Deficits in Prefrontal Cortical and Extrastriatal Dopamine Release in Schizophrenia
A Positron Emission Tomographic Functional Magnetic Resonance Imaging Study

Mark Slifstein, PhD; Elsmarieke van de Giessen, MD, PhD; Jared Van Snellenberg, PhD; Judy L. Thompson, PhD; Rajesh Narendran, MD; Roberto Gil, MD; Elizabeth Hackett, RT; Ragy Girgis, MD; Najate Ojeil, MS; Holly Moore, PhD; Deepak D’Souza, MD; Robert T. Malison, MD; Yiyun Huang, PhD; Keunpoong Lim, PhD; Nabeel Nabulsi, PhD; Richard E. Carson, PhD; Jeffrey A. Lieberman, MD; Anissa Abi-Dargham, MD

IMPORTANCE Multiple lines of evidence suggest a deficit in dopamine release in the prefrontal cortex (PFC) in schizophrenia. Despite the prevalence of the concept of prefrontal cortical hypodopaminergia in schizophrenia, in vivo imaging of dopamine release in the PFC has not been possible until now, when the validity of using the positron emission tomographic D2/3 radiotracer carbon 11-labeled FLB457 in combination with the amphetamine paradigm was clearly established.

OBJECTIVES To (1) test amphetamine-induced dopamine release in the dorsolateral PFC (DLPFC) in drug-free or drug-naive patients with schizophrenia (SCZ) and healthy control (HC) individuals matched for age, sex, race/ethnicity, and familial socioeconomic status; (2) test blood oxygenation level–dependent (BOLD) functional magnetic resonance imaging activation during a working memory task in the same participants; and (3) examine the relationship between positron emission tomographic and functional magnetic resonance imaging outcome measures.

DESIGN, SETTING AND PARTICIPANTS Positron emission tomographic imaging with carbon 11-labeled FLB457 before and following 0.5 mg/kg of amphetamine by mouth. Blood oxygenation level–dependent functional magnetic resonance imaging during the self-ordered working memory task. Twenty patients with schizophrenia recruited from the inpatient and outpatient research facilities at New York State Psychiatric Institute and 21 healthy control individuals participated, and data were acquired between June 16, 2011, and February 25, 2014.

MAIN OUTCOMES AND MEASURE The percentage change in binding potential (ΔBPND) in the DLPFC following amphetamine, BOLD activation during the self-ordered working memory task compared with the control task, and the correlation between these 2 outcome measures.

RESULTS We observed significant differences in the effect of amphetamine on DLPFC BPND (mean [SD], ΔBPND in HC: −7.5% [11%]; SCZ: +1.8% [11%]; P = .01); a generalized blunting in dopamine release in SCZ involving most extrastriatal regions and the midbrain; and a significant association between ΔBPND and BOLD activation in the DLPFC in the overall sample including patients with SCZ and HC individuals.

CONCLUSIONS AND RELEVANCE To our knowledge, these results provide the first in vivo evidence for a deficit in the capacity for dopamine release in the DLPFC in SCZ and suggest a more widespread deficit extending to many cortical and extrastriatal regions including the midbrain. This contrasts with the well-replicated excess in dopamine release in the associative striatum in SCZ and suggests a differential regulation of striatal dopamine release in associative striatum vs extrastriatal regions. Furthermore, dopamine release in the DLPFC relates to working memory–related activation of this region, suggesting that blunted release may affect frontal cortical function.

