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PET Imaging of dopamine $D_{2/3}$ receptors in the human cortex with [^{11}C]FLB 457: reproducibility studies

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Abstract

In a recent PET study we demonstrated the ability to measure amphetamine-induced DA release in the human cortex with the relatively high affinity dopamine $D_{2/3}$ radioligand [^{11}C]FLB 457 (Narendran et al., 2009). The aim of this study was to evaluate the reproducibility and reliability of [^{11}C]FLB 457 in the same imaging paradigm we used to measure amphetamine-induced DA transmission. Six healthy human subjects (3 males/3 females) were studied twice with [^{11}C]FLB 457, once at baseline and again three-hours following the end of the baseline scan. $D_{2/3}$ receptor binding parameters were estimated using a two-tissue compartment kinetic analysis in the cortical regions of interest and cerebellum (reference region). The test-retest variability and intraclass correlation coefficient were assessed for distribution volume (V_T), binding potential relative to plasma concentration (BP_P), and binding potential relative to non-displaceable uptake (BP_{ND}) of [^{11}C]FLB 457. The test-retest variability of [^{11}C]FLB 457 V_T, BP_P and BP_{ND} were ≤ 15%, consistent with the published test-retest variability for this ligand in other brain regions (Vilkman et al., 2000; Sudo et al., 2001). In addition, no significant decrease in [^{11}C]FLB 457 BP_{ND} was observed in the second scan compared to the first one. This suggests that the contribution of carryover mass of [^{11}C]FLB 457 to the measured reduction in [^{11}C]FLB 457 BP_{ND} following amphetamine was relatively low. These data support the further validation of [^{11}C]FLB 457 as a tool to measure amphetamine-induced dopamine release in the human cortex.

Keywords

PET; dopamine; $D_{2/3}$ receptors; [^{11}C]FLB 457; human cortex

Introduction

The study of dopamine transmission in the human cortex is of extreme interest in several neuropsychiatric disorders such as Parkinson's disease, attention deficit hyperactivity disorder, schizophrenia and addiction. In a previous study we contrasted the cortical binding of two high affinity dopamine $D_{2/3}$ radioligands [^{11}C]FLB 457 and [^{11}C]fallypride in terms

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of their vulnerability to endogenous competition by dopamine following an oral amphetamine challenge (Narendran et al., 2009). The results of this study, demonstrating a significant reduction in the in vivo binding of [^{11}C]FLB 457 but not [^{11}C]fallypride following amphetamine (0.5 mg/kg), support the use of [^{11}C]FLB 457 PET as a technique to measure cortical dopamine release. A critical step in validating [^{11}C]FLB 457 to measure dopamine release is to evaluate the reproducibility of its outcome measures, binding potential BP_P and BP_{ND}, in the same imaging paradigm that was used to demonstrate an effect for amphetamine. This is important because [^{11}C]FLB 457 has a relatively low signal to noise ratio (BP_{ND} ~ 0.5 to 1) in the cortical regions of interest, and poor reproducibility of the relatively low [^{11}C]FLB 457 BP_{ND} in the cortex would reduce the effect size for amphetamine-induced [^{11}C]FLB 457 displacement and thereby limit the use of this technique in clinical studies. In addition, as the baseline and post-amphetamine scan in our previous study were separated by three hours there was concern that the FLB 457 mass carried over from the baseline PET scan may have contributed to all or part of the reduction in [^{11}C]FLB 457 BP_{ND} measured following the administration of amphetamine. To address these methodological issues we conducted test-retest studies in six healthy human subjects, assessing the test-retest reproducibility of the three PET outcome measures—V_T (regional distribution volume), BP_P and BP_{ND} in a scanning paradigm similar to that of our amphetamine studies.

Methods

The study was approved by the Institutional Review Board of the University of Pittsburgh. A total of 12 PET scans were acquired for this study in six healthy control subjects over six experimental sessions. Each experimental session included two PET scans: a test scan and a retest scan with [^{11}C]FLB 457. The retest scan was performed three hours after the completion of the test scan to be consistent with the imaging paradigm used in our previous amphetamine study.

