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Dopamine Type-1 Receptor Binding in Major Depressive Disorder Assessed Using Positron Emission Tomography and [^{11}C]NNC-112

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The dopamine type-1 receptor has been implicated in major depressive disorder (MDD) by clinical and preclinical evidence from neuroimaging, *post mortem*, and behavioral studies. To date, however, selective *in vivo* assessment of D_1 receptors has been limited to the striatum in MDD samples manifesting anger attacks. We employed the PET radioligand, [^{11}C]NNC-112, to selectively assess D_1 receptor binding in extrastriatal and striatal regions in a more generalized sample of MDD subjects. The [^{11}C]NNC-112 nondisplaceable binding potential (BP_{ND}) was assessed using PET in 18 unmedicated, currently depressed subjects with MDD and 19 healthy controls, and compared between groups using MRI-based region-of-interest analysis. The mean D_1 receptor BP_{ND} was reduced (14%) in the left middle caudate of the MDD group relative to control group ($p<0.05$). Among the MDD subjects D_1 receptor BP_{ND} in this region correlated negatively with illness duration ($r=-0.53$; $p=0.02$), and the left-to-right BP_{ND} ratio correlated inversely with anhedonia ratings ($r=-0.65$, $p=0.0040$). The D_1 receptor BP_{ND} was strongly lateralized in striatal regions ($p<0.002$ for main effects of hemisphere in accumbens area, putamen, and caudate). In *post hoc* analyses, a group-by-hemisphere-by-gender interaction was detected in the dorsal putamen, which was accounted for by a loss of the normal asymmetry in depressed women ($F=7.33$, $p=0.01$). These data extended a previous finding of decreased striatal D_1 receptor binding in an MDD sample manifesting anger attacks to a sample selected more generally according to MDD criteria. Our data also more specifically localized this abnormality in MDD to the left middle caudate, which is the target of afferent neural projections from the orbitofrontal and anterior cingulate cortices where neuropathological changes have been reported in MDD. Finally, D_1 receptor binding was asymmetrical across hemispheres in healthy humans, compatible with evidence that dopaminergic function in the striatum is lateralized during reward processing, voluntary movement, and self-stimulation behavior.

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INTRODUCTION

The central dopaminergic system has been implicated in the modulation of emotional behavior, the pathophysiology of depression, and the mechanisms of antidepressant drugs, by clinical and preclinical evidence (Drevets *et al*, 1999; Nestler and Carlezon, 2006; Nutt *et al*, 2006). In experimental animals the dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens shell and medial prefrontal cortex (PFC) were important in learning associations between operant behaviors or sensory stimuli and reward, and in mediating the reinforcing properties of drugs of abuse and natural rewards (Wise and Rompre, 1989; Schultz, 1997). These observations lead to the hypothesis that reduced mesocorticolimbic DA function underlies the anhedonia, amotivation, and psychomotor slowing associated with major depression (Swerdlow and Koob, 1987; Fibiger, 1991; Nestler and Carlezon, 2006).

A variety of experimental data support this hypothesis. Reductions in dopaminergic function associated with α-methyl-*para*-tyrosine administration can induce depressive symptoms in susceptible individuals (Bremner *et al*, 2003; Hasler *et al*, 2008). Conversely, dopamine receptor agonists (eg pramipexole) exert antidepressant effects in placebo-controlled studies (Willner, 2000; Zarate *et al*, 2004). In MDD subjects DA turnover appears abnormally decreased, as concentrations of the DA metabolite, homovanillic acid (HVA), consistently are reduced in the cerebrospinal fluid (CSF) and jugular vein plasma *in vivo* (Lambert *et al*, 2000; Willner, 2000)—particularly in depressives who manifest

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psychomotor retardation or melancholic features (Asberg *et al*, 1984) and in the caudate and accumbens *post mortem* in suicide victims (Bowden *et al*, 1997). Neuroimaging studies of MDD showed reduced [^{11}C]-L-DOPA uptake across the blood–brain barrier (Agren and Reibring, 1994) and increased striatal binding to D_2/D_3 receptor radioligands that were sensitive to endogenous DA concentrations, although these latter findings were limited to cases who showed psychomotor slowing (Ebert *et al*, 1996; Drevets *et al*, 2005). In such cases the elevated D_2/D_3 receptor binding may have reflected either reduced intrasynaptic DA concentrations, or compensatory upregulation of D_2/D_3 receptor density or affinity (Todd *et al*, 1996; Laruelle and Huang, 2001). Nevertheless, studies whose samples were not predominantly composed of psychomotor slowed cases found no difference in D_2/D_3 receptor levels during depression (Klimke *et al*, 1999; Parsey *et al*, 2001; Montgomery *et al*, 2007; Hirvonen *et al*, 2008). Similarly, some (Meyer *et al*, 2001) but not other (Brunswick *et al*, 2003; Argyelan *et al*, 2005; Yang *et al*, 2008) studies of striatal DA transporter (DAT) binding reported reduced availability in MDD subjects *vs* controls.

The specific DA receptor subtypes that mediate dopaminergic function in reward processing, emotional behavior, and depression remain incompletely understood, partly due to the paucity of highly selective agonists and antagonists. In mice phenotypic analysis of DA receptor knockouts identified roles for the D_1, D_2, and D_3 receptor subtypes in mediating dopamine's effects on reward processing and/or emotional behavior. A complex role for D_1 receptors in particular was supported by both preclinical and clinical evidence. In genetically engineered mice deletion of the D_1 receptor attenuated the reinforcing properties of rewarding stimuli (reviewed in Holmes *et al*, 2004). Nevertheless, the euphoric effects of cocaine appeared blunted by D_1 receptor-like antagonist administration in cocaine addicts (Romach *et al*, 1999; Waddington *et al*, 2001; Holmes *et al*, 2004). Moreover, in rats the reduction in sucrose consumption resulting from chronic mild stress, a purported model of anhedonia, was associated with increased D_1 receptor density in the caudate–putamen (but not the accumbens or amygdala) (Papp *et al*, 1994), and in humans with schizophrenia, D_1 receptor antagonists alleviated 'negative' symptoms such as anhedonia and amotivation (Den Boer *et al*, 1995; Karle *et al*, 1995).