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The concept of cortical hypodopaminergia in schizophrenia (SCZ) has emerged from converging lines of evidence showing that working memory (WM) is deficient in SCZ,\(^2\) that WM depends critically on optimal prefrontal dopamine (DA) transmission in nonhuman primates,\(^3-10\) that it is associated with abnormal prefrontal activation during functional brain imaging studies in SCZ,\(^11\) and that it can improve with DA agonists.\(^12-15\) Furthermore, postmortem studies have reported a decrease in tyrosine hydroxylase immunolabeling in the prefrontal cortex in SCZ.\(^16-18\) While positron emission tomography (PET) studies have investigated alterations in cortical D1 receptor availability,\(^19-21\) there have been no in vivo studies examining the capacity for DA release in the frontal cortex in SCZ, a gap that contrasts with the considerable body of evidence from in vivo PET imaging studies showing an increase in stimulant-induced DA release in the striatum of patients with SCZ.\(^22-24\)

One major impediment to PET studies of cortical DA release has been the lack of a suitable PET radiotracer. For reasons that are not completely understood, D1 radiotracers have not proven to be sensitive to stimulant-induced DA release,\(^25\) whereas D2/D3 tracers have. While radiotracers, such as carbon 11-labeled raclopride and carbon 11-labeled (+)-PHNO, are useful for detecting acute fluctuations in DA levels in the striatum, the very low density and limited anatomical distribution of DA D2/D3 receptors in the cortex\(^26\) preclude their use for quantitative imaging of D2/D3 receptors in the cortex. Carbon 11-labeled FLB457 (\[^{11}C\]FLB457) is a higher-affinity PET tracer that has been shown to provide reliable quantification of amphetamine-induced DA release in the cortex\(^27,28\) (test-retest reproducibility ≤15% using conventional compartment analysis methods), although it cannot be quantified in the striatum owing to its slow washout in this high D2/D3 receptor density region. However, there are challenges in working with this tracer. Most D2/D3 tracers show negligible specific binding in the cerebellum, allowing the use of the cerebellum as a reference region.\(^29\) This is not the case for \[^{11}C\]FLB457 because approximately 20% of \[^{11}C\]FLB457 cerebellum distribution volume \((V_c)\) can be displaced by the D2 partial agonist aripiprazole.\(^30\)

In the current study, we measured amphetamine-induced DA release in the dorsolateral prefrontal cortex (DLPFC) in patients with SCZ and matched healthy control (HC) individuals using \[^{11}C\]FLB457 PET imaging. We implemented a kinetic model with shared parameters across 9 cortical regions, which addressed both the lack of a reference region and the low cortical signal, to quantify receptor availability and DA release. We hypothesized that cortical DA release capacity, especially in the DLPFC, would be reduced in SCZ compared with HC individuals. We also examined a number of brain regions where D2/D3 receptor availability is intermediate between striatal and cortical binding including the midbrain ( substantia nigra and ventral tegmental area), thalamus, and medial temporal regions (amygdala and hippocampus). To test the functional significance of cortical DA release capacity, we used functional magnetic resonance imaging (fMRI) to measure changes in the blood oxygenation level-dependent (BOLD) signal in the DLPFC during performance of the self-ordered WM task (SOWMT) and examined associations between cortical DA release capacity and WM task-related DLPFC activation. Finally, we examined the relationships between \[^{11}C\]FLB457 PET and WM-sensitive performance in patients with SCZ and HC individuals, as well as clinical symptoms in patients.

### Methods

#### Participants

This study was approved by the institutional review boards of the New York State Psychiatric Institute and Columbia University Medical Center and the Yale University human investigation committee. All participants provided written informed consent following an independent assessment of capacity by a psychiatrist who was not a member of the research team. Patients were recruited from the inpatient and outpatient research facilities at New York State Psychiatric Institute. Healthy control individuals were recruited through advertisements. Medical screening procedures included a physical examination and history, blood and urine tests, an electrocardiogram, and a structural MRI scan of the brain. Data were acquired between June 16, 2011, and February 25, 2014.

Inclusion criteria for patients were (1) lifetime DSM-IV diagnosis of SCZ, schizoaffective, or schizophreniform disorder; (2) no bipolar disorder; (3) no antipsychotics for 3 weeks prior to the PET scan; and (4) no history of violent behavior. Inclusion criteria for HC individuals were (1) the absence of any current or past DSM-IV Axis I diagnosis and (2) no (first-degree) family history of psychotic illness.

