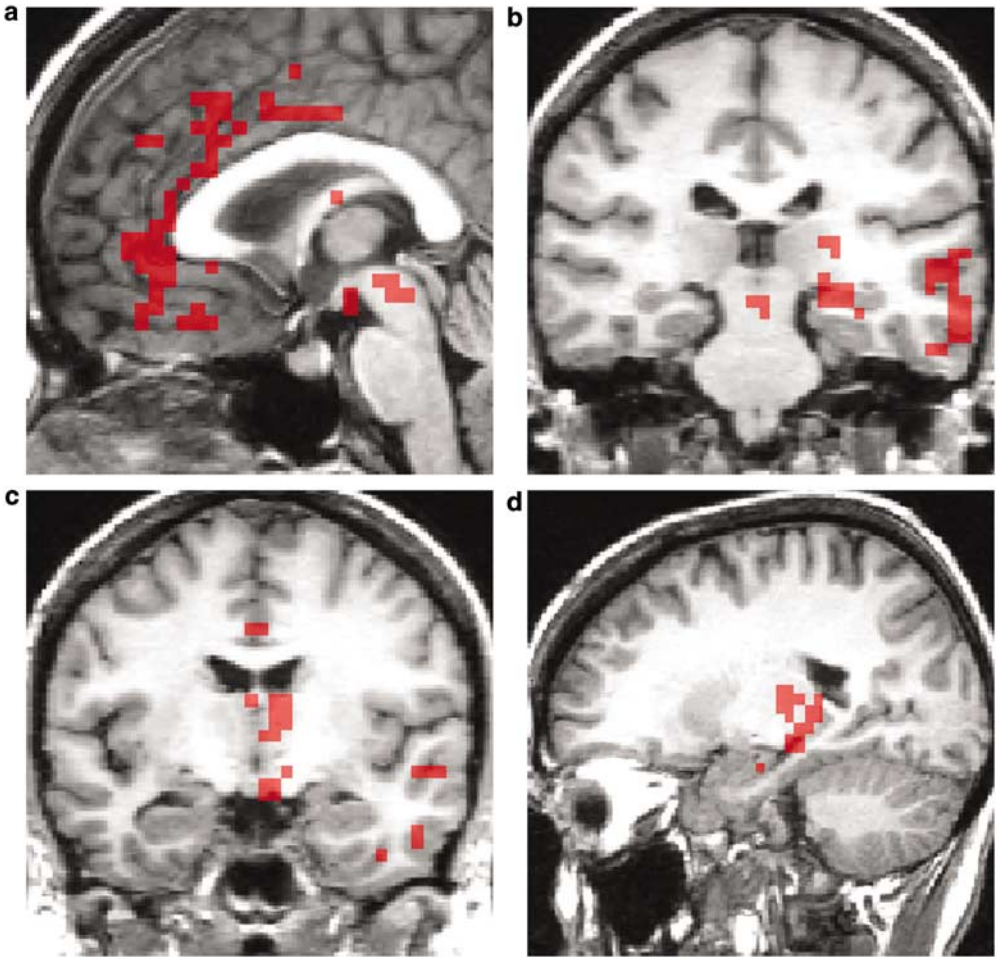

Figure 4 Significant clusters of correlations of sensation seeking with D-AMPH-induced DA release in (a) anterior cingulate, (b) left temporal cortex, (c, d) left thalamus extending into the left hippocampus.

ranging from $r=-0.53$ to -0.82 (see Figure 3). A significant cluster of correlations on performance on the symbol search task, a measure of speed of cognitive processing, was observed in the left ventral putamen ($p<0.05$, corrected for both multiple-image comparisons and behavioral tests) due to significant negative correlations, $r=-0.54$ to -0.75 (see Figure 3). Significant clusters of correlations of performance on the Stroop task, a test of attention, were seen with the left temporal cortex and insula ($p<0.02$, corrected for multiple-image and behavioral comparisons), and with a second cluster involving the right lateral and inferior temporal cortex ($p=0.01$, corrected for multiple-image and behavioral comparisons) (see Figure 3); both clusters were due to significant negative correlations, $r=-0.53$ to -0.92. No significant clusters of correlations were seen with changes in spatial working memory.

Sensation-seeking behavior demonstrated a number of significant clusters of correlations with D-AMPH-induced DA release (see Figure 4). These included a cluster involving the anterior cingulate with greatest extent in the pre and subgenual cingulate ($p=0.04$, corrected for multiple–image comparisons and behavioral tests), a cluster in the left insula and temporal cortex ($p<0.006$, corrected for multiple-image comparisons and behavioral tests), and a cluster in the left thalamus which extended into the left hippocampus/medial temporal cortex ($p<0.006$, corrected for multiple-image comparisons and behavioral tests). These clusters reflected significant negative correlations in these regions, with r's ranging from -0.53 to -0.91. No significant clusters were observed for changes in positive affect with DA release.