With respect to other emotional states, in rats intra-amygdaloid injection of D_1 receptor antagonists exerted anxiolytic effects (de la Mora *et al*, 2005) and impaired retention of inhibitory avoidance learning (fear-based memory) (Lalumiere *et al*, 2004). Moreover, D_1 receptor knockout mice showed deficits in fear extinction and reversal learning (putative correlates of resilience to stress or adaptation to behavioral reinforcement, respectively), and abnormal long-term potentiation of synapses on PFC neurons (El-Ghundi *et al*, 1999, 2001; Huang *et al*, 2004). These data appeared consistent with evidence that an optimal range of D_1 receptor stimulation is required to facilitate working memory, as intracortical administration of either agonists or antagonists for D_1 receptors impairs working memory performance in rodents and primates (Arnsten *et al*, 1994; Williams and Goldman-Rakic, 1995; Granon *et al*, 2000; Robbins, 2000).

In MDD the D_1 receptor has been assessed by genetic, *post mortem* and neuroimaging studies. Although polymorphisms in the human D_1 receptor gene have not been associated specifically with the vulnerability for developing MDD (Koks *et al*, 2006), one study (Severino *et al*, 2005) (but not another (Kato, 2007)) found an association with bipolar disorder (BD). *Post mortem* studies of D_1 receptor binding found no difference in the striatum (Bowden *et al*, 1997) or right amygdala (Klimek *et al*, 2002) in MDD subjects who were unmedicated at the time of death ($n = 28$ and 11, respectively) *vs* controls, although one of these found increased D_1 receptor density and reduced affinity in the accumbens in medicated suicide victims (Bowden *et al*., 1997). Finally, a PET-[^{11}C]SCH-23390 study reported reduced D_1 receptor binding in the striatum bilaterally in 10 depressed MDD subjects with anger attacks (Dougherty *et al*, 2006). It remained unclear whether this finding would generalize to other MDD subtypes. In subjects with BD ($n = 10$), a PET-[^{11}C]SCH-23390 study reported no difference in striatal D_1 receptor binding relative to controls, although only three of the subjects were depressed (Suhara *et al*, 1992). The latter study also reported reduced binding in the frontal cortex of BD subjects, but because ~one-half of [^{11}C]SCH-23390 binding in the frontal cortex is attributable to 5-HT_{2A} receptor binding, this difference remained difficult to interpret (Ekelund *et al*, 2006).

The recent development of a PET radioligand using (+)-5-(7-benzofuranyl)-8-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (NNC-112), a potent and selective D_1 receptor antagonist, provided sufficiently high specific-to-nonspecific binding ratios to permit meaningful assessment of D_1 receptor binding in both extrastriatal and striatal tissues (Andersen *et al*, 1992; Halldin *et al*, 1998). The current study is the first application of [^{11}C]NNC-112 in investigations of D_1 receptor binding in mood disorders, and the first *in vivo* study of D_1 receptor binding in depressed subjects selected more generally according to the criteria for MDD. We hypothesized that the mean D_1 receptor BP_{ND} would be reduced in the striatum of MDD subjects *vs* controls, based on the data reported in MDD subjects with anger attacks (Dougherty *et al*, 2006). In addition, we sought to more specifically localize D_1 receptor binding abnormalities in MDD using an MRI-based technique previously developed for characterizing the dopaminergic system in striatal subregions (Drevets *et al*, 1999, 2001).

PATIENTS AND METHODS

Participants

Right-handed volunteers 18–55 years of age, who either met DSM-IV criteria for recurrent or chronic MDD in a current major depressive episode ($n = 18$), or had no personal history of a major psychiatric disorder ($n = 19$) were studied (Table 1). Diagnosis was established by an unstructured interview with a psychiatrist and the Structured Clinical Interview for DSM-IV (APA, 1994). Exclusion criteria for all subjects included a history of psychosis, exposure to psychotropic drugs, cigarette smoking, or any medication likely to affect cerebral function within the 3 weeks before scanning (eight for fluoxetine), major medical

Table 1 Demographic and Clinical Characterization of the Study Samples

	Control ($n = 19$)	MDD ($n = 18$)
Proportion female (*n*)	58% (11)	61% (11)
Age (mean ± SD)	31 ± 8.5	31 ± 11
Proportion right-handed (*n*)	100% (19)	100% (18)
Depression ratings		
MADRS (mean ± SD)	0.47 ± 1.2	22 ± 5.3
IDS-C (mean ± SD)	0.59 ± 1.3	27 ± 6.5
Anxiety rating		
HAM-A (mean ± SD)	0.59 ± 1.2	12 ± 4.3
Anhedonia IDSC ratings (mean ± SD)	0.06 ± 0.2	9.4 ± 3.2
Psychomotor speed (response latency on RVIP)	437 ± 78	491 ± 118
Age –at –illness onset (years) (mean ± SD (range))	N/A	19 ± 10 (6–41)
Illness duration (years) (mean ± SD (range))	N/A	12 ± 8.5 (2–32)
Duration of medication free (months) (mean ± SD (range))	N/A	23 ± 35 (4–96)
Treatment naïve (*n*)	19	11
Subjects with remote history of suicide attempts (*n*)	0	4
Prior exposure to antipsychotic agent (*n*)	0	1
Remote history of alcohol (2) or marijuana (1) abuse (*n*)	0	3
Comorbid anxiety disorder (*n*)	0	5

MADRS, Montgomery Asberg Depression Rating Scale; HAM-A, Hamilton Rating Scale for Anxiety; IDS-C, Inventory of Depressive Symptoms-Clinician Rated; RVIP, Rapid Visual Information Processing.

or neurological illnesses, lifetime history of substance dependence, substance abuse within 1 year, recent suicidal behavior or serious suicidal ideation, current pregnancy, peri- or postmenopause status. Depressed subjects with secondary anxiety disorders were not excluded. Additional exclusion criteria for the controls included having a first-degree relative with a mood, anxiety, or psychotic disorder. Subjects provided written informed consent as approved by the NIMH IRB.

Data Acquisition and Processing

The severity of depressive symptoms was rated using the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Inventory of Depressive Symptoms-Clinician Version (IDS-C). Anxiety symptoms were rated using the Hamilton Anxiety Rating Scale (HAM-A (Hamilton, 1959)), and anhedonia was assessed using the anhedonia subscale of the IDS-C. Psychomotor speed was assessed using the reaction time measured during performance of the Rapid Visual Information Processing (RVIP) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd, Cambridge, UK). These computerized tasks were presented on an Advantech computer (Model PP-120T-RT) with a 10.5 in. touch screen monitor.

