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Presynaptic Dopamine Synthesis Capacity in Schizophrenia and Striatal Blood Flow Change During Antipsychotic Treatment and Medication-Free Conditions

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Standard-of-care biological treatment of schizophrenia remains dependent upon antipsychotic medications, which demonstrate D_2 receptor affinity and elicit variable, partial clinical responses via neural mechanisms that are not entirely understood. In the striatum, where D_2 receptors are abundant, antipsychotic medications may affect neural function in studies of animals, healthy volunteers, and patients, yet the relevance of this to pharmacotherapeutic actions remains unresolved. In this same brain region, some individuals with schizophrenia may demonstrate phenotypes consistent with exaggerated dopaminergic signaling, including alterations in dopamine synthesis capacity; however, the hypothesis that dopamine system characteristics underlie variance in medication-induced regional blood flow changes has not been directly tested. We therefore studied a cohort of 30 individuals with schizophrenia using longitudinal, multi-session [^{15}O]-water and [^{18}F]-FDOPA positron emission tomography to determine striatal blood flow during active atypical antipsychotic medication treatment and after at least 3 weeks of placebo treatment, along with presynaptic dopamine synthesis capacity (ie, DOPA decarboxylase activity). Regional striatal blood flow was significantly higher during active treatment than during the placebo condition. Furthermore, medication-related increases in ventral striatal blood flow were associated with more robust amelioration of excited factor symptoms during active medication and with higher dopamine synthesis capacity. These data indicate that atypical medications enact measureable physiological alterations in limbic striatal circuitry that vary as a function of dopaminergic tone and may have relevance to aspects of therapeutic responses.

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INTRODUCTION

In schizophrenia, therapeutic trials of current pharmacotherapies have reported substantial rates of non- or partial-responses (Lieberman *et al*, 2005). The variability of response to treatment across individuals hampers confident prediction, lending a stochastic quality to clinical management of this debilitating illness. Despite small differences in their overall efficacy (Samara *et al*, 2016) and in their precise constellation of receptor affinities, currently available, standard-of-care, antipsychotic medications as a class continue to be unified by inhibition (antagonism or partial agonism) at the D_2 dopamine receptor (Peroutka and Snyder, 1980; Seeman and Tallerico, 1999), although a definitive and detailed mechanistic understanding of their action in the brain has remained elusive.

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To elucidate the neurophysiology of antipsychotic treatment response, several past imaging investigations have examined regional cerebral blood flow (rCBF) and metabolic changes induced by neuroleptics. Increases in regional cerebral blood flow in the striatum, where D_2 receptors abound, have been observed after single doses of antipsychotic medication in healthy individuals measured with arterial spin labeling (Fernández-Seara *et al*, 2011; Handley *et al*, 2013; Viviani *et al*, 2013). Studies of individuals with schizophrenia have been less consistent; this same single-dose effect has been observed in a positron emission tomography (PET) [^{15}O]-water rCBF study (Lahti *et al*, 2005), but other PET experiments have failed to find acute medication effects in patients (Goldman *et al*, 1996; Volkow *et al*, 1986). Whether individuals who are consistently treated with antipsychotic medications demonstrate persistently increased striatal activity has also been addressed by several studies, and increased striatal blood flow with treatment has been reported in longitudinal PET (Corson *et al*, 2002; Lahti *et al*, 2003, 2009b; Miller *et al*, 1997a) and SPECT (Livingston and the Scottish Schizophrenia Research Group, 1998; Miller *et al*, 1997b) studies, although, again, not all published data

clearly corroborate these findings (Erkwoh *et al*, 1997; Ertugrul *et al*, 2009; Yildiz *et al*, 2000). Increases in striatal glucose metabolism have similarly been observed in several (Bartlett *et al*, 1991; Buchsbaum *et al*, 1987, 1992), although not all (Gur *et al*, 1987), reports. The suggestion that variability in antipsychotic medication-mediated functional changes in the basal ganglia may have important clinical implications has found initial explicit support from one study identifying increased ventral striatal rCBF measured with [^{15}O]-water PET after several weeks of antipsychotic treatment, relative to 2 weeks of medication withdrawal, an effect more frequently observed in individuals who responded to treatment (Lahti *et al*, 2009b).