PET Protocol

Radiolabeling of [^{11}C]FLB 457 was performed as outlined in previously published procedures (Halldin et al., 1995). Imaging experiments were conducted on the ECAT EXACT HR+ consistent with previously described image acquisition protocols (Abi-Dargham et al., 2000). Briefly, following completion of a transmission scan (~10 min) for attenuation correction of the emission data, subjects received an intravenous injection of [^{11}C]FLB 457 as a bolus over 20 sec. Based on previously published studies the maximum injected mass for [^{11}C]FLB 457 was restricted to 0.6 μg (Sudo et al., 2001). Emission data were collected for 90 min.

Following radiotracer injection, arterial samples were collected manually approximately every 6 s for the first 2 min and thereafter at longer intervals. A total of 35 samples were obtained per scan. Following centrifugation, plasma was collected in 200 μL aliquots and activities were counted in a gamma counter. To determine the plasma activity representing unmetabolized [^{11}C]FLB 457 parent compound, six samples (collected at 2, 10, 20, 40, 60 and 75 min) were further processed using HPLC methods (Olsson et al., 1999; Narendran et al., 2009). For [^{11}C]FLB 457 the six measured parent fractions were fitted using a Hill model (Hill, 1910; Gunn et al., 1998; Wu et al., 2007). The input function was then calculated as the product of total counts and interpolated parent fraction at each time point. The measured input function values were fitted to a sum of three exponentials from the time of peak plasma activity and the fitted values were used as the input to the kinetic analysis. The clearance of the parent compound (L/h) was calculated as the ratio of the injected dose to the area under the curve of the input function (Abi-Dargham et al., 1994). In addition,

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measurement of plasma free fraction (f_P) for [^{11}C]FLB 457 was performed (Gandelman et al., 1994).

MRI Protocol

To provide an anatomical framework for analysis of the PET data, MRI scans were obtained using a 1.5 T GE Medical Systems (Milwaukee, WI) Signa Scanner and a 3D spoiled gradient recalled sequence. MRI segmentation was performed using the FAST automated segmentation tool (Zhang et al., 2001) implemented in the FMRIB Software Library (v4.0, Smith et al., 2004).

Analysis of PET data

PET data were reconstructed and processed with the image analysis software MEDx (Sensor Systems, Inc., Sterling, Virginia) and SPM2 (www.fil.ion.ucl.ac.uk/spm) as described in (Narendran et al., 2009). Frame-to-frame motion correction for head movement and MR-PET image alignment were performed using a mutual information algorithm implemented in SPM2.

Time activity curves were generated for the eight cortical regions of interest using the criteria and methods outlined in (Abi-Dargham et al., 2000; Abi-Dargham et al., 2002; Lacerda et al., 2003). Sampled cortical regions (n = 8) included the medial temporal lobe MTL, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbital frontal cortex (OFC, defined using criteria outlined in Lacerda 2003), medial prefrontal cortex (MPFC), temporal cortex (TC), parietal cortex (PC), and occipital cortex (OC). The cerebellum (CER) was sub sampled in fifteen consecutive coronal MRI slices caudal to the cerebellar penduncle and used as a reference region. The sub sampling included only the gray matter and excluded the vermis, white matter, and the cerebro-cerebellar fissure.

For bilateral regions, right and left values were averaged. The contribution of plasma total activity to the regional activity was calculated assuming a 5% blood volume in the *regions* of interest (Mintun et al., 1984) and tissue activities were calculated as the total regional activities minus the plasma contribution.

The three outcome measures provided are regional tissue distribution volume (V_T, mL cm^{-3}), binding potential relative to plasma concentration (BP_P, mL cm^{-3}) and binding potential relative to non-displaceable uptake (BP_{ND}, unitless). The definition of these outcome measures is described in the consensus nomenclature for PET studies manuscript (Innis et al., 2007). Derivation of [^{11}C]FLB 457 V_T in the regions of interest and cerebellum were performed using kinetic analysis and the arterial input function (Narendran et al., 2009). A two-tissue compartment model (2TCM) described both the cerebellum and regions of interest (Olsson et al., 1999).