PET scans were acquired using a GE-Advance scanner in 3D mode (reconstructed 3D spatial-resolution = 6 mm full-width at half-maximum (FWHM)). The PET data were reconstructed using a Hanning filter and Gaussian fit scatter correction method. An 8-min transmission scan was acquired using rotating rods of $^{68}Ge/^{68}Ga$, and used to perform measured attenuation correction of the emission image. [^{11}C]NNC-112 was synthesized as described previously (Halldin *et al*, 1998). Following intravenous bolus administration of a mean injected dose = 19.5 ± 1.24 mCi (range 15.5–20.8) of high specific activity [^{11}C]NNC-112, a 90-min dynamic emission scan was acquired as 27 frames of increasing length (number × frame duration (min): 6 × 0.50; 3 × 1.0; 2 × 2.0; 16 × 5.0).

Head motion was minimized during scanning by stabilizing each subject's head position using a thermoplastic mask fixed to the scanner table. In addition, the PET data were corrected for head motion by aligning all frames to a mean image of frames 3 through 8, using AIR (Woods *et al*, 1992) as implemented in Medx (Sensor Systems Inc., Sterling, VA). To provide an anatomical framework for the PET analysis, MRI scans were acquired using a GE 1.5 or 3.0 T scanner and T_1-weighted pulse sequence optimized to enhance tissue-contrast resolution (voxel size = 0.86 × 0.86 × 1.2 mm). The realigned PET frames were coregistered to the anatomical MRI for each subject using fMRIB's Linear Image Registration Tool and a mutual information cost function (Jenkinson and Smith, 2001).

Data Analysis

The D_1 receptor binding parameter estimations were performed voxel-wise using a multilinear reference-tissue model (MRTM) using a receptor-free reference region (cerebellum) without arterial data. The BP_{ND} values thus obtained were proportional to the receptor density (B_{max}) and independent of blood flow (K_1) (Ichise *et al*, 2003). The value of k_2' was estimated by the three-parameter MRTM using regions-of-interest (ROI) time–activity curves for the striatum. The R_1 images, which reflect relative blood flow, were used for image co-registration with MRI. The generation of parametric BP_{ND} images from the dynamic [^{11}C]NNC-112 PET data was performed in PMOD 2.5 (Mikolajczyk *et al*, 1998).

Hypothesis testing was performed in five striatal ROI defined over the anteroventral striatum (AVS; accumbens area, ventromedial caudate, anteroventral putamen), dorsal caudate (DC), middle caudate (MC), ventral putamen (VP), dorsal putamen (DP), as described previously (Bowden *et al*, 1997; Drevets *et al*, 2001). On the basis of the evidence that DA release during reward processing is lateralized in healthy humans (Martin-Soelch *et al*, 2007; Tomer *et al*, 2008), hemisphere was included as a factor in the analyses. To allow comparison with previously reported negative findings from *post mortem* studies of depression (Klimek *et al*, 2002), we examined binding in the amygdala *post hoc*. Additional exploratory analyses were conducted *post hoc* in cortical regions known to contain moderately high D_1 receptor concentrations and to be implicated in the mesocorticolimbic dopaminergic system and the pathophysiology of MDD (Willner, 1995): right and left insula/lateral orbitofrontal cortex (ie sulcal BA47) (Ongur *et al*, 2003) and anterior cingulate cortex (ACC; including subgenual and pregenual areas). Amygdala, insular and ACC ROI were defined as described in (Cannon *et al*, 2007).

The reference region was defined in the cerebellar cortex, with the ROI situated at least one FWHM ventral to the occipital and temporal cortices, and away from the cerebellar vermis and brain edge.

Statistical Analysis

The mean BP_{ND} for each ROI was compared between groups using a linear mixed model and the heterogeneous compound symmetry covariance matrix performed using SPSS. For ROI where the model indicated significant group effects, *post hoc* comparisons of BP_{ND} across groups were performed using unpaired *t*-tests. In regions where group effects were detected the relationship between D_1 receptor BP_{ND} and clinical ratings of depression, anxiety, and anhedonia were assessed *post hoc* by computing Spearman's bivariate correlation coefficients (rho, ρ).

RESULTS

The groups did not differ significantly for mean age or gender composition (Table 1). Mean depression, anxiety, and anhedonia ratings were greater ($p<0.001$, $t=-4$ to -17) in MDD subjects than controls (Table 1). Reaction times on the RVIP did not differ significantly between the MDD and control groups ($t=-1.50$, $p=0.15$). Performance measured by the number of omission (HC 4.5 ± 2.7, MDD 6.9 ± 5.5, $t=-1.64$, $p=0.12$) or commission errors (HC 0.33 ± 1.29, MDD 1.35 ± 1.83, $t=-1.794$, $p=0.083$) on the RVIP also did not differ significantly between groups. Five MDD subjects had comorbid anxiety disorders (generalized social phobia ($n=4$), specific phobia ($n=1$)). Two MDD subjects had a remote history of alcohol abuse and one a remote history of marijuana abuse.

The rank order of the [^{11}C]NNC BP_{ND} values was caudate, putamen > AVS > amygdala > insula > ACC > cerebellum (Table 2), consistent with the relative D_1 receptor densities measured *post mortem* in humans (Cortes *et al*, 1989).

The mean D_1 receptor BP_{ND} was 14% lower in the left MC of the MDD subjects *vs* controls ($t=2.21$, $p=0.03$; Figures 1 and 2; Table 2). The magnitude of this difference was similar after removing the 3 subjects with a remote history of substance abuse (12.6%), the 7 previously medicated MDD subjects (13.5%), or the 5 subjects with co-morbid phobias (11%). In the remaining ROIs mean D_1 receptor BP_{ND} did not differ between the control and MDD groups (Table 2).