Although a detailed mechanism to explain how antipsychotic medications might enact striatal blood flow changes has not been empirically demonstrated, a D_2 dopamine receptor-driven model is plausible. Such a formulation is consistent with the considerable density of D_2 receptors in this region and with the D_2 receptor targeting common to all antipsychotic medications used in past experiments demonstrating this effect, including those studies employing first-generation agents (eg, haloperidol) with greater D_2 receptor selectivity (Lahti *et al*, 2009a). D_2 blockade is expected to result in disinhibition of indirect pathway medium spiny neuron (MSN) activity (Gerfen and Surmeier, 2011), consistent with early experiments demonstrating increased spontaneous striatal firing rates with 3 weeks of antipsychotic treatment (Skirboll and Bunney, 1979). Recent optogenetic-fMRI experimentation in mice has demonstrated that increasing the activity of D_2-bearing MSNs alone can drive enhanced hemodynamic responses in the striatum (Lee *et al*, 2016), suggesting that antipsychotic-induced blood flow increases may be attributable to local MSN disinhibition. This effect may be particularly pronounced in individuals with greater presynaptic dopaminergic tone, and therefore greater dopaminergic modulation of MSN populations, at baseline. Alternative dopamine receptor blockade-related mechanisms—such as increased metabolic demands due to D_2 receptor upregulation, indirect network effects via altered dopamine neuronal firing (Valenti *et al*, 2011), or disinhibition of corticostriatal glutamatergic inputs (Bamford *et al*, 2004)—may also play a role and may equally depend upon presynaptic dopamine system characteristics.

In both medicated and medication-free conditions, individuals suffering from schizophrenia on average, but not uniformly, demonstrate neurobiological phenotypes consistent with increased presynaptic dopaminergic function in the striatum. For instance, greater striatal dopamine release in response to amphetamine challenge (Abi-Dargham *et al*, 1998; Breier *et al*, 1997; Laruelle *et al*, 1996) and elevated striatal dopamine synthesis (Dao-Castellana *et al*, 1997; Hietala *et al*, 1995, 1999; Howes *et al*, 2009; Lindström *et al*, 1999; McGowan *et al*, 2004; Meyer-Lindenberg *et al*, 2002; Nozaki *et al*, 2009; Reith *et al*, 1994) have been well replicated neuroimaging observations in independent schizophrenia cohorts. There exists, however, considerable range and overlap with healthy individuals in these measurements, suggesting substantial variability in dopaminergic system characteristics among patients. It remains unproven whether such variability in presynaptic dopaminergic characteristics has any mechanistic relevance to individual differences in striatal functional responses to medication, despite prior suggestion that this may be the case (Lahti *et al*, 2009b). If so, then the degree to which an individual with primary psychosis expresses these dopaminergic phenotypes may be an important predictor of dopamine receptor-mediated neurophysiological changes with neuroleptic medications.

Hypothesizing not only that antipsychotic medication treatment would enhance striatal blood flow in a clinically meaningful manner, but also that greater presynaptic dopaminergic tone would correspond with greater blood flow changes, we studied a cohort of inpatients on the NIMH IRP schizophrenia ward who underwent a carefully observed cross-over, blinded, placebo-controlled antipsychotic medication withdrawal study with both [^{15}O]-water to measure rCBF (a gold standard indicator of regional metabolism (Fox *et al*, 1988)) and [^{18}F]-fluorodopa PET to measure presynaptic dopamine synthesis and storage.

MATERIALS AND METHODS

Participants

Thirty volunteers between ages 18 and 59 (mean 27.7 ± 8.2 years; 9 women, 11 smokers) with schizophrenia (28) or schizoaffective disorder (2) participated after providing informed consent, as approved by the National Institutes of Health (NIH) Combined Neuroscience Institutional Review Board (IRB) and the NIH Radiation Safety Committee. Participants were recruited throughout the United States with IRB-approved advertisement activities. Diagnosis based on DSM-IV criteria was confirmed via clinician-administered standardized clinical interview (SCID; First *et al*, 1996) and ongoing inpatient clinical evaluation. Patients were determined to be free of confounding psychiatric, neurological, substance-related, or major medical illness, as confirmed by structural magnetic resonance imaging (MRI), routine laboratory tests including urine toxicology, medical history, and physical examination. At the time of admission, all subjects were evaluated to be without a history of alcohol or substance addiction/dependence and were free of alcohol and substance abuse for a minimum of 3 months prior to the study. Four individuals completing all scans reported past alcohol abuse (none reported past daily use). Nine individuals in the full cohort (five in the multitracer group) reported past cannabis abuse (only three reported past daily use, although all had been abstinent for at least 2 years prior to admission, and frequency data were unavailable for one individual). All patients had a history of chronic illness and prior antipsychotic medication treatment exposure.

Each participant completed a dual-armed, balanced cross-over, blinded medication withdrawal protocol, during which clinical assessments and PET scans occurred after at least 3 weeks of active antipsychotic treatment or medication withdrawal (17 placebo arm first; mean duration of placebo arm prior to [^{15}O]-water PET scan 27.8 ± 2.1 days). Antipsychotic medications (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) were administered in therapeutic doses, and chlorpromazine equivalent dose was calculated as previously described (Andreasen *et al*, 2010). Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987), as administered by

blinded raters at both active medication and medication-free time points. Among factor analytic studies evaluating the structure of this instrument, there exists a reliable preponderance of similar five-factor solutions. We therefore adopted the consensus model approach established by Wallwork *et al* (2012), calculating the following symptom subscales: positive, negative, depressed, excited, and disorganized. Percent changes in symptoms were calculated as the medication-free rating minus the active medication rating, relative to the mean rating. This calculation was performed after rescaling the scores (subtracting one from each item) to correct for the fact that the absence of symptoms is rated 'one' (rather than 'zero') for each PANSS item, as previously discussed (Obermeier *et al*, 2010).