Statistical analysis

The reproducibility of the three PET outcome measures V_T, BP_P and BP_{ND} were evaluated for their *variability* and *reliability*.

The test-retest variability (VAR) was calculated as the absolute value of the difference between the test and retest, divided by the mean of the test and retest values.

To evaluate the within-subject variability relative to the between-subject variability, both within-subject SD (WSSD) and between-subject SD (BSSD) were calculated and expressed as fraction of mean value (WS CV and BS CV). The reliability of the measurements was assessed by the intraclass correlation coefficient (ICC) calculated as (Kirk, 1982):

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$$\frac{BSMSS - WSMSS}{BSMSS + (n-1)WSMSS}$$

where BSMSS is the mean sum of square between subjects, WSMSS is the mean sum of square within subjects and n is the number of repeated observations (n = 2 in this study). This statistic estimates the relative contributions of between and within subject variability and assumes values from −1 (i.e. BSMSS = 0) to 1 (identity between test and retest, i.e. WSMSS = 0).

In addition, the change in BP_{ND} elicited by carryover mass from the first to second scan (mass-induced ΔBP_{ND}) was calculated as the difference between BP_{ND} measured in the second scan ($BP_{ND\ RETEST}$) and BP_{ND} measured in the first scan ($BP_{ND\ TEST}$), and expressed in percentage of $BP_{ND\ TEST}$.

$$Mass - induced\ \Delta BP_{ND} = 100 * \frac{BP_{ND_{RETEST}} - BP_{ND_{TEST}}}{BP_{ND_{TEST}}} \quad \text{Eq. 1}$$

These data were analyzed with repeated measure ANOVA (RM ANOVA) and paired t test as specified.

Results

Baseline scan parameters

The mean injected dose, mass and specific activity at the time of injection for the test and re-test condition for [^{11}C]FLB 457 are listed in Table 1. No significant differences were observed between the test and the retest condition in any of these variables.

Plasma analysis

A statistically significant, but not meaningful (37% versus 41%) difference was observed in plasma free fraction between the [^{11}C]FLB 457 test and re-test conditions. The VAR for free fraction was 14% ± 18% with an ICC of 0.94. No such differences were noted in [^{11}C]FLB 457 plasma clearance (Table 1) The VAR for the clearance was 10% ± 8% with an ICC = 0.83.

Brain analysis

The mean V_T, BP_P, BP_{ND} and their corresponding VAR and ICC for the regions of interest are provided in Table 2.

The effect of carry over mass-induced change in [^{11}C]FLB 457 BP_{ND} is provided in Table 3.

Discussion

The primary objective of this reproducibility study was to assess the VAR of [^{11}C]FLB 457 binding parameters in the cortical regions of interest. Given our recent data suggesting that the in vivo binding of [^{11}C]FLB 457 is reduced by amphetamine in the cortical regions of interest, it was necessary to evaluate the reproducibility of [^{11}C]FLB 457 BP_{ND} in the same imaging paradigm that we used in our amphetamine studies. This was critical because 1) the

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signal to noise ratio for [^{11}C]FLB 457 in the prefrontal cortex is relatively low (0.5 to 1.0) and thereby more vulnerable to measurement errors and 2) it was necessary to estimate the effect of [^{11}C] FLB 457 carry over mass on the measured reduction in [^{11}C]FLB 457 BP_{ND} following the administration of amphetamine. The previously published [^{11}C]FLB 457 test-retest studies (Vilkman et al., 2000; Sudo et al., 2001) differ from this study in that their imaging methods were not comparable to that used in our amphetamine studies. For example, in the studies, conducted by Sudo et al., the test and retest scans were performed on different days as opposed to the same day; and in the studies conducted by Vilkman et al., the mean injected FLB 457 mass was 2 to 3-fold higher than the 0.6 μg mass limit adhered to in our amphetamine studies.

