

Dopamine Release in Antidepressant-Naive Major Depressive Disorder: A Multimodal [¹¹C]-(+)-PHNO Positron Emission Tomography and Functional Magnetic Resonance Imaging Study

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ABSTRACT

BACKGROUND: Mesolimbic dopamine system dysfunction is believed to contribute to major depressive disorder (MDD), but molecular neuroimaging of striatal dopamine neurotransmission has yielded mixed results, possibly owing to limited sensitivity of antagonist radioligands used with positron emission tomography to assess dopamine release capacity. This study used an agonist radioligand with agonist challenge to assess dopamine release capacity and D₂/D₃ receptor availability in MDD.

METHODS: Twenty-six treatment-naive adults with MDD and 26 healthy comparison participants underwent functional magnetic resonance imaging during a probabilistic reinforcement task, and positron emission tomography with the D₃-preferring ligand [¹¹C]-(+)-PHNO, before and after oral dextroamphetamine. MDD participants then received pramipexole treatment for 6 weeks.

RESULTS: MDD participants had trend-level greater dopamine release capacity in the ventral striatum, as measured by percent change in baseline binding potential relative to nondisplaceable compartment (ΔBP_{ND}) (−34% vs. −30%; $p = .072$, $d = 0.58$) but no difference in D₂/D₃ receptor availability (BP_{ND}). Striatal and extrastriatal BP_{ND} and percent change in baseline BP_{ND} were not significantly associated with blood oxygen level-dependent response to reward prediction error in the ventral striatum, severity of depression and anhedonia, or antidepressant response to pramipexole (response rate = 72.7%).

CONCLUSIONS: [¹¹C]-(+)-PHNO demonstrated high sensitivity to displacement by amphetamine-induced dopamine release, but dopamine release capacity and D₂/D₃ availability were not associated with ventral striatal activation to reward prediction error or clinical features, in this study powered to detect large effects. While a preponderance of indirect evidence implicates dopaminergic dysfunction in MDD, these findings suggest that presynaptic dopamine dysregulation may not be a feature of MDD or a prerequisite for treatment response to dopamine agonists.

Keywords: [¹¹C]-(+)-PHNO, Dopamine, Functional magnetic resonance imaging, Major depressive disorder, Positron emission tomography, Pramipexole

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Major depressive disorder (MDD) is often characterized by anhedonia or low reward motivation (1), features that predict poor treatment response (2), particularly to selective serotonin reuptake inhibitors (3,4). Better understanding of neurobiological processes underlying motivational symptoms in MDD has the potential to improve personalization of treatment.

Converging evidence implicates dysfunction of the mesolimbic dopamine (DA) system in reward-related deficits that have been associated with MDD. Preclinical studies show that phasic DA learning signals in midbrain and striatum mediate the ability to anticipate, learn from, and integrate reward

information (5–9). In healthy volunteers, functional magnetic resonance imaging (fMRI) studies support striatal involvement in reward processing and reinforcement learning (10,11). Positron emission tomography (PET) studies of individual differences in healthy subjects have found associations of DA receptor availability and/or DA release with self-report and behavioral measures of reward learning and motivation (12–18).

In MDD, low motivation has been linked to impairment in integrating reinforcement over time and adapting behavior (19–22). Some fMRI studies have reported diminished striatal

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reactivity during reward anticipation and reward prediction error in MDD (23–26), though others have not (27). While these fMRI findings indirectly implicate DA dysfunction in MDD, more direct assessment of DA is needed to support this association with MDD and motivational deficits. DA agonist challenge has been shown to enhance striatal response during reward learning in subjects with MDD (28) and healthy subjects (29–31). Other evidence comes from animal models of depression (32), and from MDD studies of DA depletion (33) and antidepressant response to DA agonists. The DA agonist that has been most extensively studied for depression treatment is pramipexole (34–40), a D₃-preferring agonist that increases dopaminergic transmission (41,42).

Despite evidence for DA dysfunction in MDD, molecular neuroimaging using PET or single photon emission computed tomography—among the most direct approaches for assessing DA function in the living human brain—has yielded mixed findings. Of six PET and seven single photon emission computed tomography studies assessing striatal D₂/D₃ receptor availability in MDD relative to healthy comparison (HC) subjects, four reported receptor availability to be greater in MDD (43–46), one study reported receptor availability to be less in MDD (47), and eight reported no difference (48–55). Two studies of amphetamine-induced DA release in MDD [one PET study (49) and one single photon emission computed tomography study (56)] also found no difference. These studies have been variously limited, however, by use of D₂/D₃ antagonist ligands, by limited assessment of anhedonia or reward motivation, and by variability in antidepressant exposure, substance use, and, in female subjects, menstrual status.