Exclusion criteria for both groups included significant medical and neurological illnesses, current misuse of substances other than nicotine, positive urine drug screen result, pregnancy, and nursing. Groups were matched for age, sex, race/ethnicity, parental socioeconomic status, and nicotine smoking (Table 1).

#### PET Imaging Study Design

Participants underwent 2 PET scans on 1 day with \[^{11}C\]FLB457 at the Yale University PET Center. A 90-minute baseline scan was acquired, followed immediately by oral administration of amphetamine (0.5 mg/kg) and a second 90-minute scan 3 hours after amphetamine administration. Arterial plasma data were collected to form metabolite-corrected input functions. Data were acquired on an HR+ scanner (Siemens) and reconstructed by filtered back projection with correction for attenuation, randoms, and scatter. Data were binned into a sequence of frames of increasing duration.

#### PET Data Analysis

##### Preprocessing

A high-resolution T1-weighted MRI scan was acquired for each participant. Regions of interest (ROIs) were drawn on each participant’s MRI according to previously described criteria\(^30,31,32\) (see eAppendix 1 in the Supplement for operational definitions of the amygdala and hippocampus) and included, in addition to the DLPFC, our a priori ROI, the medial frontal cor-
The PET data were coregistered to the MRI data using normalized maximization of mutual information (SPM8) and the ROI were transferred to the coregistered PET using MEDx software (Medical Numerics). Time activity curves were generated as the average activity in each frame for each ROI.

Kinetic Analysis
Data were analyzed with a 2-tissue compartment model that additionally incorporated a set of shared parameter estimates across regions to improve reliability of fits by estimating a reduced parameter set compared with conventional 2-tissue compartment model. For each participant, the distribution volume of the nondisplaceable compartment (VND) and the specific binding dissociation constant (k4) were fitted to a single value across cortical regions for both baseline and postamphetamine scans (eAppendix 2, eTable 1, and the eFigure in the Supplement). The brain delivery constant (K1) and the association constant (k3) were fitted in each region and condition. Data were weighted by frame duration; all regions were weighted equally. The same procedure was applied separately to the higher-binding subcortical regions to allow for the possibility that the fitting procedure might assign different k4 values in those regions. Distribution volume was estimated in each region and condition. Binding potential (BPND) was estimated directly from the ratio k3/k4. We report BPND, the relative change following amphetamine (∆BPND), Vr, and ∆Vr.

Statistics
In the DLPFC, 2-group t tests were applied to baseline BPND, ∆BPND, baseline Vr, and ∆Vr. Additionally, linear mixed modeling with ROIs as repeated measure and group and ROIs as fixed variables was applied across all 14 regions. Two-sided t tests were applied to scan parameters including injected activity, injected mass, plasma free fraction (fp) and estimated VND and k4. Parameter estimates are reported as mean (standard deviation).

fMRI Data Analysis
A subset of 16 patients with SCZ and 18 HC individuals participated in a BOLD fMRI study in which they performed the SOWMT (among the 20 patients with SCZ and 21 HC individuals, 4 SCZ cases and 2 HC individuals declined to participate in the fMRI procedures, and data from 1 HC individual were unusable owing to poor image quality). Complete details of the task, as well as acquisition and analysis, are in eAppendix 3 in the Supplement. Briefly, structural and BOLD images were acquired on a Philips 1.5-T Intera scanner. Blood oxygenation level–dependent images during SOWMT performance were acquired at a 3-mm isotropic voxel size with a repetition time of 2 seconds, separated into 9 runs of 160 volumes each. Blood oxygenation level–dependent images underwent slice-timing correction, motion realignment, and coregistration to the T1-weighted structural images. A separate set of BOLD images were normalized to the ICBM template for voxelwise statistical analysis. The SOWMT consists of a presentation of 8 different geometric shapes on a projection screen. Participants select 1 of the shapes; on each successive trial, the positions of shapes on the screen are ran-