The VAR of ≤ 15% for all three outcome measures V_T, BP_P and BP_{ND} in the cortical regions of interest in this study is consistent with the two previously published [^{11}C]FLB 457 reproducibility studies (Vilkman et al., 2000; Sudo et al., 2001). Furthermore, this variability is comparable to the ≤ 20% reported for other PET radioligands such as [^{11}C]NNC 112 (Abi-Dargham et al., 2000), [^{11}C]SCH 23390 (Hirvonen et al., 2001), [^{11}C]flumazenil (Salmi et al., 2008; van Velden et al., 2009) and [^{18}F] altanserin (Smith et al., 1998) that are used to measure receptor binding parameters in the human cortex. The good reproducibility of the in vivo binding parameters of [^{11}C]FLB 457 suggests that the relatively low cortical binding potential in itself does not pose a significant problem to the advancement of [^{11}C]FLB 457 as a tool to measure cortical DA release.

These results also suggest that the contribution of carryover mass (at the injected FLB 457 mass limit of < 0.6 μg) to the measured reduction in [^{11}C]FLB 457 BP_{ND} following amphetamine is relatively low (Table 3). This was evidenced by the fact that the largest mean reduction in [^{11}C]FLB 457 BP_{ND} in a cortical region of interest was 2.2%. While a much larger sample size is necessary to conclusively determine whether this level of carryover mass leads to a statistically significant change in [^{11}C]FLB 457 BP_{ND} in the proposed amphetamine-imaging paradigm, these data suggest that the contribution, if any, from carryover mass is likely to be of a much smaller magnitude that that measured following amphetamine (~10%).

Another issue that was evaluated in this dataset relates to the failure of amphetamine to displace [^{11}C]FLB 457 in the OFC (Δ [^{11}C]FLB 457 BP_{ND} −5 ± 21%, p = 0.22) in our previous study (Narendran et al., 2009). As the inability to displace [^{11}C]FLB 457 binding in the OFC was in contrast to the significant displacements observed in the DLPFC (−13 ± 15%, p = 0.01) and MPFC (−11 ± 14%, p = 0.02) we hypothesized that this was somewhat associated with the poor within-subject reproducibility for [^{11}C]FLB 457 BP_{ND} in this particular prefrontal cortical region. Consistent with this hypothesis, the within subject VAR for [^{11}C]FLB 457 BP_{ND} in the OFC (13 ± 7%) was worse than that in the DLPFC (8 ± 6%) and MPFC (6 ± 4%) when we used the same region drawing criteria outlined in our amphetamine study. One of the problems with the criteria we used to delineate the prefrontal cortical regions of interest (DLPFC, OFC and MPFC) in the amphetamine study was that it was based on a schizophrenia PET study that emphasized the anatomical delineation of the DLPFC rather than the OFC (Abi-Dargham et al., 2002). Based on the criteria outlined in Abi-Dargham et al., we had only sampled the part of the OFC that was anterior to the corpus callosum (see Figure 1) and not the subgenual OFC. Thus, for analysis of the data in this reproducibility study we used the validated criteria outlined by Lacerda et al to identify the OFC (Lacerda et al., 2003). Briefly, this criterion allowed for the delineation of the OFC in two separate parts: **the *sub genual OFC*** and ***the OFC anterior to the corpus callosum*** (which is the part comparable to the OFC defined using the Abi-Dargham criteria). The use of the new criteria led to a significant improvement in the reproducibility of [^{11}C]FLB 457 BP_{ND} in the OFC (Abi-Dargham criteria 13 ± 7%; Lacerda criteria 7 ± 6%). The factors that