Plasma D-AMPH levels were 0.45 ± 0.26 (SD) ng/ml at 1 h after administration, 0.44 ± 0.22 at 3 h, and 0.35 ± 0.13 at 5 h. There were no significant correlations of plasma D-AMPH levels at 1, 3, or 5 h with decrements in putamenal b.p.'s.

DISCUSSION

The results of this study demonstrate significant displacements of [^{18}F]fallypride by DA released by oral D-AMPH in the striatum, substantia nigra, and cortex, with a trend level change in the amygdala. The magnitude of striatal displacement is similar to that reported with either [^{123}I]IBZM or [^{11}C]raclopride using either oral (30 mg) or intravenous doses (0.3 mg/kg) of D-AMPH. [^{123}I]IBZM SPECT studies of D-AMPH-induced displacements report decrements in the striatum of 7–9% in normal subjects following an intravenous dose of 0.3 mg/kg (Abi-Dargham *et al*, 2003, 2004; Laruelle *et al*, 1996; Kegeles *et al*, 1999).

[11C]raclopride PET studies of D-AMPH (0.3 mg/kg, intravenous)-induced displacements of approximately 8–16% in striatal subdivisions have reported decrements in the dorsal putamen, 4–6% in the caudate, and 15% in the ventral striatum (Martinez *et al*, 2003; Drevets *et al*, 2001). The decrements seen in the caudate and dorsal putamen in the current study are similar to those reported with [11C]raclopride studies using intravenous D-AMPH, but are considerably lower in the ventral striatum. The only previous PET study which employed a comparable oral D-AMPH dose, that is, 30 mg, to that used in the current study, reported a striatal decrement of 13% at 2 h post-D-AMPH administration, comparable to the results in the current study in which scanning commenced at 3 h post-injection. The results of the current study indicate that [18F]fallypride has a sensitivity similar to D-AMPH-released DA in comparison to [11C]raclopride in the dorsal caudate and putamen. Although these results are consistent with primate studies (Slifstein *et al*, 2004), they are at variance with modeling studies suggesting that the magnitude of D-AMPH induced displacement decreases with ligands having b.p. greater than 10 (Endres and Carson, 1998).

The difference in ventral striatal displacements seen between the current and previous studies of Martinez *et al* (2003) and Drevets *et al* (2001) may be related to the different routes of administration. Previous studies of oral *vs* intravenous methylphenidate (Volkow *et al*, 2004) have shown that oral compared to intravenous methylphenidate administration produces slower increases in brain methylphenidate levels, comparable peak brain levels, comparable levels of dorsal striatal DA release, but significantly less positive reinforcing effects. Positive reinforcing effects were significantly and positively correlated with dorsal striatal DA release following intravenous administration of methylphenidate, but no correlation was seen following oral administration. The ventral striatum has been shown to mediate the euphorogenic effects of intravenous D-AMPH in humans (Drevets *et al*, 2001). The lesser D-AMPH-induced displacement seen in the ventral striatum in the current study may reflect different regulation of dorsal *vs* ventral striatal DA release in response to differing rates of brain uptake of DA-releasing drugs, and may be the physiological basis for the lesser positive reinforcing effects of oral *vs* intravenous psychostimulant drugs. It is noteworthy that no significant correlation cluster of positive affect with DA release was seen for the group as a whole in the current study analogous to the results seen with oral methylphenidate, another psychostimulant drug which increases extracellular DA levels (Volkow *et al*, 2004). Additional studies are needed to confirm these results and to evaluate the mechanism by which such differential regulation occurs.

Alternative explanations for the difference in ventral striatal displacements could include differences in methods and inaccuracies in image registration. To make the results comparable to the study of Martinez *et al*, 2003, we used the same anatomic criteria for delineation of the ventral striatum as used in that study (Mawlawi *et al*, 2001). The resolution of the scanners used in all the current and previous studies of Drevets and Martinez is similar (Townsend *et al*, 1998). The algorithms used for coregistration in this study have been shown to have registration errors of 1.1 mm in phantom studies and 2.6 mm in previous studies of PET/MR coregistration using an older PET scanner with 6–8 mm resolution (West *et al*, 1997; Lavely *et al*, 2004); the accuracy of coregistration is demonstrated in the relatively small standard deviations, 8–9% of the means, seen in [18F]fallypride b.p.'s in small structures such as the ventral striatum and substantia nigra. An example of PET/MR coregistration is shown in Figure 2. The difference in apparent ventral striatal DA release is probably not due to methodological factors.