Neuroimaging

Acquisition procedures. PET measurement of rCBF was conducted twice—once during placebo and once during the active treatment arm—with [^{15}O]-water PET in all 30 participants. In a separate PET session during the placebo arm, presynaptic dopamine synthesis capacity was measured with [^{18}F]-FDOPA in 18 of the 30 participants. In addition, structural MRI at 3 T was acquired for each subject separately to generate a T1-weighted anatomical image to guide PET data preparation as described below.

Caffeine and nicotine were not permitted for 4 h before all scanning sessions. In addition, prior to [^{18}F]-FDOPA PET sessions, a fasting state (minimum 6 h) was required to avoid competition for tracer central nervous system (CNS) admittance via the L-type large neutral amino-acid carrier system. Oral administration of 200 mg of carbidopa, a peripheral amino-acid decarboxylase inhibitor, was given 1 h prior to [^{18}F]-FDOPA injection to limit peripheral metabolism of circulating radiotracer and, thus, maximize its availability to the CNS.

All PET neuroimaging was performed with a General Electric Advance 3D PET camera (32 planes, 6.5 mm FWHM). To limit head motion during data acquisition, an individually molded thermoplastic mask was applied. An 8-min transmission scan for attenuation correction was collected for all PET scan sessions. For the resting-state [^{15}O]-water data, two 60-s long emission scans were collected after intravenous administration of 10 mCi (370 MBq) of [^{15}O]-water with an interscan interval of 6 min. For the [^{18}F]-FDOPA data, 27 dynamically acquired emission scan frames were collected over 90 min after intravenous administration of ~16 mCi (592 MBq) of [^{18}F]-FDOPA.

T1-weighted structural MRI scans were acquired separately on a 3 T General Electric scanner for coregistration and warping, as described below.

Data processing procedures. For all PET scans, filtered back-projection reconstruction using the 3D reprojection method (Kinahan and Rogers, 1989) and employing a Hanning filter was performed with corrections for post-injection radioactivity decay, dead time, and scatter; and a registered attenuation correction algorithm that accounted for frame-wise head motion was applied.

T1-weighted anatomical MRI images were nonparametric nonuniform intensity normalized (Sled *et al*, 1998) and aligned to the anterior–posterior commissure. Using an initial segmentation of these images by Freesurfer (http://freesurfer.net/) as a starting point, bilateral striatal regions of interest (ROIs)—caudate, putamen, and ventral striatum (defined as the nucleus accumbens and adjacent striatal tissue inferior to the anterior commissure)—were manually drawn for each individual by operators blinded to the PET data (Yushkevich *et al*, 2006) and eroded by one voxel to mitigate partial volume effects. For use as a reference region for kinetic analyses of the [^{18}F]-FDOPA data, a gray matter cerebellar reference region (excluding vermis and lateral/superior parasinus regions) was also drawn for each individual.

For the [^{15}O]-water data, a correction for background activity was performed on each scan, and the two scans obtained for each PET session were aligned and global signal normalized to account for variation across injections in overall activity counts. The resulting image pairs were averaged within each session. Each individual's T1-weighted anatomical MRI image was coregistered to his or her mean PET image along with the corresponding segmentation image generated from the ROI derivation described above. Mean striatal ROI values were then extracted. Blood flow change was calculated via simple subtraction (active—placebo) for each region. For voxel-wise analyses, the coregistered anatomical MRI image was warped to a common-space (MNI) template using ANTS software (http://stnava.github.io/ANTs/). The resulting transformation matrix was applied to the PET images. Blood flow change maps were generated by subtracting the medication-free mean rCBF maps from those of the active medication arm.

For the [^{18}F]-FDOPA data, the 4th through 27th emission frames were corrected for interscan motion by realignment to the 21st frame with a rigid body transformation using FLIRT (http://fsl.fmrib.ox.ac.uk/fsl/); the first three frames, which have lower signal to guide realignment, used the transform of the fourth frame. The T1-weighted anatomical MRI image for each subject was coregistered to the mean of his or her PET images using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Striatal ROI and cerebellar reference region time–activity curves were extracted from the emission frames, and the kinetic rate constant, K_i, representing specific tracer uptake and a measurement of dopamine synthesis capacity (DOPA decarboxylase activity), was calculated for each ROI with PMOD software (http://www.pmod.com/), using the non-invasive graphical linearization method established by Patlak and Blasberg (1985).