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likely contributed to the improved reproducibility are 1) the sampling across more gray matter voxels and 2) the higher [^{11}C]FLB 457 BP_{ND} (old criteria 0.63 ± 0.14; new criteria 0.79 ± 0.14) related to the inclusion of the subgenual OFC. Furthermore, to answer the question of whether an improved reproducibility translates to ability to measure amphetamine-induced DA release in the OFC, a reanalysis of the previously published [^{11}C]FLB 457-amphetamine data (Narendran et al., 2009) was performed with the Lacerda criteria. Consistent with the view that reproducibility is associated with the ability to detect DA release, the effect size for amphetamine-induced displacement of [^{11}C]FLB 457 in the OFC improved from 0.24 (Abi-Dargham OFC, $\Delta BP_{ND} = -5 \pm 21\%$, $p = 0.22$) to 0.53 (Lacerda OFC, $\Delta BP_{ND} = -8 \pm 15\%$, $p = 0.07$) following reanalysis. Thus, it is likely that the lower VAR for [^{11}C]FLB 457 binding potential will allow for the characterization of amphetamine-induced DA release in the OFC in clinical studies.

In summary, we conducted [^{11}C]FLB 457 test-retest studies to evaluate the reproducibility of the PET outcome measures in the same imaging paradigm that was used to demonstrate amphetamine-induced DA release in the human cortex. The results of these studies confirm that the relatively low cortical [^{11}C]FLB 457 BP_{ND} and carry over mass-induced reduction in BP_{ND} at the injected FLB 457 mass limit of < 0.6 μg are not obstacles to the advancement of this radioligand to measure DA transmission in the human cortex.

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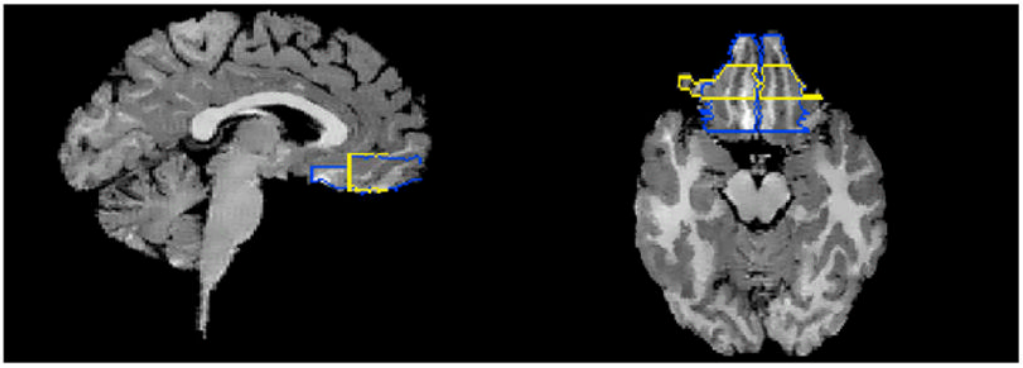

Figure 1.
MRI sagittal and transverse view showing Abi-Dargham criteria (Abi-Dargham 2002) and Lacerda criteria (Lacerda 2003) for delineating OFC. Note: the Lacerda criteria (outlined in blue) includes the sub genual OFC, whereas the Abi-Dargham criteria (outlined in yellow) does not sample this part of the OFC.

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Table 1

Baseline [^{11}C]FLB 457 scan parameters and plasma analysis (n=6 subjects)

	Test	Re-test
Injected dose (mCi)	5.3 ± 0.7	4.8 ± 0.7
SA (Ci/mmoles)	8700 ± 5720	6322 ± 5574
Injected Mass (ug)	0.3 ± 0.2	0.4 ± 0.2
Plasma free fraction (fP, %)	36.8% ± 14.2%	40.6% ± 14.0%*
Clearance (L/h)	129 ± 26	134 ± 32
Cerebellum VT (mL cm^{-3})	7.47 ± 2.43	7.43 ± 2.52

* $p < 0.05$, paired t test, test compared with re-test condition

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Table 2

Reproducibility of [^{11}C]FLB 457 total distribution volume (V_T, mL cm^{-3}), binding potential relative to plasma concentrations (BP_P, mL cm^{-3}) and binding potential relative to non specific uptake (BP_{ND}, unitless) derived via kinetic analysis.