In *post hoc* assessments, a main effect of hemisphere was evident in several regions (Figures 1 and 3), including AVS ($F=87.8$, $p=8.01e^{-11}$), VP ($F=8.84$, $p=3.10e^{-2}$), DP ($F=25.5$, $p=1.56e^{-5}$), MC ($F=308$, $p=1.09e^{-5}$), and DC ($F=98.5$, $p=1.77e^{-4}$). A group-by-gender-by-hemisphere interaction ($F=7.33$, $p=0.011$) was detected in the DP, which was accounted for by a greater interhemispheric difference in BP_{ND} in female controls *vs* female MDD subjects (Figure 4). This interaction remained significant after including age as a covariate, or after removing from analysis the subjects who had a remote history of substance abuse ($F=4.44$, $p=0.044$), previous psychotropic medication exposure ($F=6.17$, $p=0.020$) or comorbid phobia ($F=5.83$, $p=0.023$).

Table 2 The Mean and Standard Deviation of Regional [^{11}C]NNC-112 Binding Potential Values

	Healthy control		Major depressive disorder		Group difference	
Region	**Mean**	**SD**	**Mean**	**SD**	***t***	***p***
VP						
Right	2.41	0.47	2.34	0.42	0.48	0.64
Left	2.57	0.51	2.40	0.40	1.15	0.26
DP						
Right	2.49	0.45	2.50	0.33	−0.11	0.92
Left	2.66	0.42	2.57	0.34	0.72	0.48
MC						
Right	2.66	0.53	2.59	0.41	0.47	0.64
Left	2.07	0.46	1.78	0.30	2.21	**0.03***
DC						
Right	2.77	0.58	2.73	0.39	0.28	0.78
Left	2.40	0.45	2.19	0.46	1.39	0.17
AVS						
Right	2.19	0.47	2.09	0.37	0.73	0.47
Left	1.86	0.42	1.67	0.35	1.65	0.11
Amygdala						
Right	1.64	0.55	1.52	0.43	0.79	0.44
Left	1.63	0.76	1.47	0.43	0.88	0.39
Insula						
Right	0.70	0.13	0.69	0.14	−0.42	0.68
Left	0.69	0.12	0.68	0.16	−1.40	0.17
ACC						
Bilateral	1.02	0.23	1.03	0.23	−0.45	0.66

ACC, anterior cingulate cortex; AVS, anteroventral striatum; DC, dorsal caudate; DP, dorsal putamen; MC, middle caudate; VP, ventral putamen.
The *a priori* hypothesis was tested in the striatal regions-of-interest (caudate, putamen). *$p<0.05$: D_1 receptor binding was significantly lower in the left middle caudate of the MDD group relative to the control group. Analyses of D_1 receptor binding in extrastriatal tissues were performed *post hoc*.

Age correlated with BP_{ND} in the left VP ($\rho=-0.34$, $p=0.04$), left DP ($\rho=-0.33$, $p=0.04$), right MC ($\rho=-0.38$, $p=0.02$), bilateral DC (left: $\rho=-0.39$, $p=0.02$; right: $\rho=-0.38$ $p=0.02$), and left insula ($\rho=-0.42$, $p=0.01$). The relationship between BP_{ND} and age showed a trend toward significance in right VP ($\rho=-0.32$, $p=0.06$), left MC ($\rho=-0.29$, $p=0.08$), and left insula ($\rho=-0.32$, $p=0.052$) but did not approach significance ($p>0.10$) in the right DP, AVS, ACC, or amygdala. Analyses were covaried for age where relevant.

A main effect of gender on BP_{ND} was significant in the AVS ($F=4.21$, $p=0.048$), VP ($F=7.28$, $p=0.043$), MC ($F=9.72$, $p=0.026$), and DC ($F=9.77$, $p=0.026$) but not in the DP ($F=1.38$, $p=0.249$). There were no significant group-by-gender interactions in any region ($p>0.1$).

Exploratory, *post hoc* clinical correlations showed that BP_{ND} values in the left MC correlated inversely with illness duration ($r=-0.53$, $p=0.02$; Figure 5), but did not correlate significantly with depression (MADRS), anxiety (HAM-A), or anhedonia (IDS-C anhedonia subscale) severity (ie $p>0.05$). Reaction times on the RVIP correlated

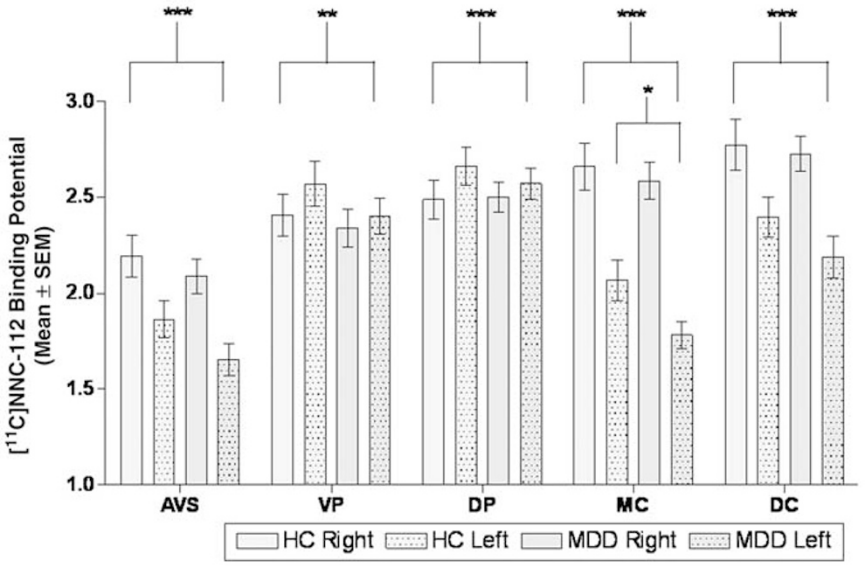

Figure 1 Dopamine D_1 receptor binding potential in healthy control and major depressive disorder (MDD) groups in the left and right hemispheres for the striatal regions-of-interest. *$p<0.05$: D_1 receptor binding was significantly lower in the left middle caudate (MC) in the MDD group relative to control group. **$p<0.05$, ***$p<0.001$: the main effect of hemisphere on binding potential (BP_{ND}) was significant in the anteroventral striatum (AVS), ventral putamen (VP), dorsal putamen (DP), middle caudate (MC), and dorsal caudate (DC) regions-of-interest.