Statistical Analyses

Statistical analyses for demographic, clinical, and striatal ROI association testing were performed in SPSS (http://www-01.ibm.com/software/analytics/spss/) with general linear modeling and, for analyses with PANSS scores, nonparametric tests. For the latter, differences across medication conditions were tested with related-samples Wilcoxon signed-rank tests. Associations between PANSS change scores and binary or continuous variables were tested with independent samples Mann–Whitney *U*-tests and Spearman's rank correlations, respectively. For tests of association between striatal PET measurements and patient characteristics, multivariate tests were conducted with the three bilateral ROI rCBF change values or K_i values as dependent variables, and significant results were followed up with *post hoc* univariate testing. For pairwise tests of association between each ROI rCBF change

Table 1 Clinical Ratings Data

Group	N	PANSS measure	Total	Depressed	Disorganized	Excited	Negative	Positive
Full	30	Active	60 (55 to 72.8)	6.5 (5 to 8)	6 (5 to 8.3)	5 (4 to 5.3)	16.5 (11.8 to 21)	8 (7 to 11)
		Placebo	68.5 (58 to 78.3)	6 (5 to 8)	7 (5 to 9.3)	5 (4 to 6)	16.5 (12.8 to 21.5)	10.5 (6 to 13)
		Percent change	9.4 (−17.4 to 36.9)	9.1 (−57.6 to 60.9)	16.8 (−31.4 to 81.4)	0 (−46.7 to 75)	0 (−25.4 to 23.4)	18.2 (−35 to 54.5)†
Multi-tracer	18	Active	58.5 (54.3 to 68.8)	6 (5 to 8)	6 (5 to 8)	4 (4 to 5)	14.5 (9.8 to 21)	8.5 (7 to 11)
		Placebo	68.5 (58.5 to 79.5)	6.5 (5 to 8.3)	7 (5 to 9.3)	5 (4 to 6.3)	15.5 (11.8 to 19.5)	11 (6.8 to 13.8)
		Percent change	20.9 (−11.3 to 36.9)*	18.2 (−40 to 60.9)	21.6 (−26.7 to 71.4)	0 (−55 to 200)	6.7 (−25 to 68.4)	23.4 (−19.9 to 50)*

For the full patient cohort who completed two regional cerebral blood flow (rCBF) scans, and for those who completed [^{18}F]-FDOPA PET scans as well as the rCBF assessments, PANSS ratings median values and interquartile ranges are provided. Asterisks indicate a significant effect of condition at $p<0.05$. Daggers indicate non-significant trend ($p<0.1$).

and their respective [^{18}F]-FDOPA K_i measurement, simple univariate tests were conducted. For finer anatomical localization of significant PET results, voxel-wise general linear model analyses of rCBF change were conducted in SPM (http://www.fil.ion.ucl.ac.uk/spm/) within the striatum with an uncorrected voxel-wise threshold of $p<0.005$. These included association tests with K_i values and PANSS change scores. The latter were rank-transformed prior to entrance in voxel-wise analyses.

RESULTS

Demographics and Clinical Characteristics

Patients had been ill for an average of 6.6 (±6.0) years prior to participation, and received standard doses of antipsychotic medication during the active arm of the protocol (mean chlorpromazine equivalent dose 303.3 ± 102.5 mg). The subsample who completed [^{18}F]-FDOPA PET scanning (injected dose 595.3 ± 28.8 MBq, specific activity 57.2 ± 18.3 MBq/μmol, mass 2.5 ± 0.9 mg) shared similar demographics as the full sample (18 subjects, all with a diagnosis of schizophrenia, 9 female, age 29.3 ± 10.2 years, 5 smokers, duration of illness 7.8 ± 7.3 years, chlorpromazine equivalent dose 278.9 ± 83.9 mg, 9 started with the placebo arm). PANSS ratings indicated symptoms in the mild-to-moderate range with considerable interindividual variation in baseline and response ratings. Although decompensation during medication withdrawal was not seen by this rating scale in all patients, in the full group, there was a trend for greater positive symptoms during the placebo arm ($z=1.77$, $p=0.077$). In the multi-tracer group (those who completed the [^{18}F]-FDOPA scans as well as the two rCBF scans), a significant effect of medication condition was observed, with greater total and positive symptom burden during the medication-free period (total: $z=2.03$, $p=0.043$; positive: $z=2.27$, $p=0.023$). In this group, a non-significant trend for greater disorganized symptoms was also noted ($z=1.65$, $p=0.099$). See Table 1.

Percent change in clinical ratings, as measured by the PANSS total or subscale scores, did not show any significant relationship with sex, chlorpromazine equivalent dose, or the order of the treatment arms in the full group or the subgroup. In the full group only, smoking was associated with total and excited symptom change (total: $U=53.5$, $p=0.026$; excited: $U=45$, $p=0.009$), such that non-smokers tended to show greater decompensation off of medication, and we therefore repeated PANSS association tests in this cohort controlling for smoking. In the multi-tracer subgroup, there was no relationship between smoking and PANSS score changes. In the multi-tracer but not the full group, older age was associated with greater disorganized symptoms increase during the placebo arm ($\rho=0.56$, $p=0.016$).