<table>
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<tr>
<th>Table 1. Demographics</th>
<th>Mean (SD)</th>
<th>Patients With Schizophrenia (n = 20; 1 Schizoaffective, 19 Schizophrenia)</th>
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<td>Parental SES</td>
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<tr>
<td>Duration of psychotic illness, y</td>
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<td></td>
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<tr>
<td>Drug-free interval, mo</td>
<td>38.4 (67.3)h</td>
<td></td>
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Abbreviation: SES, socioeconomic status.

a Two-group t tests for continuous variables, χ² for categorical.

b For 14 patients with schizophrenia.

tex, orbitofrontal cortex, anterior cingulate, occipital cortex, parietal cortex, temporal cortex, subgenu of the cingulate, insula, cerebellum, and 5 subcortical regions: amygdala, hippocampus, midbrain encompassing the substantia nigra and ventral tegmental area, thalamus, and uncus. The PET data were coregistered to the MRI data using normalized maximization of mutual information (SPM8) and the ROIs were transferred to the coregistered PET using MEDx software (Medical Numerics). Time activity curves were generated as the average activity in each frame for each ROI.
domly reordered and participants are instructed to select a shape they have not picked previously. Thus, participants are required to hold up to 7 distinct items in WM. There was a monetary incentive for correct answers ($0.25 per correct response). Complete analysis of the BOLD response to the SOWMT are presented elsewhere.34 Here, we report only the relationship between BOLD and PET data. We regressed the DLPFC ΔBPND against overall BOLD activation in the DLPFC voxels that were significantly activated during the SOWMT. A second-level task/control contrast was calculated on the ICBM-normalized BOLD data to identify voxels showing significant activation during SOWMT performance. This group-level map was transformed to the individual participants’ T1 space and the intersection of the activated region with their DLPFC ROI was used to extract BOLD signal change values within the DLPFC for each participant. We used this approach to restrict analysis to DLPFC voxels that showed evidence of involvement in the SOWMT.

Neurocognitive and Clinical Measures
Diagnostic status was determined with the Diagnostic Interview for Genetic Studies35 in patients with SCZ followed by a consensus diagnosis conference and an abbreviated version of the Structured Clinical Interview for DSM-IV Axis I disorders36 in HC individuals. The severity of symptoms was assessed with the Positive and Negative Symptoms Scale37 by trained interviewers.

As additional measures of WM, we also assessed performance on the N-back task39 and the letter-number span.40 Both tasks were acquired once on the day preceding the PET scans and a second time after the second PET scan. The N-back task contained 3 levels of difficulty including 1, 2, and 3 back. The adjusted hit rate (the percentage of properly identified targets corrected for false-positives; eAppendix 4 in the Supplement) was assessed as in the study by Abi-Dargham et al20 and ranged from a maximum possible score of 1 for perfect performance to −1 if all true targets were missed and all nontargets were incorrectly identified as targets.

Results

PET Scan Parameters
Injected activity, injected mass, plasma free fraction for baseline and amphetamine conditions, and estimated VND and k₄ are shown in Table 2. There were no significant group differences in any of these.

PET Results
Baseline DLPFC BPND did not differ significantly between groups but ΔBPND did (mean [SD], HC: −7.5% [11.4%]; SCZ: +1.8% [11.1%]; P = .01) (Table 3). Linear mixed modeling of ΔBPND showed a statistically significant effect of group (F₁,39 = 6.95; P = .01) but no significant effect of ROI or group by ROI interaction. While the interaction term was not significant, 2 regions reached trend-level group differences including the DLPFC (P = .09) and the substantia nigra and ventral tegmental area (P = .10). The BPND was higher in drug-naive than drug-free patients but there were no significant differences in any PET outcome measure when age was included as a covariate (eAppendix 5 in the Supplement). The Vₑ results are shown in eTable 2 in the Supplement. Baseline DLPFC Vₑ in SCZ did not differ significantly between groups. There was a significant difference in the DLPFC Vₑ (mean [SD], HC: −5% [7%]; SCZ: +1% [7%]; P = .01). Linear mixed modeling of ΔVₑ showed a statistically significant effect of group (F₁,39 = 4.11; P = .049) but no significant effect of ROI or group by ROI interaction.
Associations With fMRI Activation