[¹¹C]-(+)-PHNO is a D₂/D₃ agonist radioligand with potentially advantageous features for studying MDD. Because [¹¹C]-(+)-PHNO is D₃-preferring, it permits measurement of D₃ availability in regions where D₃ receptors predominate, such as the substantia nigra (57,58). D₃ receptors, which are preferentially distributed in the mesolimbic DA system, are believed to be important for affective processes (59). As an agonist, [¹¹C]-(+)-PHNO binds only to high-affinity-state receptors and is more sensitive to displacement by endogenous DA relative to antagonists, resulting in greater power to assess amphetamine-induced displacement as a measure of DA release capacity (60,61).

The aim of this study, the first to use [¹¹C]-(+)-PHNO in MDD, was to capitalize on the sensitivity of this radioligand to test whether depression is associated with abnormal striatal DA release. We hypothesized that DA release in the ventral striatum would be decreased in MDD. We also investigated associations of PET measures of D₂/D₃ availability and DA release capacity with other indicators of DA function, including ratings of motivational anhedonia, fMRI assessment of ventral striatal response to reward prediction error, and symptomatic response to pramipexole treatment.

METHODS AND MATERIALS

Participants

Participants were recruited from research clinics at the New York State Psychiatric Institute and Icahn School of Medicine at Mount Sinai between April 2014 and August 2016. Diagnoses were assessed by clinical interview and confirmed

using the Structured Clinical Interview for DSM-IV (62). Medical screenings included history and physical examination, blood and urine tests including urine toxicology, electrocardiogram, and structural MRI of the brain. Plasma estradiol and progesterone levels were obtained for female subjects on the PET imaging day. MDD participants had a current major depressive episode without psychotic features, a 17-item Hamilton Depression Rating Scale (HDRS) (63) score of 17 to 28, <2 weeks of lifetime psychiatric medication (none for the past 3 months), and no lifetime psychotic, bipolar, attention deficit, or substance use disorders (including nicotine). HC participants had no lifetime psychiatric disorders and were matched for age, gender, and race/ethnicity (see Table 1). All participants had no tobacco or illicit substance use for 3 months, had no family history of schizophrenia, were medically healthy, and were not pregnant, nursing, postmenopausal, or using hormonal contraception. This study was approved by institutional review boards of the New York State Psychiatric Institute and Icahn School of Medicine at Mount Sinai, and participants provided written informed consent.

Overall Study Design

Baseline assessments included rating scales and fMRI during a reinforcement learning task. Two PET scans were then performed on a separate day. MDD participants started pramipexole treatment 1 day after PET, returning weekly for assessments. A separate probabilistic reward task (21) without imaging was conducted pre- and posttreatment. Those results and the full fMRI results will be reported elsewhere.

Clinical Assessments

Baseline ratings included the North American Adult Reading Test (64) and the Edinburgh Handedness Scale (65). The HDRS and the Clinical Global Impressions-Change Scale were primary treatment outcome measures, rated weekly (66). As dopaminergic dysfunction has been hypothesized to be associated with anhedonia, and particularly with motivational or anticipatory anhedonia (67,68), we included pre- and post-treatment ratings designed to assess specific forms of anhedonia [the Temporal Experience of Pleasure Scale (69), assessing anticipatory and consummatory physical pleasure; and the Apathy Evaluation Scale (70), assessing motivational anhedonia], as well as ratings of anhedonia that have been commonly used in MDD [the Mood and Anxiety Symptom Questionnaire Short Form, with Anhedonic Depression subscale (71); and the Snaith-Hamilton Pleasure Scale (SHAPS) (72,73)]. The Amphetamine Interview Rating Scale (74) assessed mood hourly on the PET day. Treating clinicians administered a Side Effects Checklist devised for this study (see Supplemental Table S1).

Reinforcement Learning Task

During fMRI, participants performed a probabilistic reinforcement learning task (75,76) with two counterbalanced phases (60 nonintermixed trials each): gain (winning money) and loss (avoiding loss of money from endowment). The trials were designed to separate motor response (choice), anticipatory reinforcement feedback, and actual reward receipt. In each condition, participants 1) chose one of two stimuli, 2) received

stochastically delivered feedback (correct or incorrect, 70/30 contingency based on choice), and 3) received a monetary outcome. In the gain condition, for example, feedback of “correct” triggered a \$1 or \$0.50 monetary gain (at 50/50 contingency), whereas feedback of “incorrect” triggered a \$0.50 or \$0 monetary gain (at 50/50 contingency) (see Figure 1). Conversely, in the loss condition, “correct” triggered losing \$0 or \$0.50 and “incorrect” triggered losing \$0.50 or \$1. This yielded reward prediction error responses separately during feedback and monetary outcome. Reinforcement contingencies were learned through trial and error.