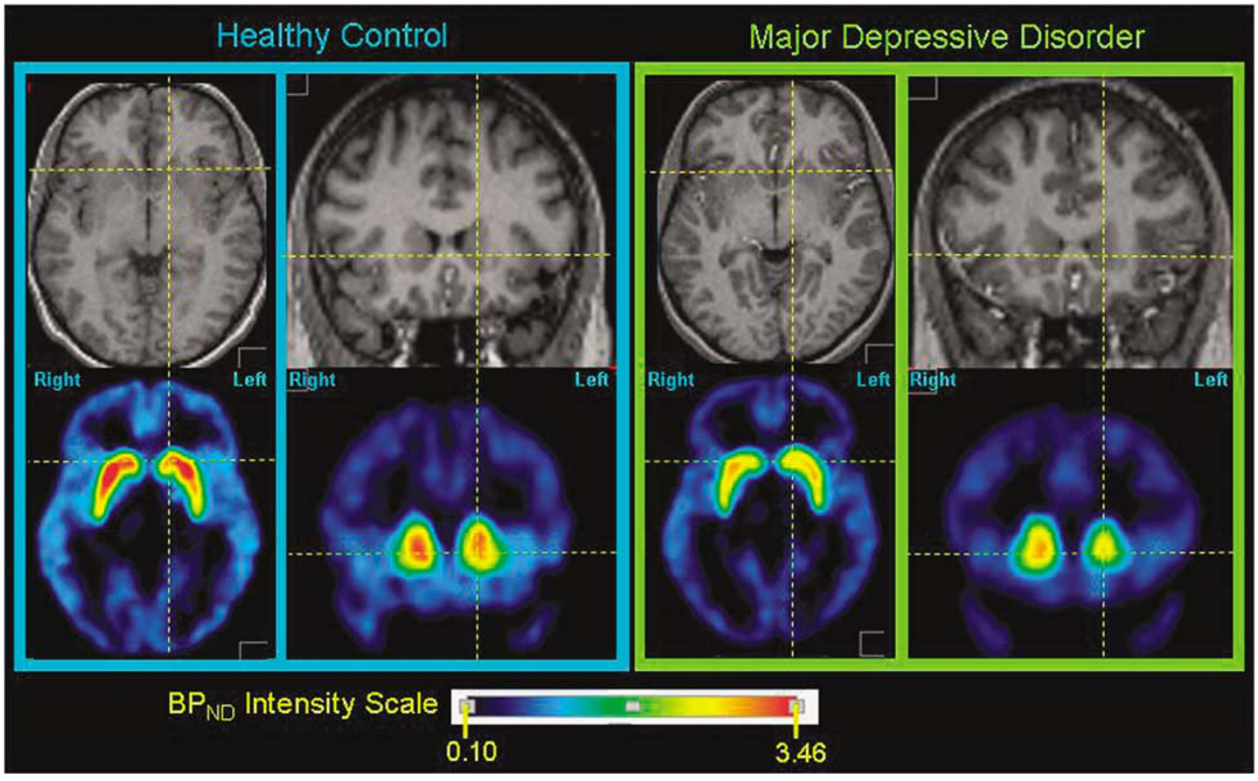

Figure 2 Representative parametric dopamine D_1 receptor binding potential (BP_{ND}) images through the striatum in a control subject (left panel) and an major depressive disorder (MDD) subject (right panel). Within each panel the upper row of images show axial (left) and coronal (right) sections through the anatomical MRI, on which the regions-of-interest (ROI) were defined (Drevets *et al*, 2001), and the lower row of images show parametric images of the nondisplaceable component of the D_1 receptor BP_{ND} modeled from PET emission images. The MRI and PET images for each subject are coregistered. The axial images show the plane containing both the anterior and posterior commissures. The orthogonal lines locate approximately the center of the caudate head on this bicommissural plane. The coronal sections pass through the anterior striatum, which at the level shown is composed predominantly of the caudate head. The middle caudate region is evident in the coronal sections, where it is situated immediately above the bicommissural plane (marked by the horizontal line). The D_1 receptor BP_{ND} consistently was higher in the right caudate than the left in both groups (Figures 1 and 3), as evinced in these representative images. The mean BP_{ND} value in the left middle caudate of the MDD group was lower than in the control group (Figure 1).

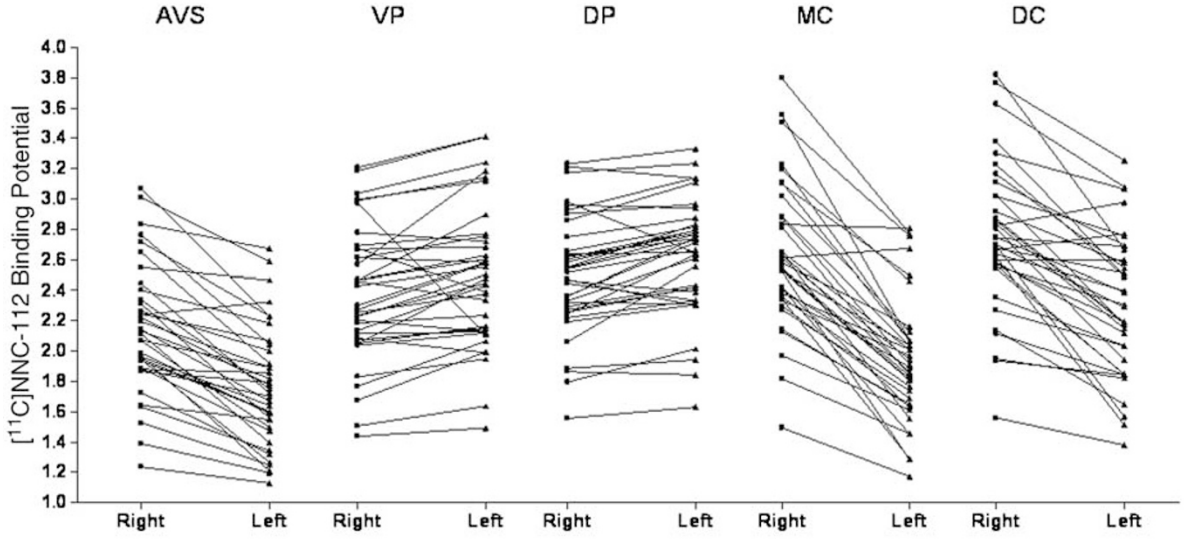

Figure 3 Dopamine D_1 receptor binding potential in the left and right hemispheres for each striatal region-of-interest showing the consistency of laterality effects. The left- and right-sided values corresponding to a single participant are connected by a line. Main effects of hemisphere on regional binding potentials were significant in all five regions-of-interest (see Figure 1 and 'Results' section for significance levels).