Neuroimaging

rCBF change with antipsychotic medication treatment. During active treatment relative to placebo, all bilateral subregions of the striatum had greater rCBF, particularly in the ventral striatum (full group: putamen $t(29)=2.65$, $p=0.013$; caudate $t(29)=2.41$, $p=0.023$; ventral striatum $t(29)=2.99$, $p=0.006$; multi-tracer group: putamen $t(17)=2.43$, $p=0.026$; caudate $t(17)=2.46$, $p=0.025$; ventral striatum $t(17)=3.61$, $p=0.002$). These findings remained significant after repeating analyses without the two individuals with schizoaffective disorder and were corroborated further by *post hoc* voxel-wise tests (peak $p=0.0001$, uncorrected; $p=0.017$, FDR corrected; see Table 2; Figure 1).

rCBF change and patient characteristics. Age did not show significant relationships with striatal rCBF percent change in the full group, but in the multi-tracer group, a trend existed (multivariate Pillai's Trace $F(3,14)=2.74$, $p=0.083$). Follow-up univariate testing suggested a trend-level association with age in the putamen ($F(1,16)=3.94$, $p=0.065$) and a significant relationship in the caudate ($F(1,16)=4.94$, $p=0.041$) where age was inversely related to medication-induced striatal rCBF enhancement. To rule out confounding age effects, we therefore repeated rCBF analyses described below for this group statistically controlling for age. Multivariate tests did not find significant relationships between striatal rCBF change and smoking, sex, chlorpromazine equivalent dose, or treatment-arm order in either group.

In the full group, there was no association between striatal rCBF change and total PANSS score change; however, percent change in the excited factor score predicted striatal rCBF change (putamen: $\rho=0.45$, $p=0.012$; caudate: $\rho=0.33$,

Table 2 Voxel-wise Analyses Results

Effect	Region		X	Y	Z	Size (voxels)	T-value	p-value (FDR)	p-value
Effect of medication									
rCBF change (active—placebo)									
	L	Ventral striatum	−31.5	−6	−7.5	632	4.25	0.017	0.00010
	R	Caudate	12	3	9	186	4.10	0.017	0.00015
	R	Ventral striatum	27	7.5	−9	465	3.85	0.017	0.00030
	R	Putamen	33	−9	−1.5	93	3.75	0.017	0.00039
	L	Putamen	−19.5	19.5	−9	4	2.80	0.020	0.0045
Effect of symptom change									
rCBF (active—placebo) association with excited factor score percent change (placebo—active) rank									
	R	Ventral striatum	24	13.5	−15	1202	5.17	0.0040	8.64E−06
	R	Ventral striatum	24	13.5	−15	1202	5.17	0.0040	8.64E−06
	L	Putamen	−24	18	1.5	208	4.22	0.0040	1.15E−04
	L	Caudate	−19.5	19.5	1.5	7	3.08	0.012	0.0023
Effect of dopamine synthesis									
rCBF percent change (active—placebo) association with ventral striatal dopamine synthesis capacity									
	L	Ventral striatum	−15	15	−12	273	4.21	0.078	0.00033

Effects of medication and symptom change reported for the full patient cohort who completed two regional cerebral blood flow (rCBF) scans. Effect of dopamine synthesis is reported for the subset of those who also completed [^{18}F]-FDOPA PET scans. FDR correction was applied voxel-wise for the striatal search volume.

$p = 0.071$; ventral striatum: $p = 0.44$, $p = 0.014$; see Figure 2). This result indicated that individuals whose excited symptoms improved most on medication also showed greater rCBF increases on medication, an effect that remained significant when the two individuals with schizoaffective disorder were removed or when partial nonparametric correlations were performed controlling for age, sex, chlorpromazine equivalent dose, or treatment-arm order. When controlling for smoking, only the putamen association remained significant. No other subscales showed any significant associations with blood flow alterations. A voxel-wise analysis of association between rCBF change and ranked change in excited subscale scores revealed corresponding effects in bilateral striatal loci, which were particularly strong in the right subcommissural striatum, including the ventral putamen (peak $p = 8.6 \times 10^{-6}$, uncorrected; $p = 0.004$, FDR corrected; see Table 2; Figure 2).

Presynaptic dopamine synthesis capacity and patient characteristics. Multivariate testing showed no associations between striatal [^{18}F]-FDOPA-specific uptake (K_i), a measure of presynaptic dopamine synthesis capacity, and age, sex, smoking status, chlorpromazine equivalent dose, treatment-arm order, [^{18}F]-FDOPA dose, [^{18}F]-FDOPA-specific activity, [^{18}F]-FDOPA mass, past alcohol use, or past cannabis use. Spearman's rank correlations revealed an association between positive symptom increases off of medication and lower caudate K_i ($\rho = -0.49$, $p = 0.037$), with a trend for the same effect in the putamen ($\rho = -0.40$, $p = 0.097$). This was retained in partial correlation analyses controlling for age, chlorpromazine equivalents, or smoking status, but only a trend-level association remained in the caudate when controlling for sex or treatment-arm order.