D-AMPH produced a mean displacement of 6.65% in the substantia nigra, which is similar to that seen in striatum. This is surprisingly high taking into consideration that extracellular DA levels at baseline and following D-AMPH administration are approximately 10% of that seen in the striatum (Gerhardt *et al*, 2002). In the substantia nigra, DA D_2 receptors are autoreceptors which are localized on the dendrites of dopaminergic neurons (Sesack *et al*, 1994) and are in the high-affinity agonist state, while in the striatum they are in both the high- and low-affinity state. It has been estimated that approximately 40% of striatal DA D_2 receptors are in the high-affinity agonist state (Ginovart *et al*, 1997; Laruelle *et al*, 1997; Laruelle, 2000). The b.p. of the substantia nigra is approximately 10% of that of the striatum (see Table 1). Endres has suggested that the sensitivity of benzamide radioligands to extracellular DA levels is greatest at a b.p. of 3–10, with decreasing sensitivity above this range (Endres and Carson, 1998). These factors may be responsible, at least in part, for the surprisingly high D-AMPH-induced displacement of [18F]fallypride in the substantia nigra. While the substantia nigra is a small structure whose apparent receptor levels are diminished by partial voluming, the borders of the substantia nigra are not adequately delineated on MRI studies, making implementation of a partial volume correction problematic. The value of a partial volume correction for D-AMPH-induced decrements in regional b.p.'s has been evaluated by Slifstein in nonhuman primates (Slifstein *et al*, 2004), who found significant spillover of striatal counts into extrastriatal regions, but no significant effect of a partial volume correction on the change in V_3'' in the striatum and extrastriatal regions.

It has been previously hypothesized that D-AMPH-released synaptic DA is responsible for displacement of benzamide radioligands in striatum (Laruelle, 2000). There are a number of studies which suggest that dopaminergic neurotransmission in extrastriatal regions is largely mediated by a volume or extrasynaptic mode. In the substantia nigra and VTA, DA release appears to be largely mediated by reverse transport by the DA transporter (Falkenburger *et al*, 2001). The lack of synaptic specializations in the substantia nigra suggests that somatodendritic DA release does not rely on typical synaptic neurotransmission (Heeringa and Abercrombie, 1995). As DA D_2 receptors are largely extrasynaptic in the substantia nigra (Sesack *et al*, 1994; Yung *et al*, 1995), it has been suggested that dopaminergic neurotransmission in the substantia nigra may be mediated by volume transmission rather than a synaptic mode (Fuxe *et al*, 2005; Cragg *et al*, 2001; Cragg and Greenfield, 1997). Previous studies of DA release and diffusion in the cortex and amygdala indicate that cortical and amygdalar dopaminergic neurotransmission is mediated largely via a volume mode (Garris and Wightman,

1994; Fuxe *et al*, 2005). Given these observations, the D-AMPH-induced displacements seen in the substantia nigra, amygdala, and temporal cortex are likely due, at least in part, to DA displacement of [^{18}F]fallypride at extrasynaptic DA D_2 receptors.

The magnitude of D-AMPH-induced displacements of [^{18}F]fallypride is lower in the temporal cortex, amygdala, and medial thalamus than in the striatum, that is, 2.84–4.36 *vs* 5.57–11.22%. This is consistent with microdialysis studies demonstrating a 10-fold lower level of baseline extracellular DA in the cortex and amygdala and 4–5-fold lesser increases in extracellular DA levels in these regions following D-AMPH administration (Moghaddam *et al*, 1993; Garris and Wightman, 1994). The greater displacements observed in primate [^{18}F]fallypride studies are likely due to the higher doses of D-AMPH administered, different routes of administration, effects of anesthesia, and species differences (Slifstein *et al*, 2004; Narendran *et al*, 2004; Tsukada *et al*, 1999a, b; 2002).

In the current study, D-AMPH was administered approximately 180 min prior to the injection of [^{18}F]fallypride for a number of reasons. The study of Cardenas demonstrated no diminution in displacement of [^{11}C]raclopride from 3 to 6 h after D-AMPH administration. As the current and previous results (Angrist *et al*, 1987) show, the plasma levels of D-AMPH remain reasonably constant from 3 to 5 h after oral D-AMPH administration. A 3 h delay in [^{18}F]fallypride administration following oral D-AMPH administration allows neuropsychological testing and scanning with a single dose of D-AMPH, permitting a within-subject comparison of change in cognition and affect with regional DA release. There are a number of factors which may affect apparent D-AMPH displacements, including changes in cerebral blood flow, and D-AMPH induced changes in the cerebellar distribution volume of [^{18}F]fallypride. The effects of D-AMPH on blood flow are minimal by 3 h (Price *et al*, 2002); Slifstein *et al*, (2004) has presented simulations showing that changes in cerebral blood flow would have only minimal effects on D-AMPH-induced displacements of [^{18}F]fallypride. It is unlikely that changes in cerebral blood flow are responsible for the apparent displacements. D-AMPH does not significantly affect the cerebellar distribution volume of [^{18}F]fallypride in nonhuman primates. In addition, the highly significant differences in regional displacements seen in the current study suggest that a change in cerebellar distribution volume is not a major factor in the regional displacements. Further studies are needed to examine this issue.