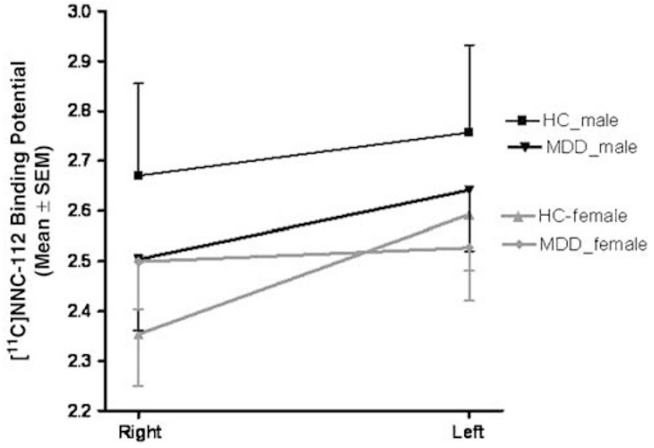

Figure 4 Mean (±SEM) binding potential values for the right and left dorsal putamen separated by sex and diagnosis. In women with major depressive disorder (MDD) the difference in D_1 receptor binding potential (BP_{ND}) between the right and left hemispheres of the dorsal putamen was significantly less than that of the female controls. In the dorsal putamen the group-by-gender-by-hemisphere interaction was significant ($F = 7.33$, $p = 0.011$). Abbreviations: HC, healthy control; MDD, major depressive disorder.

negatively with D_1 receptor binding in the left MC in controls ($r = -0.453$, $p = 0.007$) but not MDD subjects ($r = -0.096$, $p = 0.358$). The ratio of left-to-right BP_{ND} values in the MC correlated inversely with IDS-C anhedonia subscale ratings ($r = -0.65$, $p = 0.0040$) but not with depression or anxiety ratings ($p > 0.4$). MDD subjects with comorbid phobias did not differ in D_1 receptor BP_{ND} in the left MC than nonphobic depressives.

Depression severity correlated negatively with BP_{ND} in right DP (MADRS $\rho = -0.61$, $p = 0.007$; Figure 6). Anxiety severity (HAM-A) correlated negatively with BP_{ND} in right DP ($\rho = -0.48$, $p = 0.045$). Anhedonia ratings, age at onset, and illness duration did not correlate significantly with BP_{ND} in the DP ($p > 0.05$). In right DP, MDD subjects with comorbid phobias showed lower D_1 receptor BP_{ND} than nonphobic depressives ($Z = -2.3$, $p = 0.019$).

Mean BP_{ND} values for depressed subjects who previously were exposed to psychotropic medications ($n = 7$) showed no significant difference *vs* drug–naïve subjects ($n = 11$) in any region ($p > 0.10$).

DISCUSSION

The mean D_1 receptor binding was 14% lower in the left MC of MDD subjects *vs* healthy controls (Figure 1). Moreover, although significant differences in D_1 receptor binding between the right and left hemispheres existed in controls, this normal asymmetry was absent in the DP in depressed women (Figure 4). *Post hoc* assessments in the MDD sample showed that D_1 receptor binding in the left MC correlated inversely with illness duration and anhedonia ratings. In addition, the left MC D_1 receptor binding correlated inversely with psychomotor speed in the controls but not the depressives.

The abnormalities in striatal BP_{ND} in MDD likely reflect alterations in D_1 receptor density and/or affinity for [^{11}C]NNC-112. Although [^{11}C]NNC-112 binding is reversible *in vivo* (Abi-Dargham *et al*, 2000), it is insensitive to displacement by endogenous dopamine (Chou *et al*, 1999). Among DA receptors NNC-112 is highly selective for D_1 receptors (eg the D_1:D_2 receptor binding ratio = 4500) (Ekelund *et al*, 2007). The major limitation in specificity is that [^{11}C]NNC-112 is only 2- to 3-fold more selective for D_1 receptors than 5-HT_{2A} receptors (Ekelund *et al*, 2007). Thus in the frontal cortex, where the 5-HT_{2A} receptor and D_1 receptor concentrations are comparable, up to 25% of [^{11}C]NNC-112 binding is attributable to 5-HT_{2A} receptor binding (Ekelund *et al*, 2006; Slifstein *et al*, 2007). In the striatum, however, where the ratio of D_1:5-HT_{2A} receptor density is relatively higher, the 5-HT_{2A} contribution to the measured BP_{ND} is negligible (Slifstein *et al*, 2007). Thus, the abnormalities observed in the MC and DP in MDD most likely reflect differences in D_1 receptor binding.

The mean 14% decrement in D_1 receptor BP_{ND} in the left MC in our MDD subjects appeared consistent with the 13% reduction in binding in the left striatum reported by Dougherty *et al* (2006) in MDD subjects with anger attacks. Our data extended this previous finding by showing that the left striatal D_1 receptor binding was also decreased in a depressed sample selected more generally according to MDD criteria. We did not observe any abnormality in the right striatum, however, raising the possibility that a deficit in right striatal D_1 receptor binding may be specific to MDD subjects with anger attacks.

Our data more specifically localized the abnormality in left striatal D_1 receptor binding in MDD to the left MC, which showed the greatest magnitude-of-difference and effect size across the striatal ROI (Figures 1 and 3). Because of the proximity of the MC to other striatal ROI, measured signals from the MC were weakly influenced by those from the AVS and DC which were partly continuous with the MC (Drevets *et al*, 1999, 2001). As parts of these ROI were separated by less than 6 mm resolution of our PET measures, demonstrating differential regional abnormalities in MDD depended upon showing that the mean difference in BP_{ND} was greater in the MC than in the DCA or AVS. This approach was facilitated by the low [^{11}C]NNC-112-specific binding in extrastriatal areas, which reduced the number of comparisons required across adjacent regions. The ability to assess relative differences in radiotracer concentration across conditions in ROI separated by less than the FWHM resolution is central to PET's utility in localizing voxels of maximal difference in brain mapping studies (Fox *et al*, 1986; Friston *et al*, 1996). Because of these spatial resolution limitations, however, the nonsignificant trends seen in the left AVS and left DC (Figure 1) are difficult to interpret as they may reflect spilling in of radioactivity from the MC (Links *et al*, 1996).