rCBF change and presynaptic dopamine synthesis capacity. Ventral striatal [^{18}F]-FDOPA K_i predicted rCBF change in the ventral striatum ($F(1,16) = 8.018$, $p = 0.012$), but putamen and caudate K_i did not predict putamen or caudate rCBF change, respectively (Figure 3). This relationship remained significant when including age, sex, smoking status, chlorpromazine equivalent dose, or treatment-arm order in the model. Voxel-wise examination of this association localized the strongest effect to a prominent cluster abutting the left nucleus accumbens anterosuperiorly (peak $p = 0.00033$, uncorrected; $p = 0.078$, FDR corrected; see Table 2; Figure 3). For all three striatal subregions, there was not a significant correlation of [^{18}F]-FDOPA K_i and either placebo or active treatment rCBF alone (Supplementary Figures 1 and 2).

DISCUSSION

Individuals with schizophrenia showed increased striatal rCBF after at least 3 weeks of stable antipsychotic pharmacotherapy, relative to placebo treatment, in line with prior work

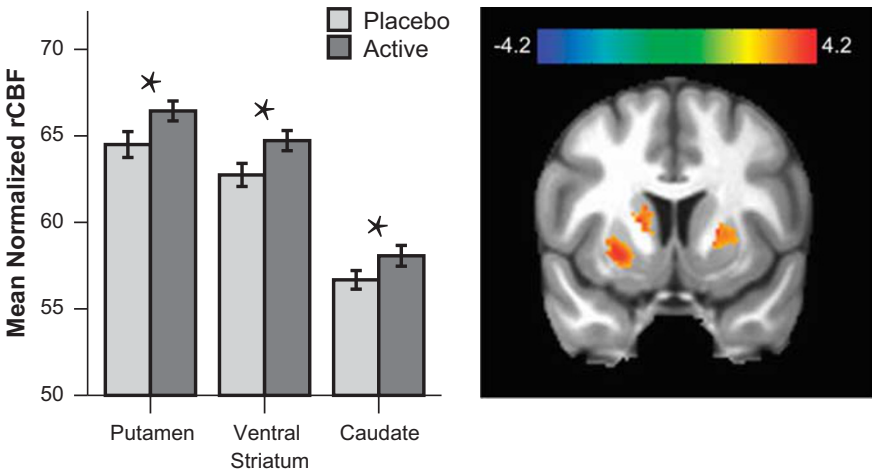

Figure 1 Antipsychotic medication effects on regional cerebral blood flow. The graph shows mean regional cerebral blood flow (rCBF) for each bilateral region of interest (ROI), with SE bars and asterisks indicating significance at $p<0.05$. The coronal slice (MNI $y=9$ mm) shows voxel-wise analysis results indicating locations of greatest medication effects in the striatum. Colored clusters represent areas where rCBF was greater during active medication relative to placebo. The color bar indicates T-values, and data are displayed by radiological convention (right hemisphere on the left side) at a voxel-wise, uncorrected threshold of $p<0.005$.

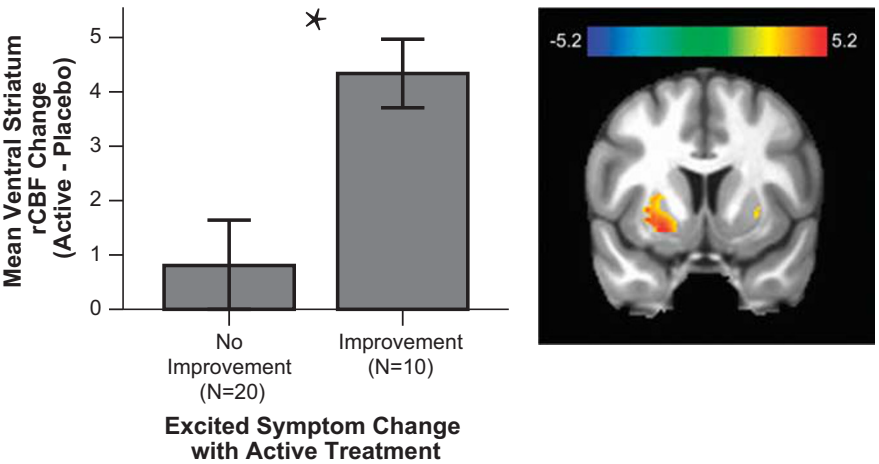

Figure 2 Relationship between regional cerebral blood flow (rCBF) change and symptoms. Mean ventral striatal medication-induced rCBF increases and SE bars are shown for the full cohort, categorized by whether PANSS-excited symptom scores improved during active medication treatment (ie, percent change >0) or not (ie, percent change $\leqslant 0$), with significance at $p<0.05$ indicated by the asterisk. The coronal slice at MNI $y=9$ mm shows results of voxel-wise analyses indicating locations of greatest correlation between ranked symptom change and blood flow change in the striatum. Colored clusters represent areas where medication-induced increases in rCBF correspond to medication-induced improvements in excited factor symptoms. Color bars indicate T-values, and data are displayed by radiological convention at a voxel-wise, uncorrected threshold of $p<0.005$.