MRI Data Acquisition

Scans utilized a GE SIGNA 3T scanner (GE Healthcare, Milwaukee, WI) with 32-channel head coil. Participants viewed images on a screen and responded using a trackball. T1-weighted structural images (1-mm isotropic voxels, 200 slices, field of view = 256 mm) and functional echo-planar images (repetition time = 2000 ms, echo time = 28 ms, flip angle = 77°, field of view = 19.2, 3-mm isotropic voxels, 40 slices) were acquired in six runs of 20 trials each. Five volumes were discarded for magnetic stabilization.

fMRI Analysis

Functional images were preprocessed with SPM12 and analyzed with NeuroElf (<http://neuroelf.net/>) software. Images were slice-time corrected and realigned to the first volume of each run for motion correction, then warped to Montreal Neurological Institute template and smoothed with a 6-mm Gaussian kernel. Data were forced to single precision to decrease the impact of rounding errors. After preprocessing, first-level analyses used a general linear model, including six stick function regressors convolved with a hemodynamic response of choice, feedback, and outcome, each with trial-specific parametric regressors (choice value, feedback prediction error, and monetary outcome prediction error). Learning rates and choice value for model-based fMRI analyses were estimated using a reinforcement learning model (77,78). A high-pass temporal filter (Fourier transform, 200 seconds) and motion parameters were incorporated as regressors of no interest.

For parametric regressors, a computational Q-learning model (79) generated behavioral learning parameters for each participant (learning rate/alpha, temperature/beta), and trial-specific learning signal regressors (prediction error) for fMRI general linear model-based analyses. Analyses here are limited to the a priori hypothesis of altered ventral striatal blood oxygen level-dependent (BOLD) response to reward prediction error in MDD. We extracted beta values reflecting each participant’s response in an a priori defined nucleus accumbens region of interest (ROI) using the Harvard-Oxford Atlas. Group difference analyses were conducted for the nucleus accumbens, small-volume corrected at $p < .05$. Each set of analyses was performed for each prediction error event (feedback and outcome) and condition (gain and loss).

PET Imaging Procedures

Participants completed two [^{11}C]-(+)-PHNO PET scans, 5 hours apart, on 1 day, following previous methods (80). A

molded polyurethane head immobilizer (Soule Medical, Tampa, FL) minimized head motion. Following a 7-second computed tomography (CT) scan for attenuation correction, a 120-minute baseline scan was acquired, followed by oral amphetamine (0.5 mg/kg) administration. Three hours later (5 hours after first radiotracer injection) another CT and 120-minute scan were administered. Data were acquired in list mode on a Biograph multispectral CT PET-CT (Siemens Healthineers, Knoxville, TN), binned into a frame sequence of increasing duration, and reconstructed by filtered back-projection using manufacturer-provided software.

PET Data Analysis

Preprocessing. ROIs, drawn on each T1-weighted MRI scan as previously described (81), included the globus pallidus, precommissural dorsal caudate, postcommissural caudate, precommissural dorsal putamen, postcommissural putamen, ventral striatum, midbrain encompassing the substantia nigra and ventral tegmentum, thalamus, and cerebellum. PET data were coregistered to MRI data using normalized maximization of mutual information (SPM8), and ROIs were transferred to coregistered PET using MEDx software, version 3.42 (Medical Numerics, Germantown, MD).

Kinetic Analysis. Time-activity curves were generated as mean activity in each frame for each ROI. Reference tissue-based kinetic modeling (simplified reference tissue model) (82) using the cerebellum as reference tissue yielded binding potential relative to nondisplaceable compartment (BP_{ND}) (83). Percent change from baseline BP_{ND} in each ROI following amphetamine ($\Delta\text{BP}_{\text{ND}}$) was taken as a measure of DA release capacity (84).

Statistics. Ventrostriatal BP_{ND} and $\Delta\text{BP}_{\text{ND}}$ were compared between groups by two-group t tests and correlated with clinical features within the MDD group. In secondary analyses, for other ROIs, groups were compared by t tests with false discovery rate correction for multiple comparisons. Additionally, all regions were tested simultaneously, both for group mean comparisons and for associations with other variables including BOLD response in the nucleus accumbens, in the mixed-model framework (SPSS version 24, IBM Corp., Armonk, NY) with ROI as repeated measure, and group and ROI as fixed effects. Paired t tests compared pre- and post-treatment values for clinical outcomes.

Treatment

Following PET, MDD participants started 6 weeks of pramipexole treatment, with dose (0.5–2.5 mg/day) adjusted at weekly visits, based on clinical response.

RESULTS

Participants

Twenty-six adults with MDD and 26 HC subjects participated. Twenty MDD and 20 HC participants completed PET with analyzable data, and 23 MDD and 24 HC participants completed fMRI with analyzable data (see CONSORT diagram in Supplemental Figure S1). Demographic and clinical features