A significant relationship between DLPFC ΔBP ND and BOLD activation in the DLPFC was observed in patients with SCZ and HC individuals. Regression of ΔBP ND onto BOLD activation had a significant effect of group (β = −10.2; t 31 = −2.707; P = .01) and a significant effect of BOLD (β = 52.9; t 31 = 2.211; P = .03) but no group by BOLD interaction; thus, the most parsimonious model contained the same slope for both groups but different intercepts: BP ND percentage decrease (HC) = 53 × BOLD (HC) % increase + 6% and BP ND percentage decrease (SCZ) = 53 × BOLD (SCZ) % increase − 4% (Figure).

Associations With WM Performance and Symptoms

Patients performed significantly worse on the following WM measures: baseline 1-back and postamphetamine 2-back task and on baseline and postamphetamine letter-number span (Table 4).

In SCZ, there were no correlations between WM performance and DLPFC BP ND, ΔBP ND, VT, or ΔVT. In HC individuals, WM performance correlated with DLPFC BP ND (baseline 2-back: r = 0.50, P = .03; baseline 3-back: r = 0.79, P < .001; SOWMT: r = 0.50, P = .03) and Vf (baseline 3-back: r = 0.68, P = .001) in the DLPFC. Exploratory analyses of correlations at...
each level of the SOWMT revealed significant correlations between DLPFC BP\textsubscript{ND} and WM performance when WM load was greatest (step 7: \(r = 0.48, P = .04\); step 8: \(r = 0.66, P = .003\)). Exploratory analyses, including all 14 ROIs using a linear mixed model with ROIs as repeated measures, resulted in an overall positive association between BP\textsubscript{ND} in the analyzed regions and baseline 2-back (\(F_{1,16.9} = 4.99, P = .04\)), 3-back (\(F_{1,16.9} = 14.18, P = .002\)), and SOWMT (\(F_{1,103.4} = 8.08, P = .005\)) in HC individuals. The same design applied to VT showed an overall positive association of VT with baseline 3-back (\(F_{1,16.6} = 14.18, P = .002\)) in HC individuals. There were no significant correlations between WM performance and ΔBP\textsubscript{ND} or ΔVT in HC individuals. There were no significant correlations between Positive and Negative Symptoms Scale scores (Table 4) and BP\textsubscript{ND}, ΔBP\textsubscript{ND}, \(V_T\), or Δ\(V_T\).

### Discussion

In this study, we observed that patients with SCZ showed blunted amphetamine-induced DA release in the DLPFC in vivo. This deficit in DA release extended to other extrastriatal regions including the midbrain. We also observed a correlation between this index of DA release capacity and WM-related activation of the DLPFC, as measured with BOLD fMRI.

Despite the prevalence of the concept of hypodopaminergia in SCZ, to our knowledge, there had been no empirical evidence for decreased cortical DA release prior to this study. This was related to the difficulty in measuring DA release in the cortex due to the low level of cortical D2 receptors\(^{27,28}\) and the small range of displacement of D2 radiotracers by DA. Here, we adopted and optimized an \(^{[11C]}\)FLB457 displacement paradigm shown to be a valid and reliable proxy for changes in extracellular DA following an amphetamine challenge.\(^{27,28,41}\)