(Lahti *et al*, 2009b). This finding is concordant with several single-dose studies in healthy individuals and patients (Fernández-Seara *et al*, 2011; Handley *et al*, 2013; Lahti *et al*, 2005; Viviani *et al*, 2013), suggesting both that neuroleptic-induced basal ganglia blood flow increases are a replicable observation even in the course of several weeks of treatment and, by the same token, that such changes are not unalterable, as, on average, they were decreased with medication withdrawal. Given the close association between regional neural activity and blood flow (Fox *et al*, 1988; Sokoloff, 1961), these findings indicate that local striatal neural operations increase with this pharmacological treatment. Although direct vascular modulation by antipsychotics at smooth muscle receptor sites cannot be ruled out and may merit future study (Afonso-Oramas *et al*, 2014; Krimer *et al*, 1998), such an effect is unlikely to fully explain the observed results, given the sheer density of neuronal dopaminergic terminals in this region and the fact that the current method controls for global intracerebral counts, and therefore for general neurovascular effects. The rCBF increase with neuroleptic treatment, although present diffusely throughout the striatum, was most robust in the ventral striatum, a central node in mesolimbic systems implicated under some models of schizophrenia and neuroleptic action (Grace, 2015; Lahti *et al*, 2003).

In agreement with past studies by Lahti *et al*, 2009b, we found that greater striatal rCBF increase was associated with greater improvements of some symptoms on active medication relative to placebo. Although total PANSS ratings did not show this relationship, the excited factor subscale did. This factor represents a group of symptoms that previously

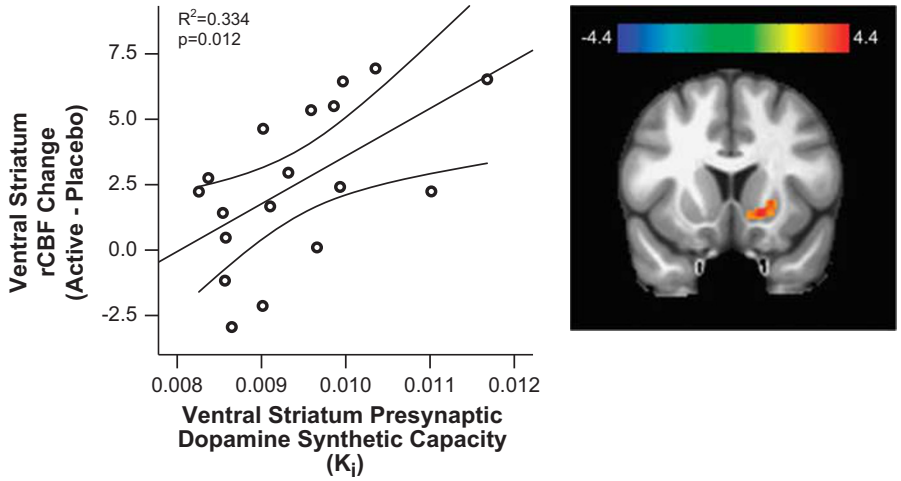

Figure 3 Relationship between regional cerebral blood flow change (rCBF) and dopamine synthesis capacity. The plot indicates ventral striatal rCBF change as a function of ventral striatal [^{18}F]-FDOPA-specific uptake (K_i). The regression line (intercept: −14.64; slope: 1.82×10^3; $R^2 = 0.334$, $R = 0.578$) and 95% confidence limits are shown. The coronal slice at MNI $y = 15$ mm shows results of voxel-wise analyses indicating locations of greatest positive association between ventral striatal presynaptic dopamine synthesis capacity (K_i) and striatal rCBF change (active-placebo). Color bars indicate T-values, and data are displayed by radiological convention at a voxel-wise, uncorrected threshold of $p < 0.005$.

have shown responsiveness to antipsychotic medications (Victoroff *et al*, 2014) and includes excitement, hostility, uncooperativeness, and impulsivity items (Wallwork *et al*, 2012). Over the duration of our study, a third of our sample demonstrated improvements on this measure with antipsychotic treatment. Therapeutic response based on the standard positive symptom subscale of the PANSS (which includes two excitement factor items), but not the standard negative symptom subscale (which includes no excitement factor items), has been associated with striatal, but not extrastriatal, D_2 antipsychotic occupancy, reaffirming the clinical importance of understanding striatal dopamine systems in this context (Agid *et al*, 2007).