Table 1. Demographics, Clinical Features, and PET Scan Parameters

| Characteristics | HC Group (n = 20) | MDD Group (n = 20) | p Value ^a |
|---|-------------------|--------------------|----------------------|
| Demographics | | | |
| Age, years | 26.9 ± 5.4 | 26.8 ± 6.9 | .95 |
| Gender | | | |
| Female | 10 (50) | 10 (50) | .00 |
| Male | 10 (50) | 10 (50) | |
| Race | | | |
| White | 8 (40) | 8 (40) | .95 |
| African American | 3 (15) | 4 (20) | |
| Asian | 3 (15) | 2 (10) | |
| Other | 6 (30) | 6 (30) | |
| Ethnicity | | | |
| Hispanic | 9 (45) | 6 (30) | .33 |
| Non-Hispanic | 11 (55) | 14 (70) | |
| Education, years | 15.3 ± 1.6 | 14.6 ± 1.4 | .13 |
| NAART (estimated verbal IQ) | 111.3 ± 8.9 | 112.1 ± 7.5 | .75 |
| Body mass index, kg/m ² | 25.2 ± 5.1 | 24.9 ± 5.0 | .87 |
| Edinburgh Handedness LQ | 67.8 ± 42.5 | 62.1 ± 39.3 | .67 |
| Clinical Features | | | |
| MDE specifier | | | |
| With melancholic features | NA | 0 (0) | |
| With atypical features | NA | 4 (20) | |
| Comorbid anxiety disorder | NA | 14 (70) | |
| Age at onset of MDD, years | NA | 16.8 ± 7.0 | |
| HDRS 17-item total | 0.2 ± 0.4 | 20.3 ± 2.5 | <.001 |
| MASQ subscale | | | |
| Anxious arousal | 19.2 ± 2.8 | 26.1 ± 7.3 | .001 |
| Anhedonic depression | 39.0 ± 9.8 | 82.4 ± 10.7 | <.001 |
| General distress anxious | 13.2 ± 2.6 | 24.4 ± 6.8 | <.001 |
| General distress depressive | 14.5 ± 2.9 | 40.2 ± 11.2 | <.001 |
| MASQ total | 87.8 ± 13.4 | 173.0 ± 27.1 | <.001 |
| Snaith-Hamilton Pleasure Scale | 19.5 ± 5.0 | 32.0 ± 7.1 | <.001 |
| TEPS subscale | | | |
| Anticipatory ^b | 47.7 ± 4.7 | 37.1 ± 8.5 | <.001 |
| Consummatory ^b | 37.6 ± 7.7 | 30.3 ± 7.8 | .005 |
| Apathy Evaluation Scale | 24.3 ± 5.3 | 40.9 ± 9.5 | <.001 |
| PET Scan Parameters and Amphetamine-Related Measures | | | |
| Baseline injected radioactivity, MBq | 267.2 ± 94.2 | 213.3 ± 85.5 | .07 |
| Postamphetamine injected radioactivity, MBq | 224.0 ± 79.4 | 197.9 ± 81.5 | .43 |
| Baseline injected mass of radiotracer, µg | 1.9 ± 0.4 | 1.9 ± 0.3 | .63 |
| Postamphetamine injected mass of radiotracer, µg | 1.9 ± 0.2 | 1.9 ± 0.2 | .86 |
| Baseline specific activity, MBq/nmol | 34.6 ± 12.7 | 28.2 ± 11.8 | .11 |
| Postamphetamine specific activity, MBq/nmol | 29.2 ± 11.7 | 26.2 ± 11.2 | .43 |
| Postamphetamine peak change in AIRS | | | |
| Happiness rating | 1.4 ± 1.6 | 2.4 ± 2.0 | .08 |
| Energy rating | 1.4 ± 2.4 | 3.3 ± 2.2 | .009 |
| Restlessness rating | 2.6 ± 2.6 | 1.9 ± 3.3 | .46 |
| Anxiety rating | 0.9 ± 1.5 | 0.3 ± 2.9 | .43 |
| Plasma amphetamine (mean of 3 levels at 0, 15, and 30 minutes postinjection of PHNO), ng/mL | 62.0 ± 13.2 | 68.4 ± 16.8 | .19 |
| Oral dose dextroamphetamine, mg | 36.8 ± 8.5 | 36.0 ± 7.9 | .78 |

Table 1. Continued

| Characteristics | HC Group (n = 20) | MDD Group (n = 20) | p Value ^a |
|---------------------------|--|--|----------------------|
| Serum progesterone, ng/mL | 2.7 ± 4.5 in n = 8 female subjects | 1.7 ± 1.7 in n = 9 female subjects | .55 |
| Serum estradiol, pg/mL | 104.0 ± 101.2 in n = 8 female subjects | 163.6 ± 274.5 in n = 8 female subjects | .57 |

Values are mean ± SD or n (%).

AIRS, Amphetamine Interview Rating Scale (change from baseline to postamphetamine maximum); HC, healthy comparison; HDRS, Hamilton Depression Rating Scale; LQ, laterality quotient; MASQ, Mood and Anxiety Symptom Questionnaire; MDD, major depressive disorder; MDE, major depressive episode; NA, not applicable; NAART, North American Adult Reading Test; PET, positron emission tomography; TEPS, Temporal Experience of Pleasure Scale.

^aTwo-group *t* test for continuous variables, chi-square, or Fisher’s exact test for categorical variables.