Precise quantification of \(^{[11C]}\)FLB457 displacement is challenging both because the signal is quite small despite the high affinity of \(^{[11C]}\)FLB457 and because the cerebellum cannot be used as a suitable reference tissue. Considering these factors, we developed a kinetic approach that was sensitive enough to detect a small change within a small signal. The shared parameter method we applied here took advantage of the fact that \(^{[11C]}\)FLB457 kinetics are similar in many cortical regions and greater parsimony can be achieved through the dramatic reduction of the number of estimated parameters. In simulations (see Appendix 2 in the Supplement), we extensively tested cases in which the underlying assumptions of the shared parameter method—uniform \(k_4\) across cortical regions and between scans as well as uniform \(V_{ND}\) between scans—were intentionally violated, and we found that the method performed more precisely than the conventional 2-tissue compartment model. We also noted that the average estimated \(V_{ND}\) was 70% of cerebellum \(V_T\), in agreement with Narendran et al.\(^{30}\)

In the primate PFC, \(^{[11C]}\)FLB457 displacement correlates with changes in extracellular DA across doses of amphetamine.\(^{41}\) Amphetamine increases synaptic and extracellular DA by reversing the DA transporter.\(^{42}\) Microdialysis measures the summed effects of a given drug on synaptic release, extrasynaptic release, and uptake. On the other hand, D2/D3 tracer displacement is considered an index of synaptic DA release. This interpretation comes from the fact that while the PET measure reliably correlates with microdialysis measurements of extracellular DA across doses of a given DA-releasing drug, the slopes of these correlations differ across drugs and across brain regions. This presumably reflects differences in the relative contributions of DA release and uptake. This may be important for our interpre-

<table>
<thead>
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<th>Table 4. Clinical and Neurocognitive Assessments</th>
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<td>Negative symptoms</td>
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<td>Postamphetamine AHR</td>
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<tr>
<td>Baseline</td>
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<td>Postamphetamine</td>
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Abbreviations: AHR, adjusted hit rate; LNS, letter-number sequencing task; PANSS, Positive and Negative Symptom Scale.
tation of regional differences in amphetamine-induced D2/D3 tracer displacement in SCZ. Regulation of DA release and reuptake in the cortex and other extrastriatal regions differs from regulation in the striatum.43-46 For example, in the cortex and other regions with noradrenergic inputs, but not in the striatum, the norepinephrine transporter is also a major regulator of extracellular DA levels.43,44,47,48 A decrease in amphetamine-induced release in the DLPFC observed in SCZ could reflect decreased synthesis and vesicular storage, altered metabolism, or altered regulation of synaptic DA by the DA transporter or norepinephrine transporter.

Our PET study uncovered widespread lower DA release in patients with SCZ compared with HC individuals, encompassing most cortical and extrastriatal regions including the ventral midbrain. Notably, this observation appears to be inconsistent with [18F]fluoro-L-DOPA PET and postmortem findings supporting an increase in DA synthesis and/or storage in the midbrain in SCZ.49,50 Further experiments are needed to confirm whether the increase in [18F]fluoro-L-DOPA uptake and decreased DA release capacity in the midbrain coexist within the same patients or whether they reflect an uncoupling of DA synthesis and release in the midbrain.

The contrast between the generalized DA deficit in cortical and extrastriatal regions and the increase in DA release in the striatum in SCZ24,49-52 is particularly intriguing. This dissociation may reflect abnormal local presynaptic regulation of DA specific to the striatum existing on a background of DA release deficits. Alternatively, a discrete DA neuron subpopulation within the midbrain, innervating the associative striatum, may be overactive. Taken together, the apparently discordant abnormalities across the midbrain, striatum, and cortex raise the possibility that SCZ involves a widespread DA release deficit, coexisting with abnormal local dysregulation of DA release or uptake in the striatum (particularly the associative striatum) and possible uncoupling of DA synthesis and storage from dendritic DA release in the midbrain. More basic research is required to clarify the mechanisms regulating DA synthesis, vesicular storage, release and reuptake—and their coupling—in the midbrain, cortex, and striatum.45,46