The MC region is the major striatal target of predominantly ipsilateral, afferent projections from the ACC and orbitofrontal cortex (OFC) (Ferry *et al*, 2000; Haber *et al*, 2006). As the grey matter volume and/or neuronal counts in these cortical areas is reduced in MDD (Drevets *et al*, 2008), the regional specificity of the reduction in D_1 receptor binding to the MC raises the possibility that this abnormality reflects a reduction in afferent neuronal terminals from the cortex, and thus in the density of synapses where D_1 receptors are expressed postsynaptically. This hypothesis appears compatible with findings that in MDD both the reduction in D_1 receptor binding in the MC (Figure 1) and the reduction in grey matter volume in the ACC and OFC are predominantly left-lateralized (Drevets *et al*, 2008). This hypothesis may also be compatible with the finding that the D_1 receptor binding in the left MC correlated inversely with illness duration (Figure 5), as the reductions in ACC volume reportedly worsen across time in mood disorders (Koo *et al*, 2008). In contrast, perturbations in D_1 receptor binding in MDD may be less likely to reflect local changes in receptor expression associated with changes in DA release, as the severe DA deficiency state accompanying Parkinson's Disease is not associated with changes in D_1 receptor binding or density (Pimoule *et al*, 1985; Shinotoh *et al*, 1993). Moreover, although changes in D_1 receptor regulation at the level of G-protein coupling may exist in the DA-depleted striatum (Gerfen *et al*, 2002),

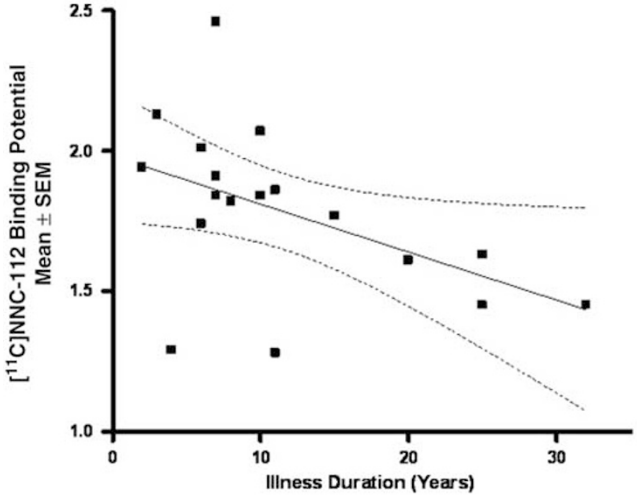

Figure 5 Relationship between dopamine D_1 receptor binding potential in the left middle caudate and illness duration in the major depressive disorder (MDD) sample. The D_1 receptor binding potential in the left middle caudate correlated inversely ($r = -0.531$, $p = 0.02$) with illness duration (calculated as time since onset of illness).

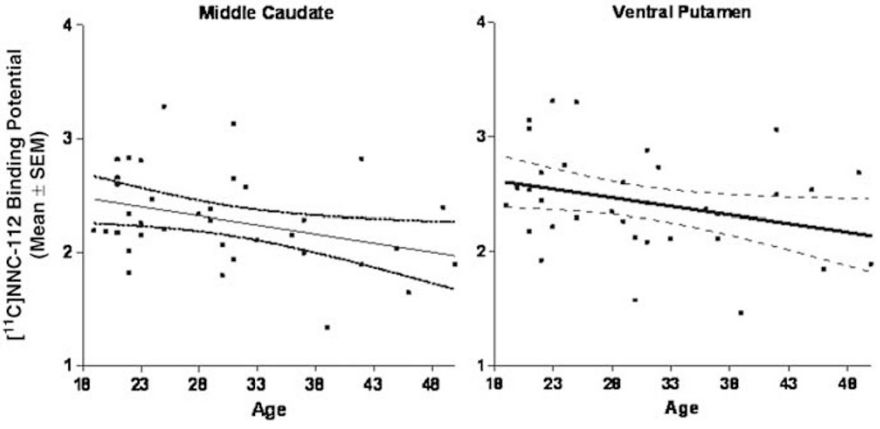

Figure 6 Relationships between age and D_1 receptor binding potential (BP_{ND}) in the middle caudate and ventral putamen for all subjects. Age correlated negatively with [^{11}C]NNC-112 BP_{ND} in the middle caudate, ventral putamen, and most of other striatal regions examined ($\rho = -0.33$ to -0.42, $p = 0.01$–0.04; see text).

such a change would not likely be evinced by corresponding changes in D_1 receptor antagonist binding to PET radioligands (Pimoule *et al*, 1985; Shinotoh *et al*, 1993) which typically bind to receptors in high *vs* low-affinity states with comparable potency.

Post hoc analyses revealed an altered interhemispheric ratio of D_1 receptor BP_{ND} that differed significantly between depressed and control women in the DP. Specifically, the depressed women showed a loss of the asymmetry in D_1 receptor binding that was evident in the controls (Figure 4). This difference was explained by D_1 receptor BP_{ND} values that were nonsignificantly lower in the left DP and nonsignificantly higher in the right DP in depressed women *vs* control women (Figure 4).

In other striatal regions the D_1 receptor binding also showed highly significant laterality effects in healthy controls, which did not differ significantly between groups. In the caudate and AVS (accumbens area), the BP_{ND} was lower in the left hemisphere than the right. In contrast, in the putamen the direction of the laterality effect was reversed (left > right). This difference between caudate and putamen may explain the absence of laterality effects in striatal [^{11}C]SCH-23390 binding in Dougherty *et al* (2006), who combined caudate and putamen into a single ROI. Other studies employing neuroimaging or autoradiographic techniques to assess D_1 receptor binding in depressed or healthy humans (De Keyser *et al*, 1988; Suhara *et al*, 1991, 1992; Bowden *et al*, 1997) or experimental animals (Cortes *et al*, 1989; Camps *et al*, 1990) did not examine laterality effects.