^bGreater scores represent less anhedonia.

of PET completer samples are shown in Table 1. Demographic and clinical features of fMRI completers and intercorrelations among clinical ratings of anhedonia and depression are shown in Supplemental Tables S2 and S3, respectively.

Positron Emission Tomography

Groups did not differ in mean injected activity, injected mass, regional volumes, or plasma amphetamine levels (Table 1). Age was significantly correlated with BP_{ND} across both groups (BP_{ND} [*F*_{1,36} = 17.34, *p* < .001], decrease = 0.9%/year [95% confidence interval, -1.3% to -0.5%], group by age interaction, not significant). Baseline BP_{ND} and ΔBP_{ND} (Table 2 and Figure 2) did not differ significantly between groups for any ROI or across all ROIs after covarying for age (BP_{ND} [*F*_{1,36.17} = 0.50, *p* = .48], ΔBP_{ND} [*F*_{1,35.70} = 1.78, *p* = .19]). There was trend-level greater DA release in the MDD group in the ventral striatum (-34% vs. -30%; *p* = .072, Cohen’s *d* = 0.58) and the globus pallidus (-27% vs. -22%; *p* = .096, *d* = 0.54) relative to HC subjects.

Baseline clinical features in the MDD group, including severity of depression and severity of anhedonia on all measures, were not significantly associated with BP_{ND} and ΔBP_{ND} across all ROIs or within any ROI. Six MDD patients who evidenced ventral striatal ΔBP_{ND} outside the range of HC participants (i.e., greater DA release) did not differ significantly from the other 14 MDD patients in any clinical features except

for greater scores on the Mood and Anxiety Symptom Questionnaire total (*t*₁₈ = 2.65, *p* = .02) and on two of its four subscales, anxious arousal (*t*_{5,49} = 2.53, *p* = .05) and general distress anxious (*t*₁₈ = 2.91, *p* = .01). These differences did not survive correction for multiple comparisons. MDD patients showed significantly greater postamphetamine increase in energy relative to HC subjects and trend-level greater increase in happiness (Table 1), but BP_{ND} and ΔBP_{ND} did not predict changes in mood after amphetamine. PET outcomes across all ROIs for BP_{ND} and ΔBP_{ND} were also not associated with antidepressant response to pramipexole, as assessed by slope of change in HDRS or SHAPS total scores over time (BP_{ND}: HDRS [*F*_{1,17} = 0.008, *p* = .93], SHAPS [*F*_{1,17} = 0.12, *p* = .73]; ΔBP_{ND}: HDRS [*F*_{1,17} = 0.59, *p* = .452], SHAPS [*F*_{1,17} = 0.18, *p* = .68]).

Functional MRI

Overall, participants performed well on the fMRI learning task, with all but 2 (control subjects) performing above chance in the gain condition, and all but 1 (control subject) in the loss condition. Similarly, maximum likelihood of the model did not differ between groups (gain [*t*₄₆ = -0.93, *p* = .36], loss [*t*₄₆ = -0.59, *p* = .56]) and showed near-chance estimates for only 1 (control subject) participant; all others were fit better than chance. However, no correlations between PET and behavioral metrics (reaction time, performance, or model-based analyses) in

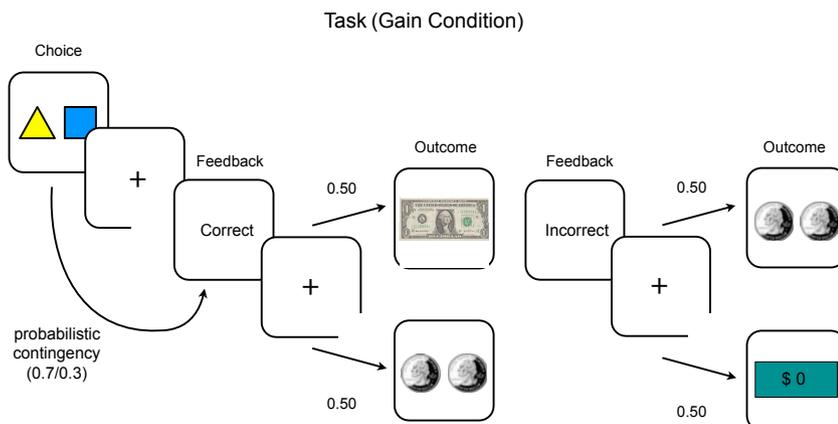


Figure 1. Probabilistic reinforcement learning task.