Because DA is important for frontal cortex-dependent cognition, including WM, we examined the relationship between DLPFC DA release capacity and fMRI BOLD activation within the DLPFC during WM performance. Dopamine release correlated with BOLD activation and did not differ between groups. The relationship between BOLD and DA release suggests that fluctuations in DA release in the DLPFC may modulate the strength of the hemodynamic (and presumably neuronal) response to cognitive processing demands placed on DLPFC circuitry. While release capacity correlated with the cortical response to the WM challenge, it did not predict performance, which was impaired in patients with SCZ. One potential explanation is that WM performance is tightly coupled to DA release dynamics during cognitive challenges,53 a measure not captured by amphetamine-induced release. Notably, we found a positive association between D2 BPND and WM performance in HC individuals but not in patients with SCZ. Consistent with reports that D2 stimulation can effectively gate synaptic plasticity in cortical projection neurons,54 this finding suggests that under normal conditions, D2 availability may be a rate-limiting factor for WM whereas in SCZ, WM capacity is limited by mechanisms upstream or independent of DLPFC D2 receptors.

Conclusions

In summary, our study established that in SCZ, amphetamine-induced DA release is deficient. This contrasts with the well-replicated increased DA storage and release in the striatum in SCZ. Moreover, the relationships between DA indices and prefrontal cortical function during WM are complex and may be modulated in part by the availability of DA receptors. These findings highlight the need to fully determine the molecular mechanisms regulating DA synthesis, storage, release, and reuptake and examine how these mechanisms operate in different DA projection fields. Such studies will lead to an understanding of the complex dopaminergic phenotype in SCZ and advance the development of a coordinated treatment strategy for symptoms and cognitive disturbances in this disorder.

ARTICLE INFORMATION

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Author Affiliations: Department of Psychiatry, Columbia University, New York, New York (Slifstein, van de Giessen, Van Snellenberg, Thompson, Gil, Girgis, Moore, Lieberman, Abi-Dargham); New York State Psychiatric Institute, New York (Slifstein, van de Giessen, Van Snellenberg, Thompson, Gil, Hackett, Girgis, Ojeil, Moore, Lieberman, Abi-Dargham); The State University of New Jersey, Rutgers (Thompson); Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Narendran); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (D’Souza, Malison); PET Center, Yale University School of Medicine, New Haven, Connecticut (Huang, Lim, Nabulsi, Carson); Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, (Huang, Lim, Nabulsi, Carson); Department of Radiology, Columbia University, New York, New York (Abi-Dargham).

Author Contributions: Drs Slifstein and van de Giessen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Slifstein and van de Giessen contributed equally to this study.

Study concept and design: Slifstein, Van Snellenberg, Narendran, Gil, Girgis, Moore, Lieberman, Abi-Dargham.

Acquisition, analysis, or interpretation of data: Slifstein, van de Giessen, Van Snellenberg, Thompson, Narendran, Hackett, Girgis, Ojeil, D’Souza, Malison, Huang, Lim, Nabulsi, Carson, Lieberman, Abi-Dargham.

Drafting of the manuscript: Slifstein, van de Giessen, D’Souza, Abi-Dargham.

Critical revision of the manuscript for important intellectual content: Slifstein, van de Giessen, Van Snellenberg, Thompson, Narendran, Gil, Hackett, Girgis, Ojeil, Moore, Malison, Huang, Lim, Nabulsi, Carson, Lieberman, Abi-Dargham.

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Cortical and Extrastriatal Dopamine in Schizophrenia

Mallon, Huang, Lim, Nabulsi, Carson, Lieberman, Abi-Dargham. Study co-sponsor: Silfstein, Van Snellenberg, Thompson, Girgis, Ojel, D’Souza, Huang, Abi-Dargham.

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