	V_T					BP_P					BP_{ND}				
Region	**Mean**	**BSSD CV**	**WSSD CV**	**VAR ± SD**	**ICC**	**Mean**	**BSSD CV**	**WSSD CV**	**VAR ± SD**	**ICC**	**Mean**	**BSSD CV**	**WSSD CV**	**VAR ± SD**	**ICC**
CER	7.45	0.33	0.03	4.5% ± 4.0%	0.99	-	-	-	-	-	-	-	-	-	-
MTL	18.33	0.35	0.06	10.5% ± 4.0%	0.95	10.88	0.37	0.08	14.8% ± 4.7%	0.91	1.46	0.14	0.06	10.7% ± 5.1%	0.70
ACC	13.15	0.32	0.05	8.1% ± 4.2%	0.96	5.70	0.31	0.10	15.4% ± 7.7%	0.83	0.78	0.14	0.08	14.8% ± 7.5%	0.50
DLPFC	11.16	0.28	0.03	6.4% ± 3.9%	0.97	3.70	0.25	0.06	9.9% ± 7.7%	0.90	0.52	0.23	0.05	8.3% ± 5.5%	0.91
OFC	13.33	0.34	0.03	5.5% ± 3.4%	0.98	5.88	0.38	0.05	6.7% ± 7.3%	0.97	0.79	0.18	0.05	6.9% ± 5.7%	0.87
MPFC	12.31	0.33	0.03	6.2% ± 3.5%	0.98	4.86	0.35	0.04	8.9% ± 5.3%	0.97	0.66	0.17	0.04	5.9% ± 4.4%	0.91
TC	20.10	0.32	0.05	10.1% ± 2.3%	0.95	12.64	0.35	0.07	13.7% ± 2.6%	0.92	1.71	0.21	0.06	9.6% ± 5.5%	0.87
PC	11.08	0.28	0.03	5.9% ± 2.0%	0.98	3.63	0.38	0.05	9.0% ± 4.8%	0.96	0.52	0.39	0.05	8.0% ± 3.6%	0.97
OC	10.16	0.27	0.03	6.1% ± 3.2%	0.97	2.71	0.33	0.05	11.4% ± 6.9%	0.95	0.39	0.38	0.05	9.6% ± 4.1%	0.96

Values are the mean of 6 subjects with each value measured twice.

BSSD CV = between subject standard deviation coefficient of variation, WSSD CV = within subject standard deviation coefficient of variation, VAR = test/retest variability, ICC = intraclass correlation coefficient.

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Table 3

Effect of carryover mass on [^{11}C]FLB 457 BP_{ND}

Region	Test BP_{ND}	Re-test BP_{ND}	Δ BP_{ND} (%)	P values
Medial Temporal Lobe	1.43 ± 0.22	1.49 ± 0.23	5.4 ± 12.1	0.387
Anterior Cingulate Cortex	0.75 ± 0.12	0.81 ± 0.13	9.4 ± 16.3	0.279
Dorsolateral prefrontal Cortex	0.53 ± 0.12	0.52 ± 0.13	−2.2 ± 10.3	0.673
Orbital Frontal Cortex	0.79 ± 0.13	0.79 ± 0.16	−0.2 ± 9.3	0.996
Medial Prefrontal Cortex	0.67 ± 0.11	0.66 ± 0.11	−1.2 ± 7.3	0.643
Temporal Cortex	1.67 ± 0.35	1.76 ± 0.40	5.6 ± 10.9	0.263
Parietal Cortex	0.52 ± 0.20	0.52 ± 0.21	0.8 ± 9.4	0.901
Occipital Cortex	0.38 ± 0.15	0.40 ± 0.16	5.4 ± 10.3	0.363

Values are the mean of 6 subjects. *P* values indicate paired t tests