Table 2. Binding Potential (BP_{ND}) and Postamphetamine Change in Binding Potential (ΔBP_{ND})

| Region | HC Group (n = 20) | | | MDD Group (n = 20) | | | MDD Group vs. HC Group | |
|-------------------|-------------------|-----------------|-----------------------|--------------------|-----------------|-----------------------|------------------------|---------------------|
| | Baseline | Postamphetamine | ΔBP _{ND} (%) | Baseline | Postamphetamine | ΔBP _{ND} (%) | p BP _{ND} | p ΔBP _{ND} |
| Anterior Putamen | 2.7 ± 0.2 | 2.1 ± 0.2 | -22.9 ± 6.0 | 2.6 ± 0.5 | 2.0 ± 0.4 | -25.8 ± 6.4 | .75 | .15 |
| Dorsal Caudate | 2.3 ± 0.2 | 1.8 ± 0.2 | -18.7 ± 5.3 | 2.2 ± 0.5 | 1.7 ± 0.4 | -19.8 ± 5.6 | .83 | .53 |
| Midbrain | 0.8 ± 0.1 | 0.5 ± 0.1 | -30.5 ± 14.6 | 0.7 ± 0.2 | 0.4 ± 0.1 | -39.2 ± 24.2 | .19 | .17 |
| Posterior Caudate | 1.3 ± 0.2 | 1.0 ± 0.2 | -23.3 ± 6.8 | 1.3 ± 0.3 | 1.0 ± 0.3 | -23.3 ± 6.6 | .76 | .20 |
| Globus Pallidus | 4.7 ± 0.6 | 3.6 ± 0.6 | -22.0 ± 8.8 | 4.5 ± 1.1 | 3.2 ± 0.8 | -26.9 ± 9.0 | .46 | .10 |
| Posterior Putamen | 2.3 ± 0.2 | 1.6 ± 0.1 | -29.5 ± 6.9 | 2.3 ± 0.5 | 1.6 ± 0.4 | -29.6 ± 5.7 | .80 | .95 |
| Thalamus | 0.6 ± 0.2 | 0.5 ± 0.1 | -22.8 ± 10.3 | 0.6 ± 0.2 | 0.5 ± 0.1 | -18.6 ± 20.5 | .95 | .42 |
| Ventral Striatum | 3.9 ± 0.4 | 2.7 ± 0.3 | -29.6 ± 7.6 | 3.9 ± 0.8 | 2.5 ± 0.6 | -34.2 ± 8.3 | .92 | .07 |

Values are mean ± SD.

ΔBP_{ND}, change in binding potential relative to nondisplaceable compartment; HC, healthy comparison; MDD, major depressive disorder.

either group survived correction. BOLD responses in the nucleus accumbens for prediction error at feedback and outcome in each condition (gain or loss) were not significantly correlated with PET outcomes in the ventral striatum or other ROIs (all $p > .05$). The MDD group had decreased prediction error responses relative to HC subjects in the ventral striatum in the gain condition during both feedback, 7 voxels, peak at (-12, 6, 0) ($t_{\max} = 3.47$, $p < .001$); and outcome, 6 voxels, peak at (18, 18, -3) ($t_{\max} = 4.06$, $p = .001$). No differences were identified in the loss condition during feedback or outcome.

Treatment

Twenty-two patients with MDD entered treatment. Twenty-one completed 6 weeks and 1 discontinued treatment at week 4 due to adverse events (nausea, headaches). Mean maximum dose was 1.6 ± 0.7 mg/day (range 0.75–2.5 mg/day). Sixteen

patients (72.7%) were responders, defined a priori by Clinical Global Impression-Change Scale score of 1 (very much improved) or 2 (much improved) at endpoint. Depressive symptoms and measures of motivational, anticipatory, and consummatory anhedonia all improved, as shown in Table 3. Treatment-emergent adverse events were generally mild (Supplemental Table S4).

DISCUSSION

This study did not find abnormal D₂/D₃ receptor availability or DA release capacity in MDD, as measured by [¹¹C]-(+)-PHNO PET before and after amphetamine administration; nor were PET outcomes associated with clinical features within the MDD group. MDD patients with the greatest DA release in the ventral striatum did evidence greater anxiety scores. These did not survive correction for multiple comparisons but suggest the need for further study of the relationship of anxiety to striatal DA. PET outcome measures showed no association with ratings of anticipatory or consummatory anhedonia and did not predict clinical response to pramipexole treatment. PET indices were also uncorrelated with ventrostriatal BOLD response to reward prediction error, which was blunted in MDD in the gain condition.

The MDD sample did have elevated anhedonia on each of several measures, including motivational anhedonia, hypothesized to be a clinical indicator of DA dysfunction. Depressive symptoms were generally responsive to treatment with the DA agonist pramipexole, suggesting DA system mediation of treatment response. Inference of a specific dopaminergic mechanism of response, however, is limited by absence of a placebo treatment group and likelihood of nonspecific influences in an antidepressant-naïve sample (85).