It is clear from the schizophrenia literature that there exists a profound heterogeneity of both clinical illness and underlying neurobiology of individuals with schizophrenia. To the extent that illness heterogeneity is a major barrier for the development of generalizable knowledge and novel treatment approaches in schizophrenia, understanding the biological foundations of such variability is essential. As a prime example, past work has shown striatal presynaptic dopamine synthesis capacity to be abnormal to varying degrees across schizophrenia patients, suggesting a broad range of dopaminergic systems functioning in this illness, which may have important therapeutic implications (Dao-Castellana *et al*, 1997; Hietala *et al*, 1995, 1999; Howes *et al*, 2009; Lindström *et al*, 1999; McGowan *et al*, 2004; Meyer-Lindenberg *et al*, 2002; Nozaki *et al*, 2009; Reith *et al*, 1994). Similar to these studies, we found that there was substantial variability in medication-induced striatal blood flow change across the present cohort. Although unmeasured aspects of pharmaceutical kinetics and metabolism cannot be ruled out as contributory, there was insufficient evidence to support the claim that this variability was driven solely by the strength of administered D_2 antagonism, given the lack of association between this treatment effect and chlorpromazine equivalent dose.

Hypothesizing that tonic dopaminergic system characteristics may be related to the magnitude of rCBF response to neuroleptics relative to the medication-free state, we tested for association between dopamine synthesis capacity (FDOPA uptake) and antipsychotic-induced rCBF change. Importantly, and in accord with this proposal, in the subcommissural striatum, where the most significant antipsychotic medication-induced rCBF change was observed, greater presynaptic dopamine synthesis capacity predicted greater blood flow increase with medications. Thus, those individuals with higher dopamine tone—and therefore greater expression of this illness-associated phenotype—demonstrated a more vigorous neurophysiological response to medication. In line with past work showing enhanced striatal activity with typical antipsychotic medications (Corson *et al*, 2002; Lahti *et al*, 2003, 2009b; Miller *et al*, 1997a), this finding suggests a dopamine-related mechanism underlying the striatal rCBF increase observed here. It is possible that greater tonic availability of dopamine associated with enhanced DOPA decarboxylase (DDC) activity, or greater quantities of DDC containing terminals, results in greater neural activity changes when dopaminergic blockade is enacted (ie, greater 'gain'); however, this speculation requires confirmation from future investigations. With respect to the subregional localization of our findings, although recent literature has highlighted the importance of more dorsal striatal regions in schizophrenia pathophysiology (Weinstein *et al*, 2017), evidence has also suggested that ventral striatal regions may be preferentially sensitive to some types of dopaminergic pharmacological interventions such as amphetamine administration (Martinez *et al*, 2003) and atypical antipsychotic medication treatment (Lahti *et al*, 2009b). Continued experimentation in larger samples is indicated to better characterize potentially important functional and neurochemical distinctions between dorsal and ventral striatal circuitry relevant both to schizophrenia and neuroleptic action. Nonetheless, our data suggest that at least some of the substantial individual variation in striatal presynaptic dopaminergic tone that has been reported over the past two decades is linked to treatment-relevant neurophysiology.

This work is subject to several caveats and limitations. The use of several different atypical antipsychotic agents in this work ensured that participants would be able to be studied under optimal, individualized therapeutic medication conditions, thereby minimizing confounds of medication intolerances and inefficacy. However, the varied agents used (and/or other potential confounds) may have added noise to the reported relationships, and future studies with larger sample sizes, powered not only to confirm the present findings but also to examine possible differences in observed effects across pharmacological agents will be even more informative. A number of uncontrolled variables could have contributed to the present findings, including hormone/menstrual status (Berman *et al*, 1997), sleep quality/arousal (Braun *et al*, 1997), and the nature of individual thought processes during resting-state rCBF acquisition (Sokoloff, 1961). However, the within-subject design, mean interscan interval of ~1 month, and consistency of medication effects with prior work offer some reassurance with respect to these concerns. The placebo-controlled, counterbalanced design carried out on the NIMH IRP inpatient ward with close clinical and medication adherence monitoring is also a strength. Although the mean ventral striatum K_i values reported here are comparable to those of healthy individuals studied elsewhere with the same scanner model (Jokinen *et al*, 2009), methodological differences require caution when comparing the present data and those published from other PET centers. In addition, future work comparing patients and matched healthy individuals on these measurements will be even more informative. Finally, we note that the preponderance of dopamine terminals in the striatum provides reasonable support for the interpretation of the striatal [^{18}F]-FDOPA signal as dopaminergic; however, we cannot exclude the possibility that other monoaminergic (eg, serotonergic) terminals that may also express DDC, contribute to the observed signal.

In conclusion, we provide confirmatory evidence for increase of striatal blood flow during antipsychotic treatment relative to medication-free states, even when both treatment and medication-free conditions are established for several weeks. This increase may be clinically relevant, given its association with excitement factor symptoms. Furthermore, its association with dopamine synthesis capacity in the ventral regions of the striatum bolsters support for a neurochemical mechanism underpinning its interindividual variability and brings together two long-standing neuroimaging phenotypes in schizophrenia.

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