We examined correlations of changes in neurocognitive functions, that is, attention, speed of cognitive processing, and spatial working memory, positive affect, as well as sensation-seeking behavior with D-AMPH-induced DA release using parametric image analyses. These behaviors have previously been shown to be modulated by cerebral dopaminergic neurotransmission (Rogers, 1986; Piazza *et al*, 1991; Hooks *et al*, 1994; Lawrence *et al*, 1998; Shah *et al*, 1997; Mehta *et al*, 1999; Marinelli and White, 2000; Drevets *et al*, 2001; Abi-Dargham *et al*, 2003). Although only a relatively small group of normal subjects was examined, significant clusters of correlations, corrected for both multiple-image and behavioral comparisons, were seen with multiple measures of attention and speed of cognitive processing, as well as with sensation seeking. These significant correlations of DA-modulated behaviors with regional DA release in the striatal and extrastriatal regions suggest that the apparent variability seen across subjects in regional DA release may reflect intersubject differences in DA release and not simply image-related noise. This is consistent with a recent PET study finding decreases in frontal and temporal DA D_2 receptor availability during performance of attentional and working memory tasks (Aalto *et al*, 2005). These results suggest that [^{18}F]fallypride PET studies can be used to study the relationship between regional DA release in the striatum and extrastriatal regions and neuropsychological function.

The lack of significant clusters of correlations with positive affect and spatial working memory, as well as the differences between the current study and that of Leyton *et al* (2002) in regard to novelty seeking, may be due to a number of factors. First, only a small group was examined which has limited power given the size and variability of the D-AMPH-induced decrements in [^{18}F]fallypride b.p.'s. As noted above, Volkow *et al*, (2004) did not observe correlations of the positive reinforcing effects of methylphenidate with dorsal striatal DA release after oral administration, although such a correlation was seen with intravenous administration. The correlation coefficient observed by Abi Dargham with D-AMPH-induced DA release with positive affect in a large group of subjects, that is, 60, was approximately 0.37. In addition, the smaller D-AMPH-induced displacement in the ventral striatum compared to previous [^{11}C]raclopride PET studies (Drevets *et al*, 2001; Martinez *et al*, 2003) may limit the ability to demonstrate a significant correlation with change in positive affect, although the smaller standard deviation in the ventral striatum in the current study (5.29 *vs* 10.6 and 11.8%) may moderate this limitation. The oral route of administration and the small size of the correlation with positive affect seen in the largest group reported to date may limit the ability of the current study to detect correlations with positive affect. Frontal cortical dopaminergic neurotransmission has been shown to modulate spatial working memory (Sawaguchi and Goldman-Rakic, 1991). The low b.p. of [^{18}F]fallypride in the frontal cortex (Mukherjee *et al*, 2002) as well as the small number of subjects in this study may limit the ability of [^{18}F]fallypride PET studies to detect D-AMPH-induced DA release in the frontal cortex. In regard to sensation-seeking and novelty-seeking behaviors, Leyton reported a significant positive correlation between D-AMPH-induced ventral striatal DA release, and novelty seeking as measured on the TPQ. Leyton examined eight male subjects using a lower oral dose of D-AMPH. Interestingly, no displacement of [^{11}C]raclopride from the caudate or putamen was observed although levels of ventral striatal DA release similar to that seen in the current study were observed. While the reasons for the discrepancies between the two studies are not clear, the use of a different rating instrument, a lower dose of D-AMPH which did not appear to affect the dorsal striatum, and the use of only male subjects may be some of the factors responsible for this discrepancy. We have found gender differences in a number of correlations of behaviors with regional DA release (Riccardi *et al*, 2005). Correlation of region of interest data showed a correlation coefficient of

0.898, $p = 0.006$ for sensation seeking with left ventral striatal DA release in male subjects, but a correlation coefficient of -0.713 in female subjects. This difference was significant at the $p = 0.005$ level. When male and female subjects are grouped together, no significant correlation is seen. As we have demonstrated (Riccardi *et al*, 2005), sex differences need to be considered in evaluating regional DA release and its relationship to behavior.

In conclusion, the results of this study demonstrate the feasibility of using [^{18}F]fallypride PET studies with oral D-AMPH to study DA release in extrastriatal and striatal regions, as well as the relationship of regional DA release to neuropsychological function. This method should allow study of DA release in schizophrenia, psychostimulant drug abuse, attention deficit disorder, depression, as well as other disorders.

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