The absence of [¹¹C]-(+)-PHNO PET outcome associations with MDD—in a sample with motivational deficits and robust response to treatment with a DA agonist—was unexpected, given the study's methodological advantages. The sample size of 20 PET completers per group constitutes one of the largest DA receptor imaging studies in MDD. The groups were well matched for features associated with DA indices in some studies, including age, gender, estradiol and progesterone levels in female subjects, and body mass index. This study was tightly controlled by exclusion of lifetime antidepressant

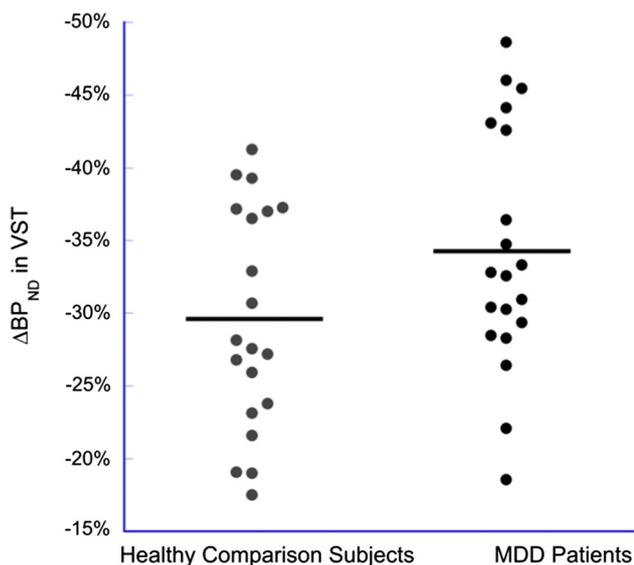


Figure 2. Positron emission tomography scatterplot of postamphetamine change in binding potential relative to nondisplaceable compartment (ΔBP_{ND}) as a measure of dopamine release in the ventral striatum (VST): healthy comparison subjects (mean $29.6 \pm 7.6\%$) vs. major depressive disorder (MDD) patients (mean $34.2 \pm 8.3\%$) ($t = 1.85$, $p = .07$).

Table 3. Treatment Outcomes

| Assessment | Baseline | Week 6 | <i>p</i> Value (Paired <i>t</i> Test) | Cohen's <i>d</i> |
|----------------------------------|--------------|--------------|---------------------------------------|------------------|
| Hamilton Depression Rating Scale | 20.2 ± 2.5 | 8.4 ± 5.4 | <.001 | 2.2 |
| MASQ Subscale | | | | |
| Anxious arousal | 23.4 ± 6.1 | 21.7 ± 6.0 | .163 | 0.3 |
| Anhedonic depression | 82.5 ± 12.1 | 59.6 ± 18.5 | <.001 | 1.3 |
| General distress anxious | 22.7 ± 6.7 | 18.0 ± 5.4 | .002 | 0.8 |
| General distress depressive | 39.3 ± 10.9 | 23.9 ± 12.9 | <.001 | 1.4 |
| MASQ Total | 167.9 ± 24.5 | 123.1 ± 36.3 | <.001 | 1.3 |
| Snaith-Hamilton Pleasure Scale | 31.8 ± 6.5 | 26.0 ± 7.5 | .005 | 0.7 |
| TEPS Subscale | | | | |
| Anticipatory ^a | 35.6 ± 10.3 | 43.2 ± 7.9 | <.001 | 0.6 |
| Consummatory ^a | 29.4 ± 7.4 | 35.6 ± 6.5 | .012 | 0.9 |
| Apathy Evaluation Scale | 42.7 ± 8.9 | 31.7 ± 9.5 | .0001 | 1.1 |

Values are mean ± SD.

MASQ, Mood and Anxiety Symptom Questionnaire; TEPS, Temporal Experience of Pleasure Scale.

^aGreater scores represent less anhedonia.

treatment and current and lifetime comorbid DA-associated conditions, including attention-deficit/hyperactivity disorder, substance use disorders, and recent subsyndromal use of psychoactive substances or tobacco. Estrogen and progesterone levels in female subjects also did not differ between groups. Clinical assessments included multiple measures of depressive symptomatology, including motivational anhedonia, that have been indirectly associated with DA function.

Validity of the PET results here is supported by replication of the well-established finding of decreased DA release with increasing age (despite a constrained range in this sample). The mean magnitude of postamphetamine ΔBP_{ND} of 29.6% in the HC group is in a similar range as that reported for a prior PHNO study at our center (80) that utilized the same dose of oral amphetamine (24.9%), suggesting that the lack of group differences here was unlikely to be due to aberrant HC sample results.

The absence of an association between PET results and BOLD response to reward prediction error in the ventral striatum suggests that D_2/D_3 receptor availability and DA release capacity may not mediate neural response to reward prediction error either within MDD or more generally. However, the lack of an association here may be due in part to the different probes: an instrumental reinforcement learning task during fMRI and pharmacological amphetamine challenge during PET. Also, PET and fMRI were performed on separate days. Reinforcement learning tasks similar to the one used here during fMRI have been associated with phasic release of striatal DA (5,14). Amphetamine, however, increases synaptic DA via multiple mechanisms, including reversing the DA transporter (86). The absence of differences in amphetamine-induced DA release observed here suggests that presynaptic DA levels may not be dysregulated in MDD. For example, the kinetics of dopaminergic cell firing and the resultant phasic DA release that tracks reward prediction error could be altered in MDD, yet DA storage in vesicles and release upon amphetamine administration may not be substantially affected. Another presynaptic PET measure, assessment of DA synthesis capacity with 6- $[^{18}F]$ fluoro-L-DOPA, was found in healthy subjects to be negatively

associated with ventral striatal learning signal using a task that isolated model-based learning, whereas our task assessed model-free learning (87). These approaches to assessing presynaptic DA and reward learning warrant further investigation in MDD.