Asymmetrical D_1 receptor binding across hemispheres is consistent with several reports of lateralized function within the dopaminergic system. The amount of DA release in human striatal subregions in response to unpredicted reward (Martin-Soelch *et al*, 2007), DA release in the rodent caudate during voluntary behavior (Yamamoto *et al*, 1982), and preference for self-stimulation induced by localized amphetamine administration in rats all show prominent laterality effects (Glick *et al*, 1980, 1981). In healthy humans greater D_2 receptor availability in the left relative to the right striatum was associated with greater positive incentive motivation (Tomer *et al*, 2008). In right-handed humans DA concentrations were higher in the left putamen than the right (Glick *et al*, 1982; de la Fuente-Fernandez *et al*, 2000), and in marmosets levels of DA and HVA were higher in the right caudate and putamen than the left (Silva *et al*, 2007). Consistent with these data humans also showed higher dopamine transporter density in the left putamen and caudate *vs* the right, irrespective of handedness (van Dyck *et al*, 2002). (Although the lateralization of motor dominance ('handedness') has been associated with variation in elements of the dopaminergic system including COMT (Savitz *et al*, 2007), it remains unclear whether handedness also would influence D_1 receptor BP_{ND}.) Finally, our finding that the loss of normal asymmetry in D_1 receptor BP_{ND} in MDD appeared specific to women was notable given evidence that the direction of asymmetry preference for self-stimulation in rats showed prominent sex effects (Glick and Badalamenti, 1986).

As the mesocorticolimbic dopaminergic system is important in the neural processing of reward and motivation, it is conceivable that either a deficit in dopaminergic function in the left MC, or alterations in the interhemispheric ratio of D_1 receptors that may result from such a deficit, may disrupt the normally lateralized function of this system and thereby contribute to the depressed mood, anhedonia, and amotivation associated with MDD (Nestler and Carlezon, 2006; Liu *et al*, 2008). Compatible with this hypothesis, the ratio of left-to-right D_1 receptor binding in the MC correlated inversely with the IDS-C anhedonia subscale ($r = -0.65$, $p = 0.0040$). In the left MC functional abnormalities have been identified during reward processing in MDD. In independent samples of MDD subjects the magnitude of DA release during unpredicted monetary reward and the hemodynamic response to anticipated monetary reward were abnormally blunted specifically in the left MC (Drevets, 2008).

The relationship between the response latencies on a sustained attention task (RVIP) and D_1 receptor binding in the left MC in healthy controls suggests that the abnormal D_1 binding group in MDD also may play a role in the psychomotor or cognitive impairment associated with MDD. The mean response latency was 12% slower in depressives than controls, as expected (Tavares *et al*, 2003), although we were underpowered to establish the statistical significance of this difference. Although reaction times measured on the RVIP reflect both psychomotor speed and sustained attention, these variables generally are confounded on neuropsychological assessments of psychomotor speed. In controls the response latencies correlated inversely with BP_{ND} in the left MC (explaining 20.5% of the variance) implying the reduction in D_1 receptor binding in this region in MDD may contribute to the psychomotor slowing associated with depression. The absence of a normal correlation between reaction time and MC-BP_{ND} in the MDD group also may be compatible with this hypothesis. Notably, psychomotor slowing previously was associated with reduced dopaminergic function in the left caudate in MDD, as (Martinot *et al*, 2001) reported that [^{18}F]DOPA was reduced specifically in the left caudate in MDD patients with psychomotor retardation compared to both healthy controls and MDD patients without psychomotor slowing.

The inverse correlation between D_1 receptor binding and age is consistent with the results of previous PET (Suhara *et al*, 1991; Iyo and Yamasaki, 1993; Wang *et al*, 1998) or autoradiography studies (Klimek *et al*, 2002) conducted in humans or experimental animals (Suzuki *et al*, 2001). In humans Wang *et al*, (1998) reported a 6–7% decline in [^{11}C]SCH-23390 binding to D_1 receptors per decade in the caudate and putamen, comparable to the 3–6% decline in the BP_{ND} for [^{11}C]NNC-112 per decade detected herein (assessed relative to the *y*-intercept for predicted value at birth; Figure 6). In contrast, the relationship between BP_{ND} and age was not significant in the amygdala, consistent with the data of Klimek *et al*. (2002) who observed no significant age effect on D_1 receptor density measured *post mortem* in the human amygdala.

A limitation of our study was that we modeled the BP_{ND} for [^{11}C]NNC-112 using a simplified reference tissue model to avoid arterial cannulation. This approach used the time-tissue radioactivity concentration in a reference region, the cerebellum, to estimate the concentration of free plus nonspecifically bound radiotracer in all regions. However, without arterial plasma we were unable to measure the distribution volume of [^{11}C]NNC-112 in the cerebellum.

Consequently, a difference in BP_{ND} between groups could have been accounted for by abnormal [^{11}C]NNC-112 binding either in the region-of-interest or the reference tissue. However, an abnormality of tracer uptake in the reference tissue could not account for the regionally specific group difference or the group-by-gender-by-hemisphere interaction found in the left MC and the DP, respectively.

In conclusion, reduced D_1 receptor binding in the left MC, and in women an altered symmetry in D_1 receptor binding in the DP, may contribute to dysfunction within the central dopaminergic system during depression. The prominent laterality effects we observed for striatal D_1 receptor binding converges with other evidence indicating that DA concentrations are lateralized within the striatum (Glick *et al*, 1982; de la Fuente-Fernandez *et al*, 2000; Silva *et al*, 2007), and that the function of the central dopaminergic system in the striatum is lateralized during reward processing (Martin-Soelch *et al*, 2007), voluntary movement (Yamamoto *et al*, 1982), and self-stimulation behavior (Glick *et al*, 1980, 1981; Glick and Badalamenti, 1986). As dopaminergic projections into the striatum modulate the neural processing of reward learning, motivated behavior, and psychomotor activity, alterations in the interhemispheric ratio of D_1 receptor binding conceivably may disrupt the normally lateralized function of this system, and thereby contribute to the depressed mood, psychomotor slowing, anhedonia, and amotivation that characterize depression.

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DISCLOSURE/CONFLICT OF INTEREST

No author has a potential conflict of interest related to this work.

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