Our observation that PET results in the MDD group were also not associated with antidepressant response to pramipexole suggests that the robust symptomatic response to a course of pramipexole treatment does not represent normalization of a deficit in dopaminergic storage or release capacity in MDD. Similarly, the tendency for the MDD group to report a greater postamphetamine increase in energy and mood [consistent with a prior report (88)] was not significantly associated with BP_{ND} and ΔBP_{ND} . The group difference in mood response may be related to ceiling effects in the HC group or to the effects of amphetamine on neurotransmitters other than DA.

An alternative to using PET with amphetamine to stimulate DA release in MDD might be to utilize a reward motivation task during PET to more directly assess DA release that occurs during reward prediction error, as has been conducted with healthy subjects (12–18). However, the relatively low temporal resolution of PET neuroreceptor imaging and the low magnitude of DA displacement in response to a behavioral reward task (relative to amphetamine or methylphenidate challenge) limit sensitivity of such as an assessment, and prior efforts to assess DA released by a behavioral task in healthy volunteer samples have had mixed results (89). Another study using a behavioral task recorded striatal DA signaling directly, from a sample of Parkinson's disease patients who had deep brain electrodes placed for therapeutic stimulation, using fast-scan cyclic voltammetry during an investment task. Comparisons to a healthy sample undergoing fMRI during the same task found only partial correspondence between direct recording signals and BOLD responses (90).

The sample size, although large for a PET study, afforded power to detect only large effects. The largest group difference in PET outcomes was for DA release in the ventral striatum, where a trend significant finding of $p = .072$ represented a

medium-sized effect of $d = 0.58$. A future study designed to detect a group difference of this magnitude with 80% power at a significance level of $p < .05$ would require 47 subjects per group, a sample size of limited feasibility given the current costs of PET imaging. The well-known heterogeneity of the diagnostic category of MDD may have limited power to detect group differences in this study. Despite strict exclusion of subjects with hypothesized confounders including comorbid substance use and prior antidepressant treatment, careful matching of comparison subjects, and exploration of dimensional features such as anhedonia and response to DA agonist treatment, unmeasured heterogeneity such as genetic variability may have limited ability to detect associations. Alternative clinical samples, such as nonresponders to first-line serotonergic medications, might be more likely to be enriched for dopaminergic dysfunction.

Other limitations involve the PET assessments. For example, the study was limited by the specificity of the PET amphetamine challenge for assessment of DA storage and release capacity, rather than other physiological aspects of DA function. Additionally, specific contributions of D_2 and D_3 receptors to [^{11}C]-(+)-PHNO binding potential could not be discriminated in regions known to contain both receptor types, including the ventral striatum. Another limitation was administration of the reinforcement learning task in a separate session on a separate day from the dual PET scans. Future studies should more directly explore the functional relationship between reward motivation tasks that putatively elicit phasic DA signals and PET metrics that track the activity of D_2 and D_3 receptors.

Additionally, other neural processes both within and outside the ventral striatum could contribute to blunting of the BOLD response to reward prediction error in MDD, in the absence of abnormal DA release capacity or D_2/D_3 receptor density. D_2/D_3 receptor interacting partners within the ventral striatum, such as DA transporter, D_1 receptors, or components of the signaling pathways downstream of D_2/D_3 receptors, could impact response to reward in MDD (91–93). The serotonergic system also modulates reward responses (94,95), and abnormalities of glutamate or DA in other brain regions, such as in the frontal cortex, could also influence BOLD response in the striatum (96,97). The role of frontostriatal pathways in anhedonic depression might be clarified by PET studies with radioligands allowing assessment of cortical D_2/D_3 receptors (e.g., [^{11}C]FLB 457) and D_1 receptors (e.g., [^{11}C]NNC 112) (97,98).

In conclusion, this multimodal imaging study, incorporating fMRI and [^{11}C]-(+)-PHNO PET with amphetamine in MDD and HC groups, did not identify group differences in D_2/D_3 receptor binding or DA release capacity, although ventrostriatal BOLD response to reward prediction error was decreased in the MDD group. PET outcomes also did not predict response of MDD symptoms to treatment with pramipexole. While the positive therapeutic response could suggest a D_2/D_3 dopaminergic dysfunction that was reversed by pramipexole treatment, the normal baseline D_2/D_3 PET and DA release measures suggest that [^{11}C]-(+)-PHNO PET with amphetamine may not target the specific molecular mechanisms underlying response to pramipexole treatment. Better understanding of the precise molecular and

functional abnormalities in the cortico-basal ganglia loops in MDD may help to explain these negative results and should guide future investigations.

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